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Highly Selective Gold-Catalyzed Arene Synthesis

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The classic route to aromatic compounds with specific substitution patterns is the aromatic substitution which introduces or exchanges substituents at an already existing arene.[1] A different mechanism but the same synthetic principle is applied in the different transition-metal-catalyzed (cross-) coupling reactions[2] or ortho-metalation and subsequent functionalization reactions.[3] Other approaches assemble the arene, e.g. use cycloaddition reactions such as the Diels−Alder reaction followed by a subsequent oxidation of the unsaturated six-membered ring to an arene.[4] Some major achievements in this field of cycloadditions or cycloisomerizations of the past years stem from transition metal catalysis.[5] For arene synthesis Vollhardt's [2+2+2] cycloaddition[6] and variations thereof[7] as well as the Dötz reaction[8] are among the most prominent.

We now want to report our results concerning the synthesis of highly substituted arenes, more specifical phenols, by gold catalysis. Gold-catalyzed *homogeneous organic reactions* are quite rare: the only examples that reached some importance are the Ito-Hayashi aldol reaction[9] and the addition of O- or N-nucleophiles to unsaturated compounds first described by Utimoto[10] and later improved by Teles.[11] Recently we reported new C−O- and C−C-bond formations catalyzed by gold; further investigation of these reactions led to the completely new results described here.[12]

When we subjected a mixture[13] of the allenyl ketone **2** and the propargyl ketone **1** in acetonitrile to $AuCl_3$, besides the expected furan **3**, a second product, the hydroxyarene **4**, could be isolated.

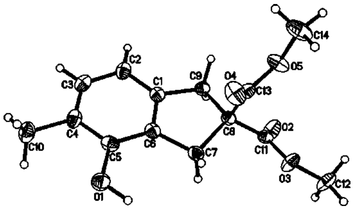
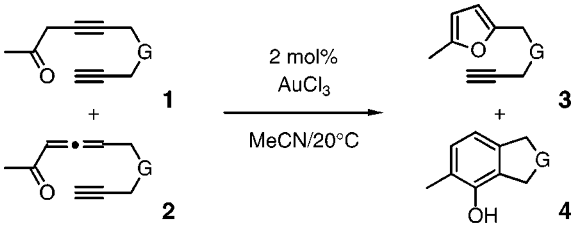


Figure 1. ORTEP plot of the solid-state structure of **4g**.

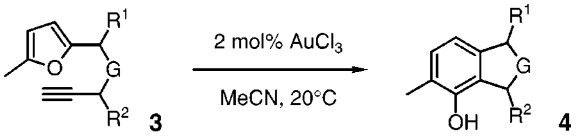
Since both allenyl and propargyl ketones are known to isomerize to furans with the gold catalyst,[12] we assumed that first **3** is formed from **1** and **2** and then **3** is transformed to **4** by the gold catalyst in a separate step.



	G	**3** (%)	**4** (%)
a	CH_2	24	35
b	O	$5^{a)}$	52
c	NTs	55	36

a) volatile material

Further experiments prove that assumption. $AuCl_3$ in acetonitrile cleanly transformed **3** to **4**. The structure of **4g** was unequivocally proven by X-ray crystal structure analyses.[14] The reactions proceeded at room temperature, neither air nor water needed to be excluded: even when 2.7 equiv of water was added, no addition of water to the alkyne was observed, only **4** was formed. No paramagnetic species were formed and no gold precipitates; the reactions could nicely be monitored by ^{1}H NMR. The spectra show that during the reaction no detectable concentrations of any intermediates build up.



	G	R^1	R^2	**4** (%)
a	CH_2	H	H	65
b	O	H	H	69
c	NTs	H	H	97
d	NTs	Me	H	94
e	NTs	H	Me	93
f	NNs	H	H	96
g	$C(CO_2Me_2)_2$	H	H	88
h	$N(Ts)CH_2$	H	H	$81^{a)}$

a) 6 mol% of $AuCl_3$

Analysis of the spectra shows that the catalyst suffers deactivation. In the reaction of **1** and **2** with $AuCl_3$ the deactivation of the catalyst seems to be even faster, therefore the further conversion of **3** to **4** is not complete when starting from these substrates. On the other hand, only a small amount (2 mol %) of catalyst is necessary for a complete reaction, which strongly suggests that if the deactivation can be prevented by modification

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(1) Electrophilic or nucleophilic: Olah, G. A. *Acc. Chem. Res.* **1971**, *4*, 240−248. Hartshorn, S. R. *Chem. Soc. Rev.* **1974**, *3*, 167−192. Pearson, D. E.; Buehler, C. A. *Synthesis* **1971**, 455−477.

(2) Negishi, E. *Acc. Chem. Res.* **1982**, *15*, 340−348. Brown, J. M.; Cooley, N. A. *Chem. Rev.* **1988**, *88*, 1031−1046. Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483. Mitchell, T. N. *Synthesis* **1992**, 803−815.

(3) Chauder, B.; Green, L.; Snieckus, V. *Pure Appl. Chem.* **1999**, *71*, 1521−1529. Snieckus, V. *Pure Appl. Chem.* **1990**, *62*, 2047−2056.

(4) Oppolzer, W. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 5, pp 315−399. Fu, P. P.; Harvey, R. G. *Chem. Rev.* **1978**, *78*, 317−361.

(5) Wender, P. A.; Snapper, M. L. *Tetrahedron Lett.* **1987**, *28*, 2221−2224. Jolly, R. S.; Luedtke, G.; Sheehan, D.; Livinghouse, T. *J. Am. Chem. Soc.* **1990**, *112*, 4965−4966. Baldenius, K.-U.; tom Dieck, H.; König, W. A.; Icheln, D.; Runge, T. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 305−307. Wender, P. A.; Jenkins, T. E.; Suzuki, S. *J. Am. Chem. Soc.* **1995**, *117*, 1843−1844. Wender, P. A.; Takahashi, H.; Witulski, B. *J. Am. Chem. Soc.* **1995**, *117*, 4720−4721. Saito, S.; Salter, M. M.; Gevorgyan, V.; Tsuboya, N.; Tando, K.; Yamamoto, Y. *J. Am. Chem. Soc.* **1996**, *118*, 3970−3971. Saito, S.; Uchiyama, N.; Gevorgyan, V.; Yamamoto, Y. *J. Org. Chem.* **2000**, *65*, 4338−4341.

(6) Vollhardt, K. P. C. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 539−556.

(7) Reppe, W.; von Kutepow, N.; Magin, A. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 727−733. Müller, E. *Synthesis* **1974**, 761−774. Grigg, R.; Scott, R.; Stevenson, P. *Tetrahedron Lett.* **1982**, *23*, 2691−2692. Schore, N. E. *Chem. Rev.* **1988**, *88*, 1081−1119. Schore, N. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 5, pp 1129−1162. McDonald, F. E.; Zhu, H. Y. H.; Holmquist, C. R. *J. Am. Chem. Soc.* **1995**, *117*, 6605−6606. Witulski, B.; Stengel, T. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 2426−2430.

(8) Dötz, K. H. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 587−608.

(9) Ito, Y.; Sawamura, M.; Hayashi, T. *J. Am. Chem. Soc.* **1986**, *108*, 6405−6406.

(10) Fukuda, Y.; Utimoto, K. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 2013−2015.

(11) Teles, J. H.; Brode, S.; Chabanas, M. *Angew. Chem., Int. Ed. Engl.* **1998**, *370*, 1415−1418.

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

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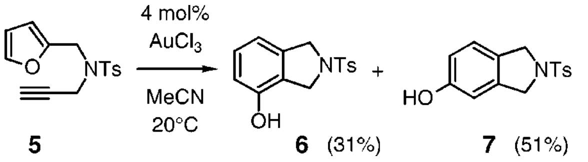
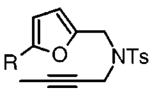
of the catalyst (at the moment a simple gold salt) an even smaller amount of catalyst might be sufficient.

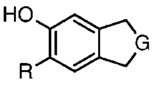
Due to their good accessibility, the use of furans **3** instead of ketones **1** and **2** is synthetically appealing. Even if the furan possesses only one substituent as in **5**, the catalysis works but two products, **6** and **7**, were formed. **6** corresponds to **4**, while **7** is an isomer without 1,2-transposition of the oxygen (vide infra).



With a disubstituted alkyne like **8** instead of a terminal one, no reaction was observed.[15] With tetrahydrothiophenegold(I)



8 R = H,Me



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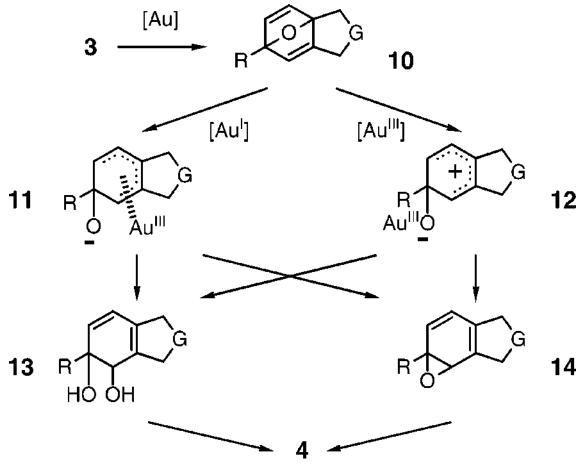
chloride or a mixture of triethylphosphanegold(I) chloride and silver tetrafluoroborate the reaction also proceeded but was much slower. No reaction was observed with $AgNO_3$, $Hg(ClO_4)_2$, $Pd_2dba_3{\cdot}CHCl_3$, $Pd(PPh_3)_4$, $Rh(PPh_3)_3Cl$, ZnI_2, $AlCl_3$, $FeCl_3$, $InCl_3$, and *p*-TsOH (all in MeCN), heating up to 170 °C in mesitylene for several hours, and at 8 kbar in MeCN for 4 h. TfOH caused an unspecific decomposition, with $Cl_2(PCy)_2Ru{=}CHPh$ at room temperature no reaction occurred, and at 80 °C a complex mixture of products was formed. Only with $PdCl_2(MeCN)_2$ were traces of **4** visible after several days at room temperature. The latter observation is in accordance with our earlier results on the synthesis of substrates of type **3** by Pd^{II}-catalyzed isomerizations of allenyl ketones without further conversion to **4**.[16] First experiments with **3h** show that an anellation of a six-membered ring with the benzene is also possible, but again ring closure competes with catalyst deactivation and thus the 3-fold amount of catalyst (6 mol %) was needed for a complete conversion to **4h**.

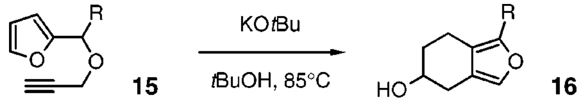
For the mechanism of the reaction, we can only offer a simple proposal that falls back on steps known from classical organic chemistry. One could assume that the gold coordinates and thus increases the electrophilicity of the triple bond. This would be quite similar to the activiation of C−C multiple bonds for nucleophilic addition mentioned above.[10,11] Now an intramolecular Diels−Alder reaction could provide **10**. Usually furans are notorious unreactive diene partners in Diels−Alder reactions that even in intramolecular cases[17] react only if the dienophile is activated by at least one electron withdrawing group or high pressure is applied for strain-activated olefins.[18]

In the next step the oxygen bridge must be broken, and this could either be induced by gold(III) acting as a Lewis acid (forming **12**) or by Au(I) which forms a Au(III)-stabilized pentadienyl cation **11**. Then either the nucleophilic oxygen atom or external water may serve as nucleophiles, and possible intermediates are **13** and **14**. They finally lead to the product **4**. Such an isomerization of oxanorbornadienes to phenols usually requires very strong acids.[19] If the opening of the oxygen bridge would occur in the other direction, the nucleophile could not attack at the position where the OH group is attached in the product. The local symmetry of the intermediates **13** or **14** for R = H would explain the formation of a mixture of **6** and **7** from **5**.

This proposal cannot explain the highly regioselective formation of **4** (no **9** or other isomers were observed), which could be evidence for a completely different mechanism. The necessity of a terminal alkyne might be evidence for an acetylide or even vinylidene complex as intermediate, then the hydroxyl group would end up at the position where the metal is attached in the intermediates.



Finally it must be mentioned that with related starting materials, namely **15**, under strongly basic conditions at 85 °C via an allenic intermediate a Kanematsu furan ring transfer reaction[20] to **16** can be achieved. In these reactions the oxygen atom always remains attached to the same carbon atom.



So our reaction not only represents a new access to arenes from easily available furans but also nicely complements the synthetic potential of substrates such as **4**. In addition, the phenolic hydroxyl group opens several possibilities for a further fuctionalization of the substrate and it should easily be possible to incorporate stereogenic centers from compounds of the chiral pool.

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Supporting Information Available: Characerization data of compounds **4a**−**4h**, **6**, and **7** and X-ray crystal analysis data for **4g** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) During workup **2** does not completely isomerize to **1**, this behavior differs from the one of terminal propargyl ketones: Hashmi, A. S. K.; Bats, J. W.; Choi, J.-H.; Schwarz, L. *Tetrahedron Lett.* **1998**, *39*, 7491−7494.

(14) Crystal data for **4g**: monoclinic, space group *P*21/*c*, colorless crystal, $a = 7.8560(12)$ Å, $b = 10.758(2)$ Å, $c = 15.490(3)$ Å, $b = 101.504(14)°$, 154(2) K, $Z = 4$, GOF = 1.342, $R1 = 0.0664$.

(15) Even in the presence of another terminal alkyne.

(16) Hashmi, A. S. K.; Schwarz, L. *Chem. Ber./Recl.* **1997**, *130*, 1449−1456.

(17) Brieger, G.; Bennett, J. N. *Chem. Rev.* **1980**, *80*, 63−97 (specifically p 81). Roush, W. R. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 5, pp 513−550.

(18) Buback, M.; Heiner, T.; Hermans, B.; Kowollik, C.; Kozhushkov, S. I.; de Meijere, A. *Eur. J. Org. Chem.* **1998**, 107−112.

(19) Batt, D. G.; Jones, D. G.; La Greca, S. *J. Org. Chem.* **1991**, *56*, 6704−6708. Epsztajn, J.; Jóźwiak, A.; Szcześniak, A. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2563−2567.

(20) Yamaguchi, Y.; Tatsuta, N.; Hayakawa, K.; Kanematsu, K. *J. Chem. Soc., Chem. Commun.* **1989**, 470−472. Kanematsu, K.; Nishizaki, A.; Sato, Y.; Shiro, M. *Tetrahedron Lett.* **1992**, *33*, 4967−4970. For related results, see: Wu, H.-J.; Yen, C.-H.; Chuang, C.-T. *J. Org. Chem.* **1998**, *63*, 5064−5070.