Gold-catalyzed Synthesis of [N,O]-Spiroacetals

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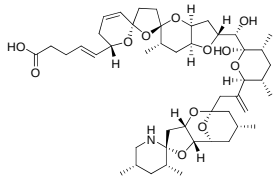
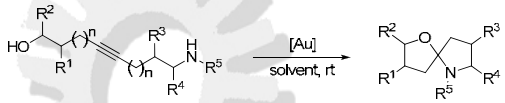
Introduction

Many natural products contain [N,O]-spiroacetals as characteristic structure elements. An example is the alkaloid Azaspiracid **1**, a seasonally occurring marine toxin isolated from *Mytilus edulis*.[1,2]



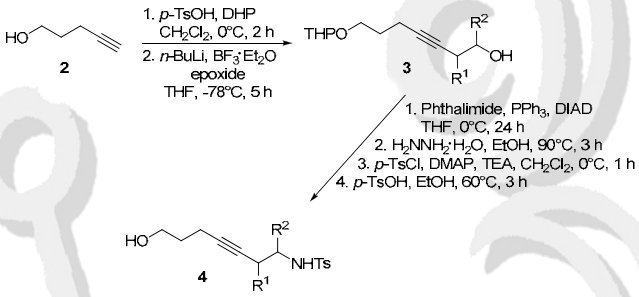
Azaspiracid (**1**)

Previously, we have shown that tetrahydrofuranyl ethers are accessible by gold-catalyzed tandem cycloisomerization-hydroalkoxylation of homopropargylic alcohols.[3] We now disclose a new access to [N,O]-spiroacetals by cyclization of aminoalkynols in the presence of a gold catalyst. The method tolerates various substituents and protecting groups and can be used to access spiroacetals with five- or six-membered rings.



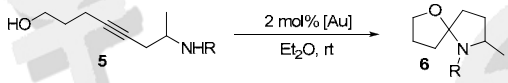
Results

Synthesis of the Aminoalkynols



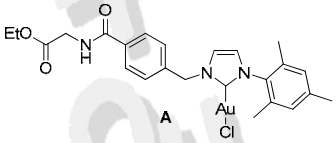
The aminoalkynoles were easily synthesized in six steps obtaining the required compound **4** in moderate yield. As starting material we chose 1-pentyn-4-ol (**2**). The key step is a Yamaguchi-Hirao alkylation of the alkynol. Thereby it is possible to build up a large number of substrates for the gold-catalyzed cyclization reactions.

Cyclization



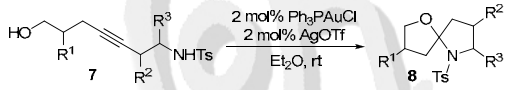
Entry	R	Catalyst	Time	Yield	dr
1	Ts	$Ph_3PAuCl/AgOTf$	40 min	74 %	88:12
2	Ts	Au(IPr)Cl/AgOTf	3 h	82 %	91:9
3	Ts	**A**/AgOTf	2 h	60 %	95:5
4	Ts	AgOTf	1 d[a]	traces	84:16
5	Boc	$Au(III)Cl_3$	8 h[a]	n.d.	58:42
6	Boc	Au(I)Cl	2 h	n.d.	62:38
7	Boc	$Ph_3PAuCl/AgOTf$	15 min	94 %	68:32
8	Boc	$Ph_3PAuCl/AgBF_4$	10 h	65 %	67:33
9	Boc	Au(IPr)Cl/AgOTf	15 min	57 %	63:37
10	Boc	**A**/AgOTf	20 min	76 %	63:37
11	H	$Ph_3PAuCl/AgOTf$[b]	2 d[a]	---	---

[a] reaction aborted, [b] 5 mol%



A

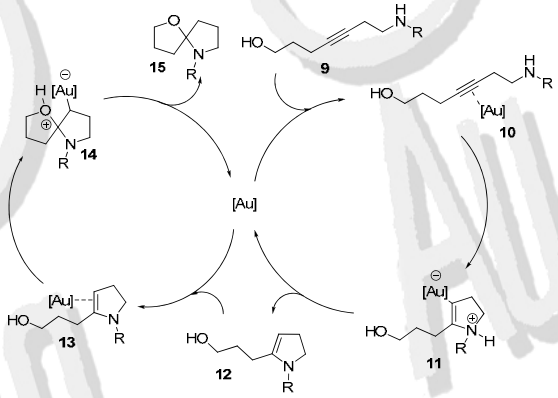
The cyclization reactions of the tosylated aminoalkynol **6** showed a successful formation of the [N,O]-spiroacetal in good yield and stereoselektivity. However, the Boc-protected substrate gave lower dr's but also good yield. Attempts to carry out the reaction with the unprotected aminoalkynol failed.
Further experiments with different substrates also gave the bicyclic product in good yield and selectivity.



Entry	R^1	R^2	R^3	Time	Yield	dr
1	H	H	Ph	40 min	72 %	86:14
2	H	C_4H_8		90 min	94 %	88:12
3	C_5H_{10}	H	Me	30 min	82 %	86:14
4	C_5H_{10}	H	Ph	40 min	75 %	82:18
5	H	H	Me	40 min	74 %	88:12
6	H	H	Et	60 min	45 %	90:10

Proposed mechanism

For the catalytic cycle we proposed the formation of a monocyclic intermediate **12**. Via kinetic NMR-spectroscopy we were able to confirm this assumption by observing an increasing signal of an olefinic proton, while the signal of the amino group decreased.



Conclusion

We were able to sythesize various [N,O]-spiroacetals in good yield and selectivity. The cyclization occured without formation of side products and is easy to perform. This makes the new method attractive for the application in natural product synthesis and shows the versatile opportunities of gold catalysis.

References

[1] M.Satake, K. Ofuji, H. Naoki, K. J. James, A. Furey, T. McMahon, J. Silke, T. Yasumoto, *J. Am. Chem. Soc.* **1998**, *120*, 9967-9968.

[2] K. C. Nicolaou, Y. Li, N. Uesaka, T. V. Koftis, S. Vyskocil, T. Ling, M. Govindasamy, W. Qian, F. Bernal, D. Y. Chen, *Angew. Chem. Int. Ed.* **2003**, *42*, 3643-3648.

[3] V. Belting, N. Krause, *Org. Biomol. Chem.* **2009**, *7*, 1221-1225.