ORGANIC LETTERS

2004
Vol. 6, No. 22
4121−4123

Gold Catalysis in Organic Synthesis: Efficient Cycloisomerization of α-Aminoallenes to 3-Pyrrolines

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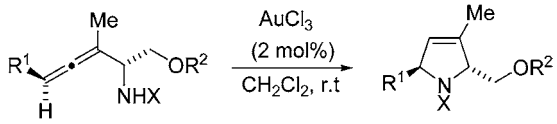
Received September 8, 2004

ABSTRACT



The gold(III) chloride-catalyzed cycloisomerization of various α-aminoallenes gave the corresponding 3-pyrrolines in good to high chemical yields. An interesting dependence of the chirality transfer and reactivity on the N-protecting group was observed. The 3-pyrrolines are highly useful intermediates for the synthesis of functionalized pyrrolines, pyrrolidines, and other natural products.

Functionalized pyrrolines and pyrrolidines are of great importance in natural product synthesis because of their high and diverse biological activities (Figure 1).[1] These include

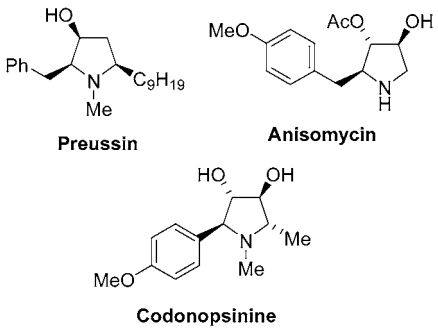


Figure 1. Naturally occurring pyrrolidines.

antifungal compounds (e.g., preussin, anisomycin[2]), hypotensive activity (codonopsinine[3]), anti-HIV activity, as well as various enzyme inhibitors such as lentiginosine, swainsonine, and alexine.[1]

Thus, it is not surprising that numerous pathways for the synthesis of substituted pyrrolines and pyrrolidines have been developed, and in recent years much work has focused on metal-mediated approaches. To control the relative and absolute configuration of stereogenic centers in position 2 and/or 5 of the heterocycles, the cyclization/cyloisomerization of sterically defined α-aminoallenes is particularly promising, and metals such as Pd(0 or II),[4] Ag(I),[5] and Hg(II)[6] as well as organolanthanides[7] have been used for this purpose.

(1) (a) O'Hagen, D. *Nat. Prod. Rep.* **2000**, *17*, 435. (b) Mauger, A. B. *J. Nat. Prod.* **1996,** *59*, 1205. (c) Huwe, C. M.; Blechert, S. *Tetrahedron Lett.* **1995**, *36*, 1621. (d) Anderson, W. K.; Milowsky, A. S. *J. Med. Chem.* **1987**, *30*, 2144.

(2) (a) Schwartz, R. E.; Liesch, J. Hensens, O.; Zitano, L.; Honeycutt, S.; Garrity, G.; Fromtling, R. A.; Onishi, J.; Monaghan, R. *J. Antibiot.* **1988,** *41*, 1774. (b) Johnson, J. H.; Phillipson, D. W.; Kahle, A. D. *J. Antibiot.* **1989**, *42*, 1184. (c) Hulme, A. N.; Rosser, E. M. *Org. Lett.* **2002**, *4*, 265. (d) Overhand, M.; Hecht, S. M. *J. Org. Chem.* **1994**, *59*, 4721. (e) Deng, W.; Overman, L. E. *J. Am. Chem. Soc.* **1994**, *116*, 11241. (f) McGrane, P. L.; Livinghouse, T. *J. Am. Chem. Soc.* **1993**, *115*, 11485. (g) Pak, C. S.; Lee, G. H. *J. Org. Chem.* **1991**, *56*, 1128.

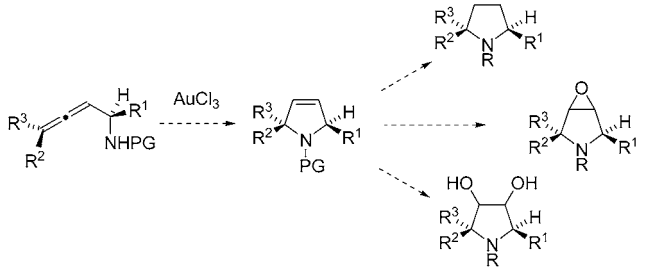
(3) (a) Matkhalikova, S. F.; Malikov, V. M.; Yunusov, S. Y. *Khim. Prir. Soedin* **1969,** *5*, 607. (b) Matkhalikova, S. F.; Malikov, V. M.; Yunusov, S. Y. *Khim. Prir. Soedin* **1969,** *5*, 30. (c) Severino, E. A.; Correia, C. R. D. *Org. Lett.* **2000**, *2*, 3039. (d) Yoda, H.; Nakajima, T.; Takabe, K. *Tetrahedron Lett.* **1996**, *37*, 5531. (e) Wang, C.-H. J.; Calabrese, J. C. *J. Org. Chem.* **1991**, *56*, 4341. (f) Iida, H.; Yamazaki, N.; Kibayashi, C. *J. Org. Chem.* **1987**, *52*, 1956.

(4) (a) Ma, S.; Yu, F.; Gao, W. *J. Org. Chem.* **2003**, *68*, 5943. (b) Dieter, R. K.; Yu, H. *Org. Lett.* **2001**, *3*, 3855. (c) Kang, S.-K.; Kim, K.-J. *Org. Lett.* **2001**, *3*, 511. (d) Karstens, W. F. J.; Klomp, D.; Rutjes, F. P. J. T.; Hiemstra, H. *Tetrahedron* **2001**, *57*, 5123. (e) Ohno, H.; Toda, A.; Miwa, Y.; Taga, T.; Osawa, E.; Yamaoka, Y.; Fijii, N.; Ibuka, T. *J. Org. Chem.* **1999**, *64*, 2992. (f) Karstens, W. F. J.; Rutjes, F. P. J. T.; Hiemstra, H. *Tetrahedron Lett.* **1997**, *35*, 6257. (g) Davis, I. W.; Scopes, D. I.; Gallagher. *Synlett* **1993**, 85. (h) Kimura, M.; Fugami, K.; Tanaka, S.; Tamaru, Y. *J. Org. Chem.* **1992**, *57*, 6377. (i) Prasad, J. S.; Liebeskind, L. S. *Tetrahedron Lett.* **1988**, *29*, 4257.

10.1021/ol0481838 CCC: $27.50
Published on Web 10/08/2004

Recently, we reported a highly efficient gold(III)-catalyzed[8] cycloisomerization of α-hydroxyallenes that provides 2,5-dihydrofurans with complete axis to center chirality transfer.[9] This method is compatible with various functional groups present in the substrate and therefore highly suitable for application in natural product chemistry.[10] We anticipated that a similar reaction with an α-aminoallene would bring about an efficient cycloisomerization to afford a 3-pyrroline, the double bond of which can then be utilized for further transformations, e.g., reductions, oxidations, etc. (Scheme 1).

Scheme 1

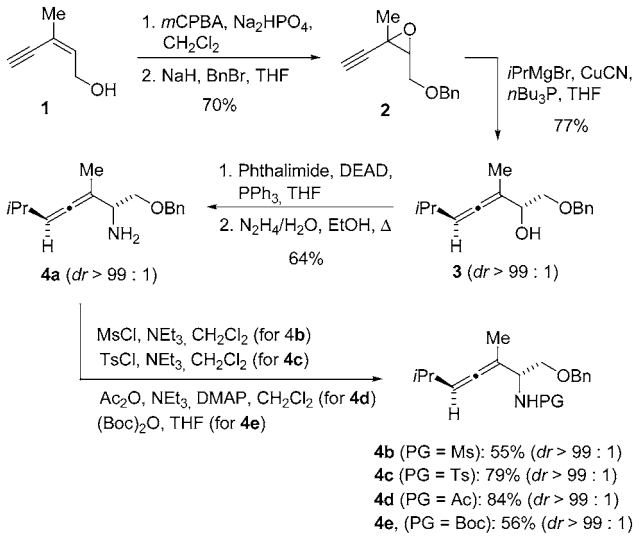


The synthesis of the starting materials, the diastereomerically pure aminoallenes **4a**−**e**, is shown in Scheme 2. Epoxidation of enyne **1**, followed by benzylation gave a 70% yield of oxirane **2**. The corresponding hydroxyallene **3** was prepared via *anti*-selective S_N2' substitution reaction of oxirane **2** with a magnesium cyanocuprate in the presence of *n*-Bu_3P.[9,10] The α-aminoallene **4a** was prepared from **3** via Mitsunobu reaction with phthalimide, followed by hydrazinolysis.[11] For an initial screening of the effect of various N-protecting groups in the gold-catalyzed cyclization, aminoallene **4a** was reacted with a selection of acylating and sulfonylating agents.

Treatment of the diastereomerically pure α-aminoallenes **4a**−**e** with 2 mol % of $AuCl_3$ in dry CH_2Cl_2 at room temperature gave the corresponding 3-pyrrolines **5a**−**e** in good to excellent yields (Table 1).

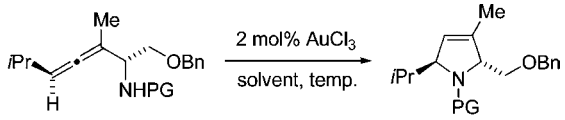
The reactions were complete after 30 min at room temperature for the N-protected aminoallenes **4b**−**e** (entries 2−7), whereas the unprotected substrate required a much longer reaction time (entry 1). A slight erosion of the stereoselectivity was observed in the cycloisomerization of the sulfonylated substrates **4b** and **4c** which was not affected

Scheme 2



by the solvent or temperature (entries 2−5). This effect was even more pronounced for the acylated aminoallenes **4d** and **4e** (entries 6 and 7). Only the unprotected aminoallene **4a** afforded the diastereomerically pure 3-pyrroline (entry 1).

Table 1. $AuCl_3$-Catalyzed Cycloisomerization of α-Aminoallenes **4** to 3-Pyrrolines **5**



4 **5**

entry	**4**	PG	solvent	*T* (°C)	time	**5** (yield, %)	dr
1	**4a**	H	CH_2Cl_2	rt	5 days	**5a** (74)	>99:1
2	**4b**	Ms	CH_2Cl_2	rt	30 min	**5b** (77)	94:6
3	**4c**	Ts	CH_2Cl_2	rt	30 min	**5c** (93)	95:5
4	**4c**	Ts	CH_2Cl_2	0	1 h	**5c** (95)	96:4
5	**4c**	Ts	THF	rt	1.5 h	**5c** (95)	93:7
6	**4d**	Ac	CH_2Cl_2	rt	30 min	**5d** (80)	70:30
7	**4e**	Boc	CH_2Cl_2	rt	30 min	**5e** (69)	46:54

To further examine the scope of the gold-catalyzed cycloisomerization of α-aminoallenes, we prepared the substrates **6a**−**c** with a variable substituent pattern. These were efficiently converted into the corresponding 3-pyrrolines **7a**−**c** in good yields with complete chirality transfer (Table 2).

A plausible mechanism of the gold(III) chloride-catalyzed cycloisomerization of α-aminoallenes is shown in Scheme 3. Thus, coordination of the carbophilic gold catalyst to an allenic double bond (complex **A**) would be followed by formation of the metallacyclopropane **B**. As a consequence of the increased electrophilicity, cyclization via an S_N2-type transition state and subsequent proton transfer would produce the 3-pyrroline with complete axis-to-center chirality transfer.

(5) (a) Amombo, M. O.; Hausherr, A.; Reissig, H.-U. *Synlett* **1999**, 1871. (b) Davis, I, W.; Gallagher, T.; Lamont, R. B.; Scopes, I. C. *J. Chem. Soc. Chem. Commun.* **1992**, 335. (c) Kinsman, R.; Lathbury, D.; Vernon, P.; Gallagher, T. *J. Chem. Soc., Chem. Commun.* **1987**, 243.

(6) (a) Fox, D. N. A.; Lathbury, D.; Mahon, M. F.; Molly, K. C.; Gallagher, T. *J. Chem. Soc., Chem. Commun.* **1989**, 1073.

(7) Arrendondo, V. M.; Mcdonald, F. E.; Marks, T. J. *J. Am. Chem. Soc.* **1998**, *120*, 4871.

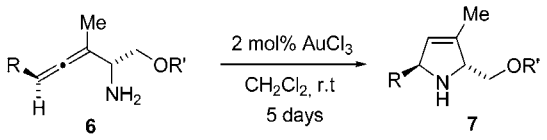
(8) Recent reviews on gold catalysis in organic synthesis: (a) Hashmi, A. S. K. *Gold Bull.* **2004**, *37*, 51. (b) Arcadi, A.; Di Giuseppe, S. *Curr. Org. Chem.* **2004**, *8*, 795.

(9) Hoffmann-Röder, A.; Krause, N. *Org. Lett*. **2001**, *3*, 2537.

(10) Krause, N.; Hoffmann-Röder, A.; Canisius, J. *Synthesis* **2002**, 1759.

(11) Roush, W. R.; Straud, J. A.; Brown, R. T. *J. Org. Chem.* **1987**, *52*, 5127.

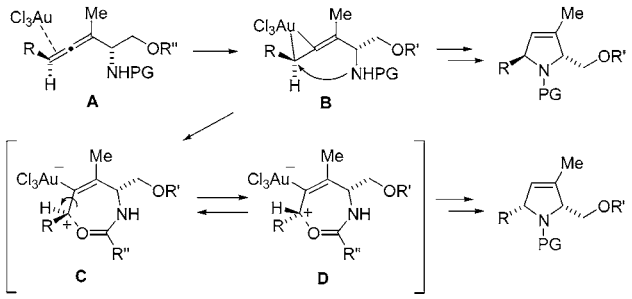
Table 2. $AuCl_3$-Catalyzed Cycloisomerization of α-Aminoallenes **6** to 3-Pyrrolines **7**



entry	**6**	R	R′	dr	**7** (yield, %)	dr
1	**6a**	Me	Bn	90:10	**7a** (71)	90:10
2	**6b**	*n*-hexyl	TBS	85:15	**7b** (82)	85:15
3	**6c**	Ph	TBS	>99:1	**7c** (79)	>99:1

In the case of the N-protected aminoallenes **4b**−**e**, however, an oxygen atom of the protecting group could stabilize the zwitterionic complex **C** by coordination, and the cyclization would proceed with partial isomerization (via single bond rotation) to complex **D**, leading to a diminished diastereoselectivity.

Scheme 3



In conclusion, we have developed a new efficient gold(III)-catalyzed cycloisomerization reaction of various α-aminoallenes to the corresponding 3-pyrrolines. An interesting dependence of the chirality transfer and reactivity on the N-protecting group was observed. Compared to the corresponding Ag(I)-catalyzed cyclization of aminoallenes,[5] our catalytic system is advantageous in terms of a very low catalyst loading (2 mol %), which renders the method much more economical.

We are now searching for more active and selective gold catalysts, which should allow for shorter reaction times in case of the unprotected α-aminoallenes, and for higher stereoselectivities in case of the N-protected substrates. Furthermore, application of the method to the synthesis of functionalized pyrrolines, pyrrolidines, and other natural products is actively pursued.

Acknowledgment. Continuous support of our work by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie is gratefully acknowledged.

Supporting Information Available: Experimental procedure and ^1H and ^{13}C NMR data of 3-pyrrolines. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0481838