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Highly Regioselective Gold-Catalyzed Ring-Opening Allylation and Azidation of Dihydrofurans

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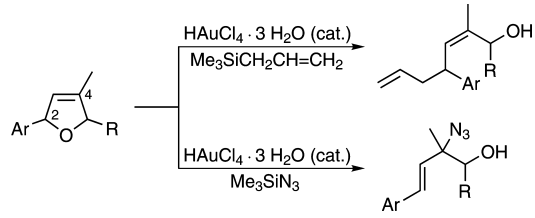
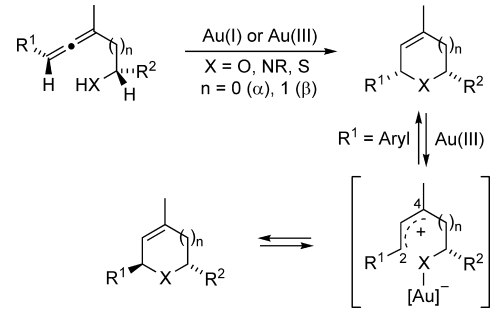
ABSTRACT



The ring-opening allylation and azidation of 2,5-dihydrofurans has been accomplished with allyltrimethylsilane or Me_3SiN_3 in the presence of catalytic amounts of $HAuCl_4{\cdot}3H_2O$. Whereas the allylation proceeds regioselectively in the 2-position to afford 2,6-dien-1-ols, the azidation takes place in the 4-position exclusively.

Due to its unique ability to activate C−C double and triple bonds in the presence of reactive functionalities, gold is one of the most versatile metals in transition metal catalysis.[1] For the stereoselective synthesis of 5- or 6-membered heterocycles, the gold-catalyzed endoselective cycloisomerization of allenes[2] bearing a hydroxyl,[3] amino,[4] hydroxylamino,[5] or thiol[6] group in the α- or *β*-position is particularly useful (Scheme 1). These transformations proceed with complete transfer of chirality from the allenic chirality axis to the new stereogenic center in most cases, allowing application of the method in stereoselective target-oriented synthesis.[7]

Scheme 1. Gold-Catalyzed *endo*-Cycloisomerization of Functionalized Allenes



In contrast to alkyl-substituted allenes, substrates bearing phenyl or electron-rich aryl substituents R^1 undergo epimerization when treated with gold(I) or gold(III) precatalysts in

(1) Recent reviews: (a) Jimenez-Nunez, E.; Echavarren, A. M. *Chem. Commun.* **2007**, 333–346. (b) Gorin, D. J.; Toste, F. D. *Nature* **2007**, *446*, 395–403. (c) Fürstner, A.; Davis, P. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 3410–3449. (d) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180–3211. (e) Bongers, N.; Krause, N. *Angew. Chem., Int. Ed.* **2008**, *47*, 2178–2181. (f) Widenhoefer, R. A. *Chem. Eur. J.* **2008**, *14*, 5382–5391. (g) Shen, H. C. *Tetrahedron* **2008**, *64*, 3885–3903. (h) Skouta, R.; Li, C.-J. *Tetrahedron* **2008**, *64*, 4917–4938. (i) Muzart, J. *Tetrahedron* **2008**, *64*, 5816–5849. (j) Li, Z.; Brouwer, C.; He, C. *Chem. Rev.* **2008**, *108*, 3239–3265. (k) Arcadi, A. *Chem. Rev.* **2008**, *108*, 3266–3325. (l) Jimenez-Nunez, E.; Echavarren, A. M. *Chem. Rev.* **2008**, *108*, 3326–3350. (m) Gorin, D. J.; Sherry, B. D.; Toste, F. D. *Chem. Rev.* **2008**, *108*, 3351–3378.

(2) Krause, N.; Belting, V.; Deutsch, C.; Erdsack, J.; Fan, H.-T.; Gockel, B.; Hoffmann-Röder, A.; Morita, N.; Volz, F. *Pure Appl. Chem.* **2008**, *80*, 1063–1069.

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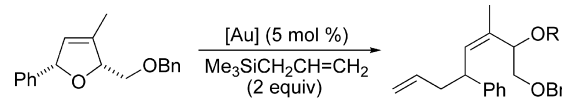
unpolar solvents.[3d] Moreover, the *cis*-disubstituted dihydrofuran or -pyran (R^1 = Aryl) is epimerized to the *trans*-isomer in the presence of $AuCl_3$ in dichloromethane (Scheme 1).[3d,8] This epimerization probably occurs via a zwitterionic intermediate comprising a benzyl cation substructure and an anionic aurate moiety.[3d,9] On the basis of this assumption, we reasoned that it might be possible to trap the benzyl cation with a suitable nucleophile, a process that would result in a ring-opening of the heterocycle with formation of a new C−C or C−heteroatom bond in the 2- or 4-position. There is little precedent for such a transformation in homogeneous gold catalysis[10] whereas classical protocols for the nucleophilic ring-opening of unsaturated cyclic ethers by zirconium-catalyzed carbomagnesiation[11] or ethylalumination[12] involve C−C bond formation with strong nucleophiles and are limited with regard to regioselectivity and functional group compatibility. Also, there appear to be no examples for the ring-opening of unsaturated ethers with heteronucleophiles.

We first examined the reaction of 2,5-dihydrofuran **1a**[3d] with allyltrimethylsilane as carbon nucleophile[10,13] in the presence of various gold precatalysts (Table 1). With 5 mol % of $AuCl_3$ and 2 equiv of $Me_3SiCH_2CH{=}CH_2$ in CH_2Cl_2 at room temperature, the 2,6-dien-1-ol **2a** resulting from nucleophilic attack of the silane in the 2-position of **1a** was

Table 1. Gold-Catalyzed Allylative Ring-Opening of 2,5-Dihydrofuran **1a**



1a
cis : *trans* = 97 : 3

2a (R = H)
3a (R = $SiMe_3$)

entry	[Au]	solvent	temp (°C)	time (h)	**1a/2a/3a**[a] (yield/%)
1	$AuCl_3$	CH_2Cl_2	rt	16	56/19/0
2	$AuBr_3$	CH_2Cl_2	rt	3	80/13/7
3	$HAuCl_4{\cdot}3H_2O$	CH_2Cl_2	rt	1	56/37/0
4	$HAuCl_4{\cdot}3H_2O$	CH_2Cl_2	rt	24	45/23/0
5	$HAuCl_4{\cdot}3H_2O$	CH_2Cl_2	0	2	50/24/26
6	$HAuCl_4{\cdot}3H_2O$	CH_2Cl_2	−40 to −5	5	30/50/13
7[b]	$HAuCl_4{\cdot}3H_2O$	CH_2Cl_2	−40 to −5	2	3/10/84
8[c]	$HAuCl_4{\cdot}3H_2O$	CH_2Cl_2	−40 to −35	0.3	0/12/86
9	$HAuCl_4{\cdot}3H_2O$	THF	−40 to rt	24	–[d]
10	$HAuCl_4{\cdot}3H_2O$	toluene	−40 to rt	24	–[d]

[a] **2a** and **3a** were obtained as a 1:1 mixture of diastereomers. [b] With 3 equiv of allyltrimethylsilane. [c] With 4 equiv of allyltrimethylsilane. [d] No conversion.

obtained with low yield (19%), and 56% of the starting material was recovered (entry 1). In contrast, gold(III) bromide gave a mixture of **2a** and the corresponding silyl ether **3a**, but the conversion was still low (entry 2). A higher reactivity was observed with $HAuCl_4{\cdot}3H_2O$ (entry 3), whereas other gold(I) or gold(III) precatalysts ($Au(OAc)_3$, $Au(OH)_3$, $NaAuCl_4$, $Ph_3PAuCl/AgBF_4$) and traditional Lewis acids (CuI, $Cu(OTf)_2$, AgOTf, $InBr_3$) gave no conversion at all.

Optimization of the reaction conditions with $HAuCl_4{\cdot}3H_2O$ as precatalyst revealed a strong influence of the solvent, temperature, and amount of silane (Table 1). An increase of the reaction time caused a lower yield of product **2a** (23 vs. 37%; entries 3 and 4). Interestingly, the furan formed by oxidation of **1a** was isolated as side product under these conditions. This side reaction can be suppressed by lowering the reaction temperature (entries 5 and 6); at −40 °C, **2a** and **3a** were obtained with 63% combined yield (entry 6). Even lower temperatures or the use of other solvents (THF or toluene; entries 9 and 10) resulted in no conversion. In contrast to this, an increase of the amount of allyltrimethylsilane gave better results (entries 7 and 8); with 4 equiv of the silane, a fast reaction with complete conversion of **1a** and an excellent combined yield of **2a/3a** (98%) was achieved (entry 8). In all cases, the products of the allylative ring-opening were obtained as a 1:1 mixture of diastereomers, as is expected for the mechanism involving a benzyl cation intermediate.

Application of the optimized reaction conditions (Table 1, entry 8) to various 2,5-dihydrofurans **1**[3] afforded the allylation products **2** with moderate to high yield (Table 2) after treatment of the crude product with *n*-Bu_4NF. Both electron-rich (entry 1) and electron-deficient aryl groups (entries 2 and 3) are tolerated. The method is also applicable

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(8) (a) Epimerization/rearrangement of alkynyl and aryl C-glycosides with $AuCl_3$: Yeager, A. R.; Min, G. K.; Porco, J. A., Jr.; Schaus, S. E. *Org. Lett.* **2006**, *8*, 5065–5068. (b) Epimerization of a 2,5-dihydrofuran during the gold-catalyzed cycloisomerization of an allenamide: Hyland, C. T.; Hegedus, L. S. *J. Org. Chem.* **2006**, *71*, 8658–8660.

(9) In accordance with this assumption, the epimerization can be suppressed by decreasing the Lewis acidity of the gold catalyst.[3d]

(10) Gold-catalyzed bisallylation of oxabicyclic benzene derivatives: Hsu, Y.-C.; Datta, S.; Ting, C.-M.; Liu, R.-S. *Org. Lett.* **2008**, *10*, 521–524.

(11) (a) Suzuki, N.; Kondakov, D. Y.; Takahashi, T. *J. Am. Chem. Soc.* **1993**, *115*, 8485–8486. (b) Morken, J. M.; Didiuk, M. T.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1993**, *115*, 6997–6998. (c) Morken, J. M.; Didiuk, M. T.; Visser, M. S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1994**, *116*, 3123–3124. (d) Visser, M. S.; Hoveyda, A. H. *Tetrahedron* **1995**, *51*, 4383–4394. (e) Visser, M. S.; Heron, N. M.; Didiuk, M. T.; Sagal, J. F.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1996**, *118*, 4291–4298. (f) Heron, N. M.; Adams, J. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1997**, *119*, 6205–6206.

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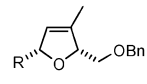
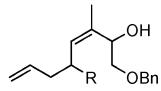
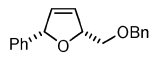
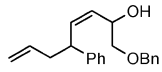
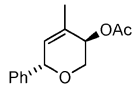
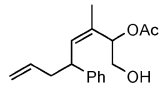
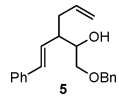
(13) Gold-catalyzed reactions of allylsilanes with electrophiles: (a) Georgy, M.; Boucard, V.; Campagne, J.-M. *J. Am. Chem. Soc.* **2005**, *127*, 14180–14181. (b) Lin, C.-C.; Teng, T.-M.; Odedra, A.; Liu, R.-S. *J. Am. Chem. Soc.* **2007**, *129*, 3798–3799. (c) Lin, C.-C.; Teng, T.-M.; Tsai, C.-C.; Liao, H.-Y.; Liu, R.-S. *J. Am. Chem. Soc.* **2008**, *130*, 16417–16423. (d) Matsuda, T.; Kadowaki, S.; Yamaguchi, Y.; Murakami, M. *Chem. Commun.* **2008**, *24*, 2744–2746.

Table 2. Gold-Catalyzed Allylative Ring-Opening of Dihydrofurans and Dihydropyrans[a]

entry	substrate (*cis*:*trans*)	product	*dr*	yield/%
				
1	**1b** R = 4-MeOC$_6$H$_4$ (55:45)	**2b**	60:40	90[b]
2	**1c** R = 4-MeO$_2$CC$_6$H$_4$ (80:20)	**2c**	56:44	48
3	**1d** R = 4-BrC$_6$H$_4$ (89:11)	**2d**	55:45	82[b]
4	**1e** R = Me$_2$C=CH (50:50)	**2e**	50:50	35
5	**1f** R = *i*-Pr (>99:1)	**2f**	–	–[c]
6	 **1g** (97:3)	 **2g**	60:40	60[d]
7	 **4** (32:68)	 **6**	–	–[c]

[a] Conditions: $HAuCl_4 \cdot 3H_2O$ (5 mol %), $Me_3SiCH_2CH{=}CH_2$ (4 equiv), CH_2Cl_2, −40 to −20 °C, 1−4 h, then treatment with *n*-Bu_4NF. [b] With 15 mol % of $HAuCl_4 \cdot 3H_2O$. [c] No conversion. [d] Accompanied by 13% (*dr* = 60:40) of the regioisomer **5**:


5

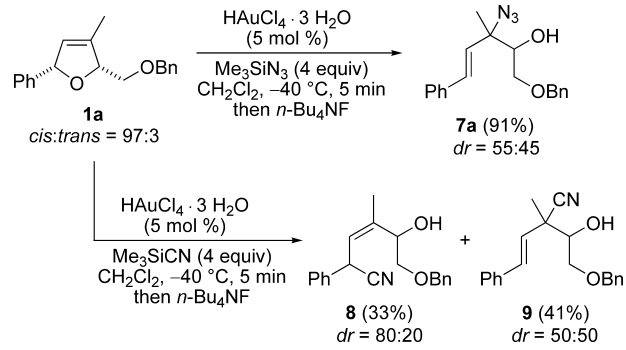
to the alkenyl-substituted dihydrofuran **1e** even though the yield of product **2e** was low (35%; entry 4). As expected, the alkyl-substituted dihydrofuran **1f** does not undergo gold-catalyzed ring-opening (entry 5). The substrate **1g** lacking the methyl group (entry 6) turned out to be less reactive than its counterpart **1a**, whereas the dihydropyran **4**[3c] did not react (entry 7). In all cases, product formation was accompanied by extensive or complete epimerization of the stereogenic center bearing the aryl or alkenyl substituent. The allylative ring-opening took place regioselectively with exclusive attack of the nucleophile at C-2 of the dihydrofuran, except for substrate **1g**, which also afforded 13% of the regioisomer **5** resulting from attack in the 4-position.

Whereas the application of the gold-catalyzed ring-opening of dihydrofurans to substituted allylsilanes met with limited success,[14] other nucleophiles proved to be more reactive (Scheme 2). Thus, reaction of **1a** with 4 equiv of trimethylsilylazide[15] in the presence of 5 mol % of $HAuCl_4 \cdot 3H_2O$ gave the azido alcohol **7a** (resulting from exclusive attack of the nucleophile at C-4) with 91% yield after just 5 min at −40 °C. This is the first example for a ring-opening reaction of an unsaturated cyclic ether with a nitrogen nucleophile. In contrast to this highly regioselective transformation, the corresponding reaction of **1a** with trimethylsilylcyanide[16]

(14) Reaction of **1a** with trimethyl(2-methylallyl)silane (4 equiv) in the presence of $HAuCl_4 \cdot 3H_2O$ (5 mol %) gave 1-(benzyloxy)-3,7-dimethyl-5-phenylocta-3,7-dien-2-ol with 20% yield, whereas the corresponding reaction of **1a** with crotyltrimethylsilane afforded 1-(benzyloxy)-3,6-dimethyl-5-phenylocta-3,7-dien-2-ol with 59% yield.

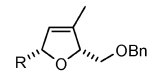
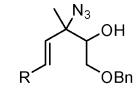
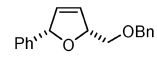
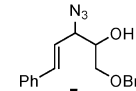
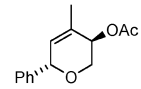
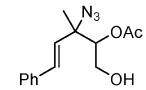
(15) For the reaction of Me_3SiN_3 with gold(I) acetylides, see: Partyka, D. V.; Updegraff, J. B., III; Zeller, M.; Hunter, A. D.; Gray, T. G. *Organometallics* **2007**, *26*, 183–186.

Scheme 2. Gold-Catalyzed Nucleophilic Ring-Opening of 2,5-Dihydrofuran **1a**



afforded a mixture of the regioisomers **8** and **9** with 74% combined yield. The product ratio was not affected by a change of the reaction temperature or the stoichiometry of the reactants.

Table 3. Gold-Catalyzed Ring-Opening of Dihydrofurans and Dihydropyrans with Me_3SiN_3[a]

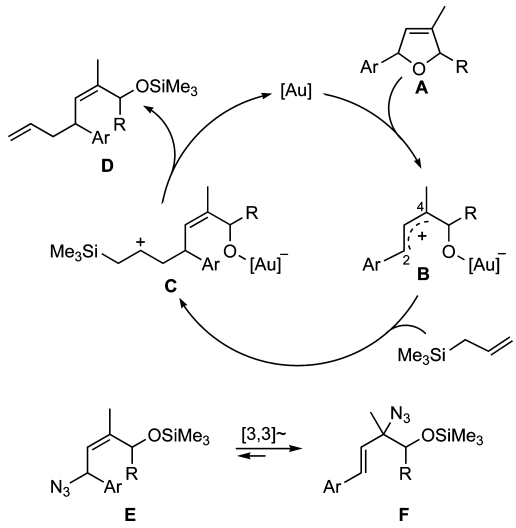
entry	substrate (*cis*:*trans*)	product	*dr*	yield/%
				
1	**1b** R = 4-MeOC$_6$H$_4$ (55:45)	**7b**	50:50	70
2	**1c** R = 4-MeO$_2$CC$_6$H$_4$ (80:20)	**7c**	70:30	12[b]
3	**1d** R = 4-BrC$_6$H$_4$ (89:11)	**7d**	60:40	85
4	**1e** R = Me$_2$C=CH (50:50)	**7e**	–	–[c]
5	**1f** R = *i*-Pr (>99:1)	**7f**	–	–[d]
6	 **1g** (97:3)	 **7g**	70:30	83
7	 **4** (32:68)	 **10**	50:50	81

[a] Conditions: $HAuCl_4 \cdot 3H_2O$ (5 mol %), Me_3SiN_3 (4 equiv), CH_2Cl_2, −40 to −20 °C, 0.5−2 h, then treatment with *n*-Bu_4NF. [b] 76% of **1c** was recovered. [c] A complex product mixture was formed. [d] No conversion.

Encouraged by the high reactivity and regioselectivity observed in the gold-catalyzed azidation of substrate **1a**, we applied these conditions to various dihydrofurans and -pyrans (Table 3). As in the corresponding allylation, electron-rich (entry 1) and electron-deficient aryl groups (entries 2 and 3) are tolerated, even though the yield of the ester-substituted azidation product **7c** was very low (12%; entry 2). This pronounced reactivity difference is in agreement with the proposed benzyl cation intermediate. In contrast to the aryl-substituted dihydrofurans, substrate **1e** bearing an alkenyl group gave a complex product mixture (entry 4), whereas isopropyl-substituted dihydrofuran **1f** did not react (entry 5). Finally, we were pleased to observe a smooth conversion of

dihydrofuran **1g** and even dihydropyran **4** to the corresponding azido alcohols (entries 6 and 7). The latter transformation took place without concomitant acetate migration.[3d] Similar to the allylation, the gold-catalyzed azidation of dihydrofurans and -pyrans occurred with extensive epimerization of the stereogenic center next to the aryl substituent. Interestingly, the azido alcohols **7** are converted back to the dihydrofurans **1** by traces of acid.

Scheme 3. Proposed Mechanism of the Gold-Catalyzed Nucleophilic Ring-Opening



In mechanistic terms, the reactivity (R = 4-$MeOC_6H_4$ > Ph > 4-$MeO_2CC_6H_4$ ≫ *i*-Pr) in the gold-catalyzed allylation and azidation of 2,5-dihydrofurans **1**, as well as the epimerization observed for these substrates, clearly points to a benzyl cation intermediate. But how is the opposite regioselectivity of these transformations to be explained? We assume that formation of the zwitterionic intermediate **B** from starting material **A** and the gold(III) catalyst (Scheme 3) is followed by a kinetically controlled attack of the allylsilane at C-2 of the benzyl cation moiety, affording β-silyl cation **C**. Cleavage of the carbon−silicon bond then leads to the ring-opening product **D** and regenerates the gold catalyst. The formation of product **5** resulting from attack at C-4 of dihydrofuran **1g** indicates that the steric properties of the benzyl cation contribute to the regioselectivity of the gold-catalyzed allylative ring-opening.

The products of the gold-catalyzed allylation and azidation of dihydrofurans and -pyrans can undergo [3,3]-sigmatropic rearrangements. Whereas strong heating is required for a thermal Cope rearrangement of 1,5-dienes,[17] allylazides equilibrate very rapidly even below room temperature.[18] Thus, there are two possible explanations for the formation of allylazides **F** (Scheme 3): either the zwitterionic intermediate **B** is attacked by Me_3SiN_3 directly in the 4-position, or the initially formed regioisomer **E** rearranges rapidly to the (thermodynamically more stable) product **F**. Investigations dedicated to elucidate these mechanistic issues are in progress.

In conclusion, we have achieved the first examples for a highly regioselective gold-catalyzed ring-opening allylation and azidation of dihydrofurans and dihydropyrans. These transformations require the presence of an aryl or alkenyl group in the 2-position of the substrate and probably proceed via a zwitterionic intermediate comprising a benzyl cation substructure and an anionic aurate moiety. We continue to expand the scope of gold-catalyzed ring-opening reactions for the regio- and stereoselective synthesis of highly functionalized linear products.

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Supporting Information Available: Experimental procedures and selected NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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