Gold Catalysis

DOI: 10.1002/anie.200902355

Structural Diversity through Gold Catalysis: Stereoselective Synthesis of *N*-Hydroxypyrrolines, Dihydroisoxazoles, and Dihydro-1,2-oxazines**

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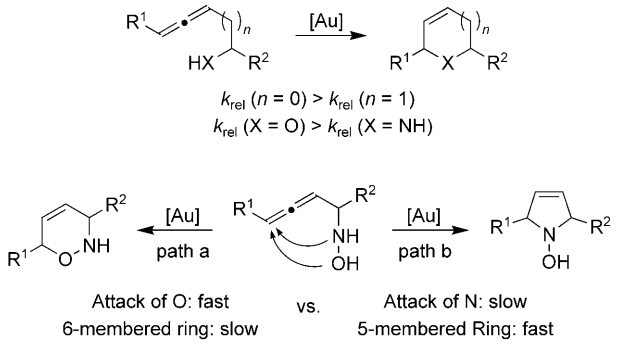
The gold-catalyzed *endo*- or *exo*-selective cycloisomerization of functionalized allenes is a valuable method for the synthesis of chiral heterocycles.[1] To date, these transformations have provided access to five- or six-membered oxygen-,[2,3] nitrogen-,[4,5] or sulfur-containing[6] heterocycles. Interestingly, the gold-catalyzed *endo* cycloisomerization of α-hydroxyallenes[2a–d] is usually faster than that of the corresponding aminoallenes;[4a,b] this behavior is possibly due to the deactivation of the gold catalyst by the Lewis basic amine. Furthermore, the *endo* cyclization of α-functionalized allenes to five-membered heterocycles is normally faster than the formation of dihydropyrans or dihydropyridines from β-functionalized allenes[2c,d] (Scheme 1).

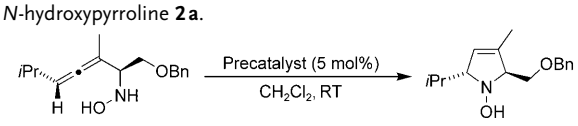


Scheme 1. Different reaction rates in the *endo* cycloisomerization of functionalized allenes and possible consequences for the cyclization of *N*-hydroxy-α-aminoallenes.

This observation has interesting implications for the gold-catalyzed *endo* cycloisomerization of allenes with two adjacent heteroatoms, for example, *N*-hydroxy-α-aminoallenes (Scheme 1). On one hand, attack of the hydroxy group at the allene terminus should be kinetically favored, whereas formation of the six-membered dihydrooxazine should be disfavored (path a). On the other hand, nucleophilic attack of the nitrogen atom should be slow, but formation of the five-membered *N*-hydroxypyrrolines should be fast (path b). Since the outcome of this competition between cyclizations is uncertain, and since reports of gold-catalyzed cycloisomerizations of allenic substrates are limited to the synthesis of heterocycles that contain just one heteroatom,[7] we decided to examine the cyclization of various allenic hydroxylamines in detail.

We started our investigation with the allenic hydroxylamine **1a**, which was prepared from the corresponding α-hydroxyallene[4a,b] by Mitsunobu inversion with *N*,*O*-Boc-protected hydroxylamine[8] (Boc = *tert*-butoxycarbonyl) and subsequent deprotection. Treatment of **1a** with 5 mol% $AuCl_3$ in CH_2Cl_2 at room temperature led to a regioselective 5-*endo*-cyclization within 30 minutes to give *N*-hydroxypyrroline **2a**[9] in 77% yield (Table 1, entry 1). Use of gold(I) chloride resulted in an excellent yield of 94% (Table 1, entry 2). A decrease of the catalyst loading to 1 mol% AuCl gave almost the same yield of **2a** after an extended reaction time of 7 hours (Table 1, entry 3). In contrast, the use of the cationic gold complexes **A**,[10] **B**,[10] or $[AuCl(PPh_3)]/AgBF_4$ (Table 1, entries 4–6) resulted in slower reactions and decreased yields of **2a** because of incomplete conversion

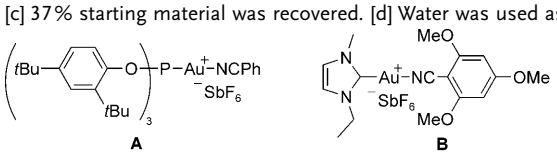
Table 1: Gold-catalyzed cycloisomerization of allenic hydroxylamine **1a** to *N*-hydroxypyrroline **2a**.



1a (d.r. > 99:1) **2a** (d.r. > 99:1)

Entry	Precatalyst	*t* [h]	Yield [%]
1	$AuCl_3$	0.5	77
2	AuCl	0.5	94
3[a]	AuCl	7	87
4	**A**	18	40[b]
5	**B**	1	62[c]
6	$[AuCl(PPh_3)]/AgBF_4$	16	43
7	$AgBF_4$	2	88
8[d]	$HAuCl_4/LiCl$	2	64

[a] 1 mol% of AuCl was used. [b] 7% starting material was recovered. [c] 37% starting material was recovered. [d] Water was used as solvent.



A **B**

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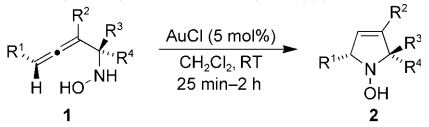
[**] We thank the Konrad-Adenauer Stiftung for a scholarship to C.W. and Prof. A. M. Echavarren (ICIQ Tarragona, Spain) for samples of gold precatalysts **A** and **B**.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.200902355.

and partial decomposition of the substrate. The conversion of **1a** to **2a** was also catalyzed by $AgBF_4$, although the reaction took longer and the yield was slightly lower compared to the reaction with AuCl (Table 1, entry 7). The cyclization of **1a** can also be carried out efficiently in water using chloroauric acid[11] (Table 1, entry 8). All cycloisomerizations proceeded with exclusive 5-*endo* regioselectivity and complete axis-to-center chirality transfer.

To examine the scope of the reaction, we treated various substituted *N*-hydroxy-α-aminoallenes **1b–g** with AuCl in CH_2Cl_2 and obtained the *N*-hydroxy-3-pyrrolines **2b–g** in high yields (Table 2). Substrate **1b**, which is the diastereomer of **1a**, selectively afforded the product **2b** (Table 2, entry 1), thus demonstrating the high level of stereocontrol in these cyclizations. The reaction tolerates alkyl and aryl substituents at the allene groups, as well as free hydroxy and ester groups (Table 2, entries 4 and 6, respectively). The gold-catalyzed cyclization of substrate **1e**, which bears three nucleophilic groups in the α- and β-position (Table 2, entry 4), is particularly noteworthy; of these functionalities, only the amino group reacts to afford pyrroline **2e** in good yield.

Table 2: Gold-catalyzed synthesis of *N*-hydroxypyrrolines **2b–g**.



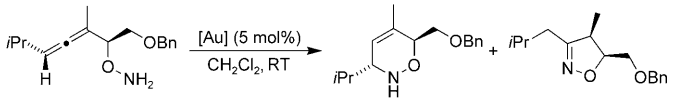
1 **2**

Entry	**1**	R^1	R^2	R^3	R^4	**2** (Yield [%])
1	**1b**	*i*Pr	Me	H	CH_2OBn	**2b** (76)
2	**1c**	*n*Bu	Me	CH_2OBn	H	**2c** (80)
3	**1d**	Ph	Me	CH_2OBn	H	**2d** (73)
4	**1e**	*n*Bu	Me	CH_2OH	H	**2e** (67)
5[a]	**1f**	Me	H	H	$(CH_2)_2Ph$	**2f** (78)
6	**1g**	*i*Pr	H	H	$(CH_2)_2CO_2Et$	**2g** (77)

[a] **1f** was used as a diastereomeric mixture (1:1).

Encouraged by the high regioselectivity in the gold-catalyzed cyclization of *N*-hydroxy-α-aminoallenes **1**, we next examined allenic substrates in which the heteroatom positions were exchanged. The hydroxylamine ether **3a** was synthesized by Mitsunobu reaction of the corresponding α-hydroxyallene[4a,b] with *N*-hydroxyphthalimide and subsequent hydrazinolysis.[12] Treatment of **3a** with AuCl in CH_2Cl_2 at room temperature afforded a mixture of the 3,6-dihydro-1,2-oxazine **4a** (47% yield) and the 4,5-dihydroisoxazole **5a** (19%; Table 3, entry 1). Again, both heterocycles were formed by the nucleophilic attack of the nitrogen atom, and the dihydrooxazine **4a** was formed with complete chirality transfer. Use of $AuCl_3$ as the precatalyst, and a decrease of the Lewis acidity of the gold catalyst in the presence of acetonitrile or by using THF as the solvent (Table 3, entries 2–4) had only a slight effect on the product ratio and caused only a small shift in favor of **5a**. A highly regioselective cyclization of the allenic hydroxylamine ether **3a** to 4,5-dihydroisoxazole **5a** could be achieved in the presence of cationic gold(I) complexes $[Au(PPh_3)]BF_4$ or **A**[10] (Table 3, entries 5 and 6). Here, the more reactive gold complex **A** gave not only the highest yield of 81%, but also the best *cis*-selectivity of 94:6.

Table 3: Gold-catalyzed cycloisomerization of allenic hydroxylamine ether **3a** to dihydro-1,2-oxazine **4a** and dihydroisoxazole **5a**.



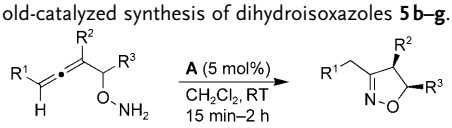
3a (d.r. > 99:1) **4a** **5a**

Entry	Precatalyst	*t* [h]	**4a**: Yield [%] (d.r.)	**5a**: Yield [%] (d.r.)	**4a/5a**
1	AuCl	2.5	47 (>99:1)	19 (87:13)	71:29
2	$AuCl_3$	2.5	49 (>99:1)	15 (89:11)	77:23
3[a]	$AuCl_3$	3.0	35 (>97:3)	16 (87:13)	69:31
4[b]	$AuCl_3$	62	40 (>98:2)	26 (87:13)	61:39
5	$[Au(PPh_3)]BF_4$[c]	1.5	3 (n.d.)[d]	69 (79:21)	4:96
6	**A**	1.5	3 (n.d.)[d]	81 (94:6)	4:96

[a] A stock solution of $AuCl_3$ in MeCN was used. [b] Reaction performed in THF. [c] Prepared in situ from $[AuCl(PPh_3)]$ and $AgBF_4$. [d] Not determined.

Under these optimized conditions, various allenic hydroxylamine ethers **3b–g** were converted into the corresponding dihydroisoxazoles **5b–g** in high yields (Table 4). The reaction tolerates benzyl and silyl ethers (Table 4, entries 1–3) as well as ester groups (entry 6) and terminal allenes (entries 2 and 3). It is interesting to note that the benzyl-protected dihydroisoxazoles **5a–c** were formed with high *cis*-selectivity whereas the *tert*-butyldimethylsilyl (TBS) ether **5d** (Table 4, entry 3) was obtained as a 1:1 mixture of diastereomers. A mechanistic model for the *cis*-selective formation of **5a–c** is shown in Scheme 2.

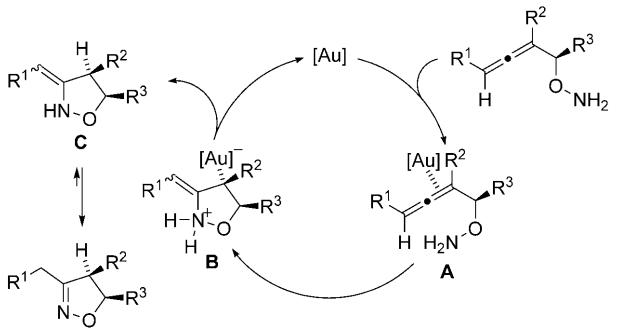
Table 4: Gold-catalyzed synthesis of dihydroisoxazoles **5b–g**.



3 **5**

Entry	**3**	R^1	R^2	R^3	**5** (Yield [%])	d.r.
1	**3b**	*n*Bu	Me	CH_2OBn	**5b** (77)	95:5
2	**3c**	H	Me	CH_2OBn	**5c** (72)	95:5
3	**3d**	H	Me	CH_2OTBS	**5d** (78)	51:49
4	**3e**	Me	H	$(CH_2)_2Ph$	**5e** (87)	
5	**3f**	Me	H	Me	**5f** (86)	
6	**3g**	*i*Pr	H	$(CH_2)_2CO_2Et$	**5g** (86)	

Coordination of the gold catalyst to the allenic double bond adjacent to the hydroxylamine moiety affords π complex **A**, which undergoes a 5-*endo* cyclization to the zwitterionic species **B**. In this case, the bulky gold moiety is preferentially situated *trans* to the group R^3 in order to



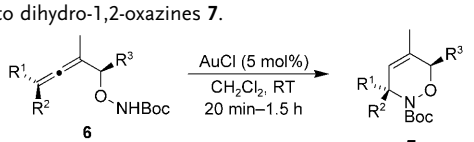
Scheme 2. Proposed mechanism for the formation of *cis*-substituted dihydroisoxazoles **5a–c**.

minimize steric interactions. Protodeauration with retention of configuration led to the exocyclic enamine **C**, which isomerized to the more stable dihydroisoxazole. An alternative mechanism that involves coordination of the gold catalyst at the allenic double bond distal to the hydroxylamine moiety, followed by 5-*exo* cyclization, would also lead to the dihydroisoxazoles **5**, but does not give a suitable explanation for the formation of the *cis* diastereomer.

Having established a highly regio- and stereoselective cyclization of allenic hydroxylamine ethers **3** to dihydroisoxazoles **5**, we returned to the corresponding 6-*endo* cycloisomerization. Fortunately, use of the *tert*-butoxy carbamate **6a** instead of the unprotected hydroxylamine ether **3a** led to a regio- and stereoselective formation of the Boc-protected dihydrooxazine **7a** upon treatment with 5 mol% AuCl in CH_2Cl_2 at room temperature (Table 5, entry 1). Analogous results were obtained with protected hydroxylamine ethers **6b–d**. The low stability of the precursor for **6c** means that this allene could only be used in an impure form, and may explain the rather low yield of the phenyl-substituted dihydrooxazine **7c** (30%; Table 5, entry 3). In contrast to the reaction with AuCl, use of $AuCl_3$ gave only incomplete conversion, and cationic gold complexes ($[Au(PPh_3)]BF_4/AgBF_4$ or **A**) or $AgBF_4$ induced decomposition of the substrate.

In conclusion, we have established new highly regio- and stereoselective routes to three different chiral heterocycles—*N*-hydroxy-3-pyrrolines, 4,5-dihydroisoxazoles, and 3,6-dihydro-1,2-oxazines—by gold-catalyzed cycloisomerization of allenic hydroxylamine derivatives. To the best of our knowledge, these reactions represent the first examples for the gold-catalyzed synthesis of heterocycles with two heteroatoms from allenic precursors. In all cases, the nitrogen atom acts as the nucleophile and attacks the allene in a 5- or 6-*endo* cyclization. In the case of allenic hydroxylamine ethers, the regioselectivity can be shifted either towards dihydroisoxazoles by employing cationic gold precatalysts, or in favor of dihydrooxazines by using *N*-Boc-protected precursors. Our method is particularly versatile as all three types of heterocycles can be obtained in a stereoselective manner from the same α-hydroxyallene. We continue to expand the scope of coinage-metal catalysis with allenic substrates and to apply our methods in target-oriented synthesis.

Table 5: Gold-catalyzed cycloisomerization of allenic hydroxylamine ethers **6** to dihydro-1,2-oxazines **7**.



Entry	**6**	R^1	R^2	R^3	**7** (Yield [%])
1	**6a**	*i*Pr	H	CH_2OBn	**7a** (75)
2	**6b**	*n*Bu	H	CH_2OBn	**7b** (85)
3	**6c**	Ph	H	CH_2OBn	**7c** (30)
4	**6d**	Me	Me	CH_2OMe	**7d** (82)

Experimental Section

In an oven-dried Schlenk tube, allene **1a** (60.0 mg, 230 μmol) was dissolved in dry dichloromethane (4 mL) and treated with AuCl (2.7 mg, 11.5 μmol). After complete conversion (30 min, monitored by TLC), the solvent was removed under reduced pressure and the crude product was purified by flash column chromatography (SiO_2, cyclohexane/ethyl acetate/triethylamine = 91:6:3), to afford 56.5 mg (94%) of *N*-hydroxypyrroline **2a** as a yellow oil.

Received: May 3, 2009
Published online: July 15, 2009

Keywords: allenes · cycloisomerization · gold · heterocycles · homogeneous catalysis

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