Gold-Catalyzed Cycloisomerization of α-Functionalized Allenes to *N*-Hydroxypyrrolines, Dihydroisoxazoles and Dihydro-1,2-oxazines

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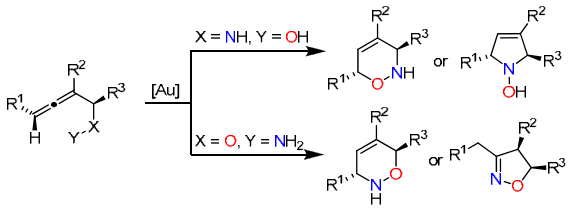
Introduction

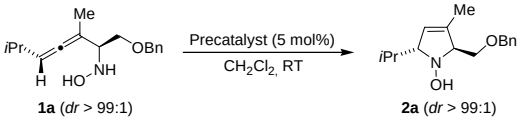
The gold-catalyzed *endo*- or *exo*-selective cycloisomerization of functionalized allenes is a highly valuable method for the synthesis of five- or six-membered oxygen-,[1,2] nitrogen-,[2,3] or sulfur-containing[4] heterocycles containing one or several stereogenic centers. Since the gold-catalyzed cycloisomerization of allenes is so far limited to the synthesis of heterocycles containing just one heteroatom, we decided to examine the cyclization of various allenic hydroxylamines.[5]
These investigations are particularly interesting due to the ambident nature of hydroxylamines which can result in the formation of different heterocycles.



Is it possible to control the regioselectivity of the cycloisomerization?

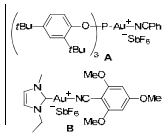
Results and Discussion

Cycloisomerization of Allenic Hydroxylamines to *N*-Hydroxypyrrolines



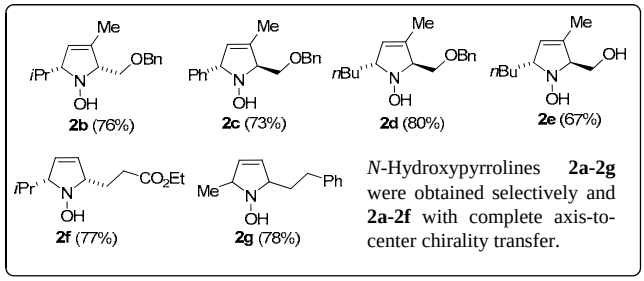
1a (*dr* > 99:1) **2a** (*dr* > 99:1)

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
5	**B**	1	62
6	Ph_3PAuCl / $AgBF_4$	16	43
7	$AgBF_4$	2	88
8[b]	$HAuCl_4$ / LiCl	2	64



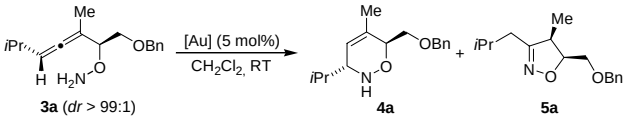
[a] 1 mol% of AuCl was used. [b] Water was used as solvent (see ref. 6).

The cycloisomerization of allenic hydroxylamine **1a** selectively led to the formation of *N*-hydroxypyrroline **2a** with full axis-to-center chirality transfer. The best result was obtained by using 1-5 mol% AuCl, whereas the cationic gold complexes [Ph_3PAuBF_4], **A**[7] or **B**[7] led to incomplete conversion and/or decomposition.



N-Hydroxypyrrolines **2a-2g** were obtained selectively and **2a-2f** with complete axis-to-center chirality transfer.

Cycloisomerization of Allenic Hydroxylamine Ether to Dihydro-1,2-oxazines or Dihydroisoxazoles

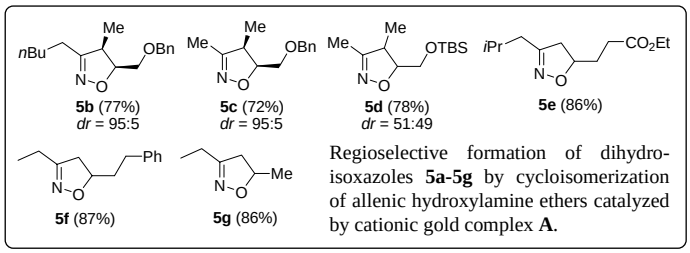


3a (*dr* > 99:1) **4a** **5a**

Entry	Precatalyst	t [h]	**4a**: Yield [%] (*dr*)	**5a**: Yield [%] (*dr*)	**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	Ph_3PAuBF_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

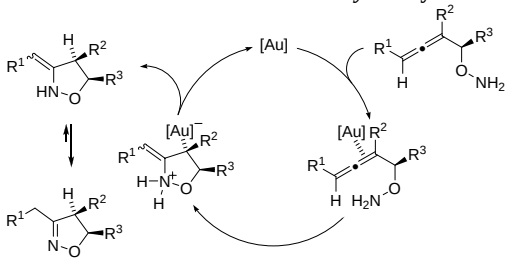
[a] A stock solution of $AuCl_3$ in MeCN was used. [b] Reaction performed in THF. [c] Prepared *in situ* from Ph_3PAuCl and $AgBF_4$. [d] Not determined.

By employing AuCl or $AuCl_3$ the cycloisomerization of allenic hydroxylamine ether **3a** resulted in a mixture of dihydrooxazine **4a** and dihydroisoxazole **5a**. Fortunately, the use of cationic complex **A** led nearly exclusively to the formation of dihydroisoxazoles **5a-5g**.
The high diastereomeric excess in case of **5a-5c** can be explained by coordination of precatalyst **A** to the allenic double bond adjacent to the heteroatoms. After 5-*endo*-cyclization the bulky gold moiety is preferably situated *trans* to the group R^3 in order to minimize steric interactions.

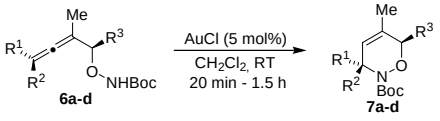


Regioselective formation of dihydroisoxazoles **5a-5g** by cycloisomerization of allenic hydroxylamine ethers catalyzed by cationic gold complex **A**.

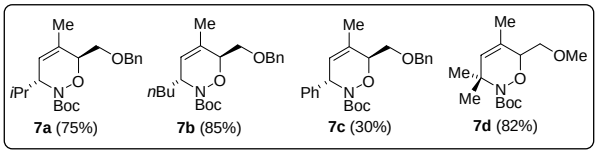
Proposed Mechanism for the Formation of *syn*-Dihydroisoxazoles



Cycloisomerization of Allenic Hydroxylamines to Dihydro-1,2-oxazines



6a-d **7a-d**



The selective formation of dihydro-1,2-oxazines **7a-7d** was achieved by treating the carbamates **6a-d** with AuCl. In contrast to the formation of dihydroisoxazoles **5**, the use of cationic gold precatalysts led to decomposition of the substrates.

Conclusion

Three different chiral heterocycles are obtained by highly efficient regio- and stereoselective gold-catalyzed cycloisomerization of allenic hydroxylamine derivatives. In all cases, nitrogen acts as the nucleophile and attacks the allene in a 5- or 6-*endo*-cyclization. Careful choice of the gold precatalyst and of the protecting group at the nitrogen are the key factors for controlling the regioselectivity.

References

[1] A. Hoffmann-Röder, N. Krause, *Org. Lett.* **2001**, *3*, 2537-2538. [2] B. Gockel, N. Krause, *Org. Lett.* **2006**, *8*, 4485-4488. [3] a) N. Morita, N. Krause, *Org. Lett.* **2004**, *6*, 4121-4123; b) N. Morita, N. Krause, *Eur. J. Org. Chem.* **2006**, 4634-4641. [4] N. Morita, N. Krause, *Angew. Chem.* **2006**, *118*, 1930-1933; *Angew. Chem. Int. Ed.* **2006**, *45*, 1897-1899. [5] C. Winter, N. Krause, *Angew. Chem.* **2009**, *in press*. [6] C. Winter, N. Krause, *Green Chem.* **2009**, DOI: 10.1039/B905823K. [7] a) C. H. M. Amijs, V. López-Carrillo, M. Raducan, P. Pérez-Galán, C. Ferrer, A. M. Echavarren, *J. Org. Chem.* **2008**, *73*, 7721–7730; b) E. Jiménez-Núñez, C. K. Claverie, C. Bour, D. J. Cárdenas, A. M. Echavarren, *Angew. Chem.* **2008**, *120*, 8010–8013; *Angew. Chem. Int. Ed.* **2008**, *47*, 7892–7895.

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