Gold Catalysis: On the Phenol Synthesis
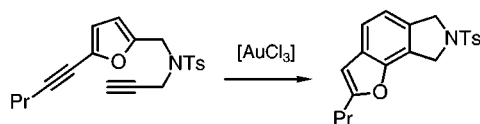
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Received September 10, 2001

ABSTRACT

For the gold-catalyzed phenol synthesis an intramolecular migration of the oxygen atom was proven. Several other late transition metals with d[8] configuration allow this conversion, providing evidence for Au(III) being a catalytically active species. On the other hand gold was still the most active catalyst and gives the cleanest conversion. With additional alkynyl substituents another ring could be closed to provide doubly annellated arenes.
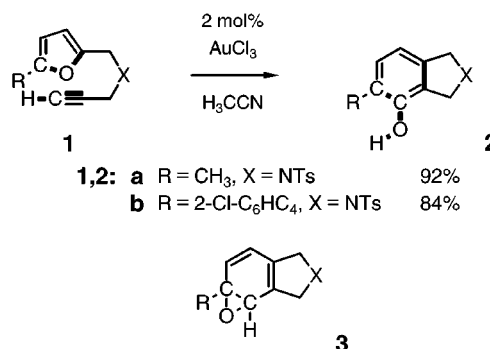
The transformation of furans **1** to highly substituted phenols **2**[1] has received considerable interest[2] for two reasons. On the one side gold catalysis still is rare in organic synthesis but seems to offer new possibilities.[3,4] On the other side the old problem of a regioselective introduction of substituents at a benzoid arene is now shifted to a furan, where such control of selectivity is much easier for both electrophilic attack or metalation. Furthermore, the substrates **1** can be prepared from furfural, the cheap product from treatment of agricultural waste with acid and thus based on renewable resources.

As we have previously only offered a simple proposal for the mechanism,[1] which is based on classical organic chemistry, we wanted to address some mechanistic aspects of the transition metal-catalyzed conversion of **1** to **2**.

The first point of interest was the origin of the phenolic oxygen atom. During the reaction four bonds are broken and four new bonds are formed (drawn bold in Scheme 1). A transposition of the oxygen from the carbon atoms of the furan to the former terminal carbon atom of the alkyne seems to have occurred. Two of these carbon atoms are neighbors in **2**. The reaction of **1a** and **1b** in the presence of 5 equiv and 2.3 equiv of $H_2^{18}O$[5] revealed not only that the chemoselectivity of the reaction was high (no addition of water to the alkyne as in the Utimoto−Teles reaction)[6] but also that the oxygen transfer was mainly intramolecular. (By MS analysis of the isotope pattern of the molecular ion, less than 1% of incorporation of ^{18}O was detected.) When the reaction was run in methanol as solvent, also no incorporation of this

(1) Hashmi, A. S. K.; Frost, T. M.; Bats, J. W. *J. Am. Chem. Soc.* **2000**, *122*, 11553−11554.

(2) The Editor, *Science* **2000**, *290*, 1465.

(3) Hashmi, A. S. K.; Schwarz, L.; Choi, J.-H.; Frost, T. M. *Angew. Chem.* **2000**, *112*, 2382−2385; *Angew. Chem., Int. Ed.* **2000**, *39*, 2285−2288.

(4) Dyker, G. *Angew. Chem.* **2000**, *112*, 4407−4409; *Angew. Chem., Int. Ed.* **2000**, *39*, 4237−4239.

(5) From Chemotrade, Leipzig; 94.6%.

(6) Fukuda, Y.; Utimoto, K. *J. Org. Chem.* **1991**, *56*, 3729−3731. Teles, J. H.; Brode, S.; Chabanas, M. *Angew. Chem.* **1998**, *110*, 1475−1478; *Angew. Chem., Int. Ed.* **1998**, *37*, 1415−1418.

Scheme 1. Gold-Catalyzed Phenol Synthesis

1,2: **a** R = CH₃, X = NTs 92%
b R = 2-Cl-C₆HC₄, X = NTs 84%

stronger nucleophile was observed. This is in accordance with the arene epoxide **3** that we already suggested as intermediate and relates the second phase of the conversion of **3** to **2** to the type of steps well-known from the NIH-shift reaction[7] (key word "oxygen walk"), which proceeds via cationic intermediates. Further support for this came from substrates such as **4**, where in addition to the synthesis of **5** a C−C bond cleavage to **6** and the highly sensitive **7** (polymerizes readily, thus the low yield) was observed. During this C−C bond cleavage the arenium ion dissociates into the stable arene and a well-stabilized furylmethyl cation (Scheme 2).

Scheme 2. C−C Bond Cleavage in the Case of Substituents that Stabilize a Positive Charge
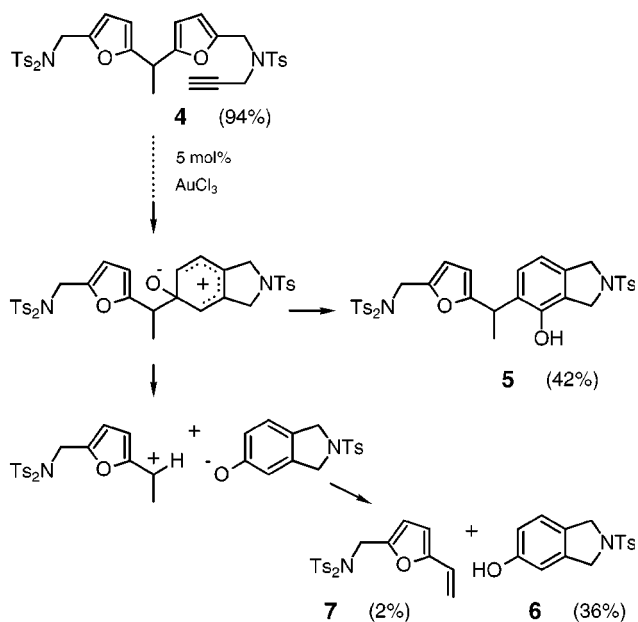
How would such an intermediate **3** be generated, and what is the role of the gold catalyst? Here we discovered that the transformation is not restricted to Au(III) as a precatalyst. Pd(II), Pt(II), Rh(I), and Ir(I), all d[8] systems like Au(III), were also able to convert **1** to **2** (Table 1). Still, gold was

far more active than the other metals. Other oxidation states of these metals as precatalysts, for example, Pd(0) or Rh(III), were inactive. This observation provides strong evidence for gold(III) being the active species. Gold(I) compounds showed a very low activity, which we assign to the known disproportionation to gold(0) and gold(III). With Ag(I) the immediate precipitation of silver acetylides was observed. Exclusion of oxygen or humidity was not necessary in these conversions, and thus our test of Cu(I)Cl only delivered the diyne **8** (Figure 1) as the product of a slow Glaser coupling.[8]
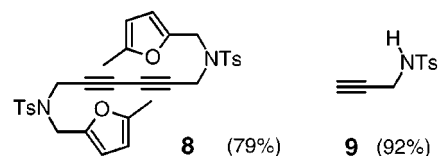

Figure 1. Other products derived from transition metal catalysis.

Yamamoto et al.[9] have shown that hafnium(IV) is able to activate triple bonds for the reaction with allyl silanes as electron-rich olefins. With **1** in acetonitrile no reaction was observed; in CH_2Cl_2 and with 54 mol % of $HfCl_4$ only the cleavage to **9** (Figure 1) occurred.

For gold(III) acetonitrile is the best solvent, in acetone the reaction is slightly faster but less selective, and in DMF even after long reaction times apart from starting material only traces of product could be detected.

Unfortunately we are not yet able to provide a convincing model for the first phase of the reaction, the transformation of **1** to **3** by such a d[8] metal species.[10] One of the major questions is still why only terminal alkynes **1** deliver the phenols **2**.

So far we have investigated dialkyl furans, which led to trialkyl phenols.[1] Compound **4** is an example of a benzyl-like substituent, **1b** for an aryl alkyl furan, which delivers the biaryl compound **2b**. Continuing this sequence of sp^3 and sp^2 substituents, we now turned to sp substituents in the form of alkynyl furans such as **10**. Here two products could be isolated, the alkynyl phenol **11** and the benzofuran **12** (Scheme 3; now even five bonds are broken and five new bonds are formed).[11] $AuCl_3$ in MeCN efficiently catalyzes the conversion of **11** to **12** and thus proved how **12** was formed. Similar cyclizations of *o*-alkynyl phenols by Pd(II) catalysts are well-known in the literature.[12] As benzofurans such as **13** do not react, a further reaction of another terminal alkyne substituent in the side chain with the newly formed furan-substructure in **12** is not possible.

Table 1. Reaction of **1** with Different Transition Metal Complexes[a]

complex	yield of **2** [%]	T [°C]	time for 50% conversion [h]
5 mol % AuCl₃	92	20	≪1
5 mol % KAuCl₄	95	20	24
7 mol % PdCl₂(MeCN)₂[b]	25	20	48
5 mol % PtCl₂(MeCN)₂	31	50	24
18 mol % PtCl₂[c]	95	20	16
5 mol % [Rh(COD)Cl]₂[b]	30	20	≫240
5 mol % [Ir(COD)Cl]₂	95	50	3
6 mol % [Ir(COD)(PPh₃)(Py)]	80	50	96

[a] If not noted otherwise, all reactions were performed in MeCN. [b] Not a clean reaction. [c] In acetone (no reaction in MeCN).

(7) Guroff, G.; Daly, J. W.; Jerina, D. M.; Renson, J.; Withop, B.; Udenfried, S. *Science* **1967**, *157*, 1527−1530.

(8) Glaser, C. *Chem. Ber.* **1869**, *2*, 422.

(9) Yoshikawa, E.; Gevorgyan, V.; Asao, N.; Yamamoto, Y. *J. Am. Chem. Soc.* **1997**, *119*, 6781−6786.

(10) Apart from the simple proposal discussed in our first publication there exist other possibilities involving carbene, acetylid, or vinylidene complexes as intermediates.

Scheme 3. Closure of One More Ring to the Benzofuran **12**
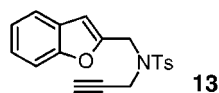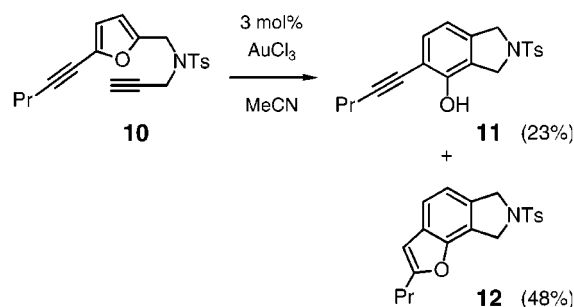
The structure of **12** was unambiguously proven by a crystal structure analysis (Figure 2).[13] The fused tricyclic system is, apart from the slightly pyramidalized nitrogen atom, perfectly planar. The tolyl ring is almost perpendicular to this plane, leading to an L-like shape of the whole molecule.

The incomplete conversion of **10** to **12** is in accordance with our earlier results. We always observed that two-step
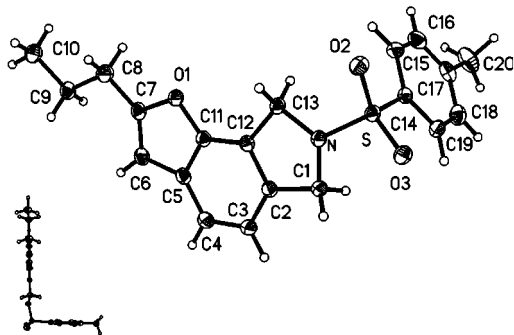

Figure 2. X-ray crystal structure of **12** (ORTEP plot).

one-pot reactions with low amounts of gold catalysts were problematic, while each single step behaved quite well. We assign this to the noble character of gold, which is easily deactivated by reduction.[1,3]

In conclusion, we have demonstrated that during the reaction the oxygen atom is transferred intramoleculary. The reaction proceeds through cationic intermediates and is quite general. Many late transition metal complexes with d^8 configuration are capable of catalyzing the reaction, but gold clearly is the most active one. A wide range of substituents such as alkyl, benzyl, aryl, and alkynyl is tolerated, the latter allowing an additional ring closure.

(11) Selected spectroscopic data for **11** and **12**. **11**: mp 149−152 °C; R_f (hexane/ethyl acetate/dichloromethane, 5:1:2) = 0.34; IR (film) 3440 cm^{-1}, 1459, 1348, 1307, 1235, 1163, 1098, 1062, 813; ^{1}H NMR (CDCl$_3$, 250 MHz) δ 0.96 (t, J = 7.3 Hz, 3H), 1.49−1.64 (m, 2H), 2.33 (s, 3H), 2.36 (t, J = 7.1 Hz, 2H), 4.52 (s, 4H), 5.79 (s, 1H), 6.57 (d, J = 7.8 Hz, 1H), 7.10 (d, J = 7.8 Hz, 1H), 7.24 (d, J = 8.2 Hz, 2H), 7.70 (d, J = 8.2 Hz, 2H); ^{13}C NMR (CDCl$_3$, 62.9 MHz) δ 13.4 (q), 21.3 (q), 21.4 (t), 22.0 (t), 51.4 (t), 54.0 (t), 73.7 (s), 98.1 (s), 109.1 (s), 114.0 (d), 121.6 (s), 127.4 (d, 2C), 129.7 (d, 2C), 131.3 (d), 133.5 (s), 138.0 (s), 143.5(s), 151.3 (s); MS (70 eV) m/z (%) 355 (35)[M$^+$], 199 (100), 170 (84); HRMS (70 eV) C$_{20}$H$_{21}$-NO$_3$S calcd 355.1242, found 355.1242 **12**: mp 120−123 °C; R_f (hexane/ethyl acetate/dichloromethane, 5:1:2) = 0.48; IR (film) 1597 cm^{-1}, 1437, 1348, 1165, 1098, 1064; ^{1}H NMR (CDCl$_3$, 250 MHz) δ 0.99 (t, J = 7.3 Hz, 3H), 1.67−1.82 (m, 2H), 2.39 (s, 3H), 2.71 (t, J = 7.6 Hz, 2H), 4.72 (d, J = 1.6 Hz, 2H), 4.84 (d, J = 1.6 Hz, 2H), 6.36 (s, 1H), 6.98 (d, J = 8.0 Hz, 1H), 7.29−7.37 (m, 3H), 7.78−7.82 (dm, J = 8.3 Hz, 2H); ^{13}C NMR (CDCl$_3$, 62.9 MHz) δ 13.5 (q), 20.8 (t), 21.3 (q), 30.2 (t), 51.2 (t), 53.9 (t), 102.0 (d), 116.4 (d), 118.3 (s), 119.9 (d), 127.5 (d, 2C), 128.6 (s), 129.6 (d, 2C), 131.8 (s), 133.7 (s), 143.5 (s), 148.8 (s), 159.8 (s); MS (70 eV) m/z (%) 355 (31)[M$^+$], 199 (100), 170 (79); C$_{20}$H$_{21}$NO$_3$S (355.5) calcd C 67.58, H 5.96, N 3.94; found C 67.25, H 6.11, N 3.99

(12) Two out of many publications: Arcadi, A.; Cacchi, S.; Del Rosario, M.; Fabrizi, G.; Marinelli, F. *J. Org. Chem.* **1996**, *61*, 9280−9288. Larock, R. C.; Tian, Q. *J. Org. Chem.* **1998**, *63*, 2002−2009.

(13) Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-168784 (**12**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, U.K. [Fax: (internat) + 44-1233/336-033; E-mail: deposit@ccdc.cam.ac.uk].