Gold(I)-Catalyzed Cycloisomerization of β-Hydroxyallenes to Dihydropyrans and Application in the Synthesis of Bicyclic Compounds

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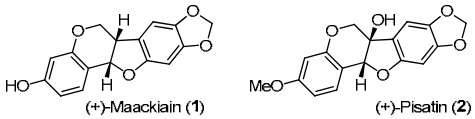
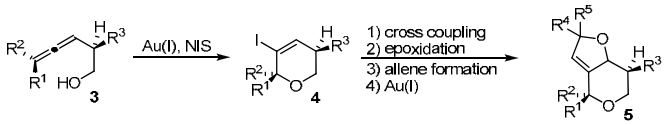
Introduction

The synthesis of annulated cyclic ethers is of high interest in organic chemistry due to the occurrence of this heterocyclic structure unit in a variety of natural products. The phytoalexins (+)-Maackiain (**1**) and (+)-Pisatin (**2**) are produced by garden pea and chickpea and have antifungal activity.[1] Furthermore, (+)-Maackiain (**1**) shows antimalarial activity against *P. falciparum*[2] and antitumor activity in mice.[3] The bicyclic core of these natural products can be synthesized from an iodinated dihydropyran, the double bond can be used for further transformations.



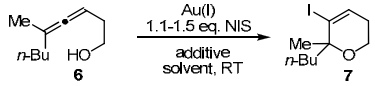
An elegant route to chiral dihydrofurans and dihydropyrans is the highly efficient and stereoselective gold-catalyzed cycloisomerization of α- and β-hydroxyallenes.[4] Based on these cyclizations and the gold-catalyzed reactions of alkynes in the presence of *N*-iodosuccinimide (NIS)[5] we have developed the first gold-catalyzed 6-*endo* cycloisomerization of β-hydroxyallenes in presence of stoichiometric amounts of NIS leading to iodinated dihydropyrans.



Results

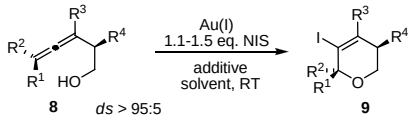
Cycloisomerization of β-Hydroxyallenes to Iodinated Dihydropyrans

The β-hydroxyallene **6** was converted under different conditions in a very fast reaction into the desired iodinated dihydropyran **7**. In the absence of a gold catalyst, the reaction is much slower and the yield is diminished.



Entry	Amount [mol%]	Au-Salt	Solvent	Time	Yield [%]
1	5	$Ph_3PAuCl/AgBF_4$	toluene	1 min	52
2	5	AuCl	CH_2Cl_2	1 min	56
3	0.5	AuCl	CH_2Cl_2	20 min	49
4	5	AuCl/Pyridin	CH_2Cl_2	1 min	50
5	-	-	toluene	2 d	45

In contrast to the gold-catalyzed reaction without NIS[4d] the stereochemical information was partly lost in many cases. The change of the gold precatalyst to $Ph_3PAuCl/AgBF_4$ improved the diastereomeric ratio.
The relative configuration of compound **9g** was determined by NOE measurements.

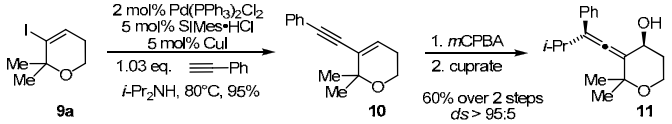


Entry	8	R^1	R^2	R^3	R^4	Conditions[a]	9	Yield [%]	*ds*
1	**8a**	Me	Me	H	H	**A**, 1 min	**9a**	61	-
2	**8b**	*n*-Bu	*n*-Bu	H	OAc	**A**, 10 min	**9b**	52	-
3	**8c**	*i*-Pr	*n*-Bu	H	OAc	**B**, 50 min	**9c**	69	88:12
4	**8d**	H	*n*-Bu	Me	OAc	**B**, 1 min	**9d**	52	61:39
5	**8d**	H	*n*-Bu	Me	OAc	**C**, 1 min	**9d**	73	89:11
6	**8e**	H	*i*-Pr	Me	OAc	**C**, 1 min	**9d**	73	>95:5
7	**8f**	H	Bn	Me	OAc	**C**, 1 min	**9f**	71	>95:5
8	**8g**	H	Ph	Me	OAc	**B**, 30 min	**9g**	69	60:40[b]
9	**8h**	H	Ph	Me	OMe	**B**, 1 h	**9h**	68	93:7

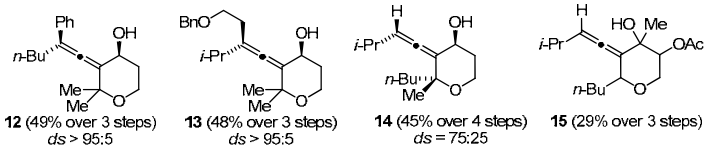
[a] Conditions **A**: 1 mol% AuCl, CH_2Cl_2; Conditions **B**: 5 mol% AuCl, CH_2Cl_2; Conditions **C**: 5 mol% $Ph_3PAuCl/AgBF_4$, toluene. [b] *ds*(**8g**) = 92:8.

Sonogashira Cross Coupling and Second Allene Formation

The obtained vinyl iodides were converted into enynes by palladium-catalyzed cross couplings in high yield. Epoxidation and *anti*-selective S_N2'-reaction led to α-hydroxyallens **11**-**15** in smooth reactions.

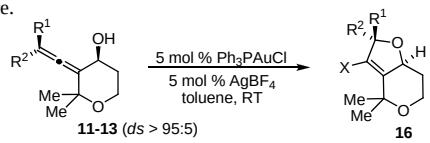


Synthesized Allenes:



Cycloisomerization to Bicyclic Compounds

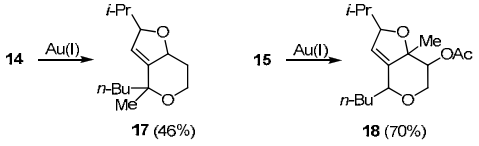
The second gold-catalyzed cycloisomerization was accomplished with $Ph_3PAuCl/AgBF_4$ as precatalyst in smooth and fast reactions. Moreover, iodinated dihydrofuran **16b** was obtained in a very high yield of 96% by addition of NIS to the reaction mixture.



Entry	No	R^1	R^2	X	16	Time	Yield [%]	*ds*
1	**11**	Ph	*i*-Pr	H	**16a**	2 h	76	89:11
2	**11**	Ph	*i*-Pr	I	**16b**	25 min[a]	84	> 95:5
3	**12**	Ph	*n*-Bu	H	**16c**	1.5 h	96	96:4
4	**13**	$(CH_2)_2OBn$	*i*-Pr	H	**16d**	1 min	84	> 95:5

[a] 1.5 eq. NIS were used additionally.

Interestingly, the allenes **11**-**13** with two methyl groups at the tetrahydropyran react with complete axis-to-center chirality transfer, whereas epimerisation occurred in case of allenes **14** and **15**.



Conclusion

We have developed an efficient gold-catalyzed 6-*endo* cycloisomerization of various β-hydroxyallenes in presence of NIS leading to the corresponding iodinated dihydropyrans. The utility of the obtained vinyl iodides was demonstrated in Sonogashira cross couplings, whose products can be transformed in few steps to annulated cyclic ethers.

References

[1] a) J. Enkerli, G. Bhatt, S. F. Covert, *Mol. Plant-Microbe Interact.* **1998**, *11*, 317-326; b) L. M. Delserone, D. E. Matthews, H. D. VanEtten, *Phytochemistry* **1992**, *31*, 3813-3819; c) T. Aoki, T. Akashi, S.-I. Ayabe, *J. Plant. Res.* **2000**, *113*, 475-488. [2] R. Chanphen, Y. Thebtaranonth, S. Wanauppathamkul, Y. Yuthavong, *J. Nat. Prod.* **1998**, *61*, 1146-1147. [3] R. Kojima, S. Fukushima, A. Ueno, Y. Saiki, *Chem. Pharm. Bull.* **1970**, *18*, 2555-2563. [4] a) A. Hoffmann-Röder, N. Krause, *Org. Lett.* **2001**, *3*, 2537–2538; b) C. Deutsch, B. Gockel, A. Hoffmann-Röder, N. Krause, *Synlett* **2007**, 1790–1794; c) C. Winter, N. Krause, *Green Chem.* **2009**, DOI: 10.1039/B905823K; d) B. Gockel, N. Krause, *Org. Lett.* **2006**, *8*, 4485–4488. [5] a) A. Buzas, F. Gagosz, *Org. Lett.* **2006**, *8*, 515-518; b) S. F. Kirsch, J. T. Binder, B. Crone, A. Duschek, T. T. Haug, C. Liébert, H. Menz, *Angew. Chem.* **2007**, *119*, 2360-2363; *Angew. Chem. Int. Ed.* **2007**; *46*, 2310-2313; c) M. Yu, G. Zhang, L. Zhang, *Org. Lett.* **2007**, *9*, 2147-2150.