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Gold Catalysis: Deuterated Substrates as the Key for an Experimental Insight into the Mechanism and Selectivity of the Phenol Synthesis

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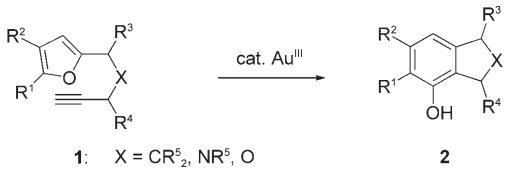
Abstract: The second phase of the gold-catalyzed phenol synthesis, the ring opening of the intermediate arene oxide, follows general acid catalysis. The product selectivity is determined by the substrate only and can be explained by the stability of the intermediate arenium ions. Thus, even remote substitutents can be used to control the chemoselectivity of the overall reaction by electronic influences and their influence is stronger than the steric influence of neighboring substituents. This is supported by quantum chemical calculations of the intermediates. The lack of exchange of deuterium labels excludes even equilibria with acetylide or vinylidene intermediates and the observed deuterium distribution in the final products is in accord with the NIH-shift reaction. In addition, these findings now explain previously obtained results.

Keywords: gold · homogeneous catalysis · quantum chemical calculations · reaction mechanisms · selectivity

Introduction

The gold-catalyzed synthesis of highly substituted arenes **2** from ω-alkynyl furans **1** is a very efficient tool for organic synthesis (Scheme 1).[1–4] Early ^{18}O labeling experiments proofed an intramolecular migration of the furan oxygen atom (which finally becomes the phenolic oxygen atom), which is evidence for a 1,2-migration via an arene oxide intermediate.[1a]



Scheme 1. Gold-catalyzed phenol synthesis.

In attempts to establish catalysts that are more stable and reactive than simple gold halides,[2] we found a catalyst which allowed the detection of the intermediate arene oxides **G** or oxepines **H** (Scheme 2) as a transient species by in situ NMR spectroscopy.[3] Furthermore, it was possible to trap the intermediate **G** as the product of a [4+2] cycloaddition. While the Au^{III}-catalyzed reactions were highly selective, with the less-selective Pt^{II} catalysts Echavarren observed side products which could be formed by hydrolysis of an intermediate of type **F** (pathway II).[4] Accompanying theoretical work favored pathway II, passing through a carbene complex intermediate, over pathway I, proceeding by an initial [4+2] reaction.[1b] Only recently, similar side products have been reported for special substrates in gold-catalyzed reactions.[4c] Other conceivable pathways include vinylidene complexes **M** or alkynyl complexes **P** (pathways IV

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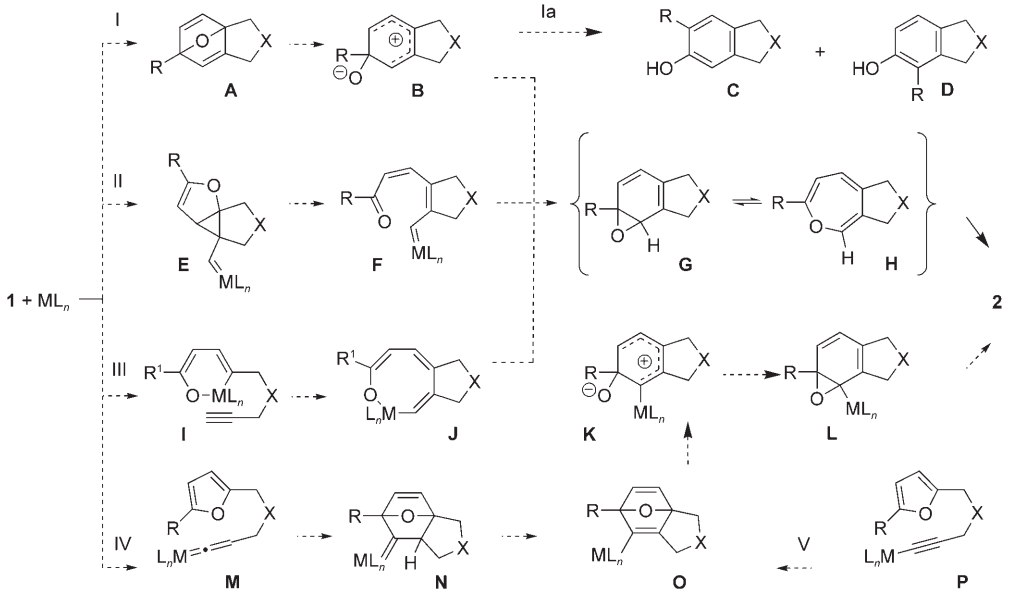

Scheme 2. Possible pathways of the gold-catalyzed phenol synthesis.

and V), or, if the catalyst system would be reduced in situ, an insertion into the C(sp^2)–O bond of the furan, followed by a second insertion of the alkyne moiety, to deliver **J**.

Results and Discussion

With the ability to investigate the intermediate arene oxide[3a] or oxepine,[3b] we first used the deuterated alkyne **3** (Figure 1) and catalyst **4**. ^{1}H NMR spectroscopy clearly showed that even in water containing solvent almost all the deuterium was still present at the corresponding position in the oxepine intermediate **H** (Figure 1). The alkynyl complex **P** from pathway V (Scheme 2) would eliminate the deuterium. For a vinylidene species **M** the same problem would occur, even if **M** would be formed by a 1,2-D-shift and thus keep the deuterium label, it would be finally eliminated during formation of the sp^2-carbon atom of the oxepine system (for example, from **N** to **O**).

As the deuterium was still present in **H**, we could now monitor its way right up to the product **5a**. As expected for a 5-substituted furan, the deuterium was finally eliminated in the aromatization step, thus we decided to use unsubstituted furans, which were known to give a mixture of two regioisomeric phenols, at the 5-position.[1a,b] The deuterated alkyne **6** in the reaction with $AuCl_3$ led to the two phenols **7a** and **7b** (Figure 2). Analysis of the proton NMR spectrum shows that in product **7a**, in which the oxygen atom did not migrate to another carbon atom, the deuterium also maintained its position. More than 90% of the deuterium was retained. Product **7b**, in which the oxygen atom migrated to the carbon atom bearing the deuterium, still possessed 45% of the deuterium, but it had moved to the neighboring carbon atom by a 1,2-shift. So, in the pathway to **7b**, in addition to the simple loss of D^+, a NIH-shift[5] was observed. Encouraged by these results, we decided to deuterate the 5-position of the furan by deprotonation of diethyl acetal-protected

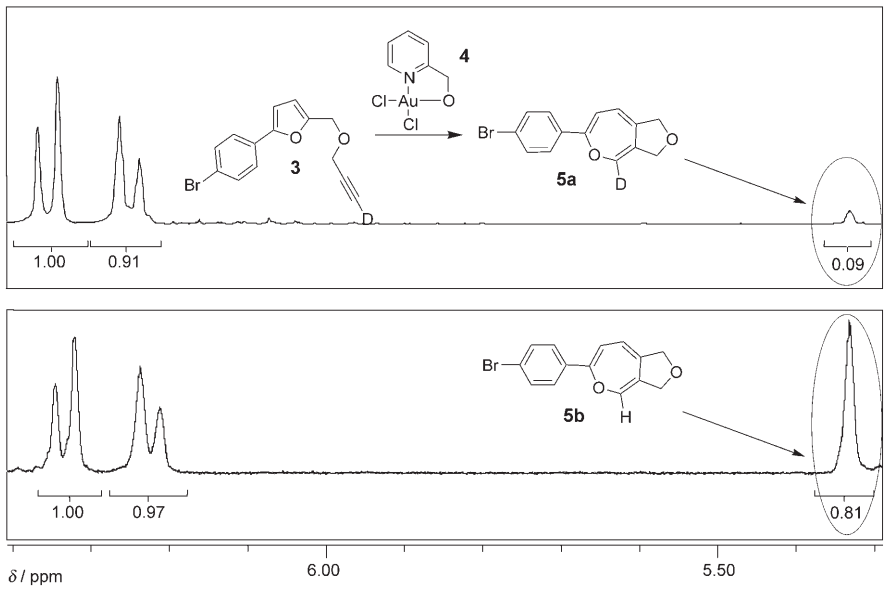

Figure 1. Deuterium at the corresponding oxepine position in **5a**.

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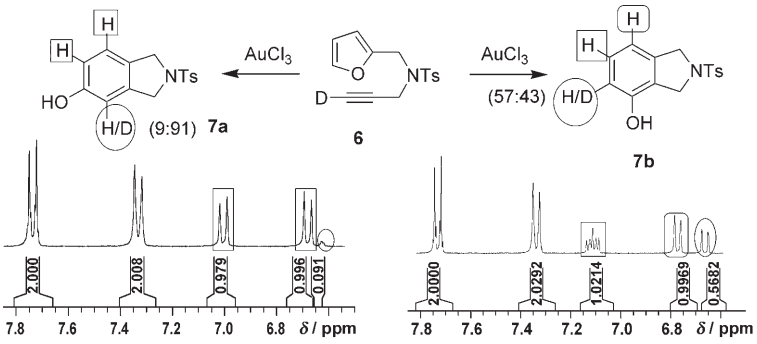


Figure 2. Deuterium distribution in the products obtained from **6**.

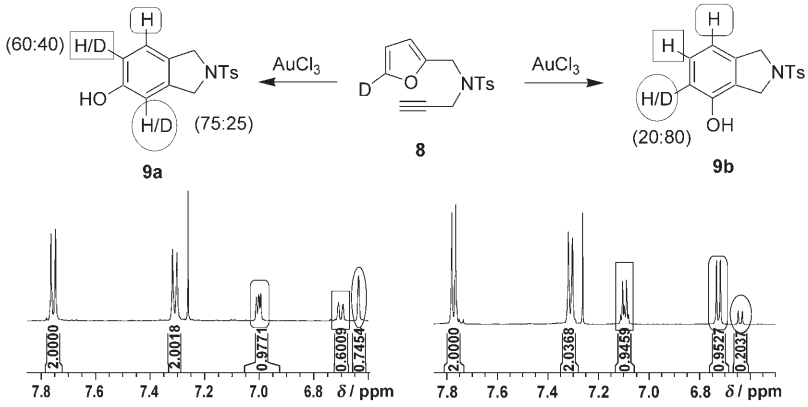
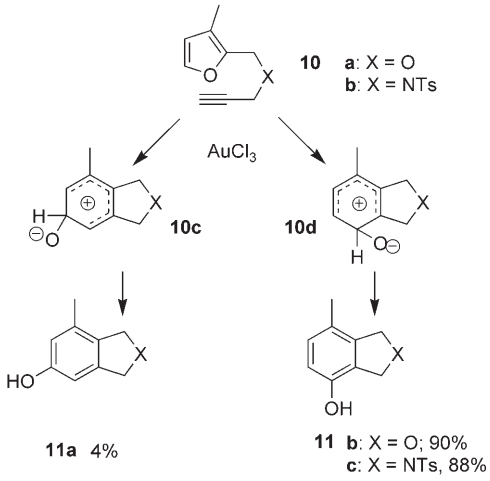


Figure 3. Deuterium distribution in the products obtained from **8**.

furfural with *n*BuLi and quenching with D_2O.[6] Deprotection of the acetal, imine formation with propargylamine, reduction, and tosylation delivered **8**. After gold catalysis, product **9b** (Figure 3) still held 80% of the deuterium, whereas two isotopomers of **9a** with deuteration levels of 40 and 20% were obtained.

These experiments showed that in the second phase of the reaction, the transformation of the arene oxide/oxepine to the phenol, a NIH-shift reaction was involved. As in all substrates, two different NIH-shifts were possible and a direct loss of a proton in general is a third possibility, it was difficult to interpret the product distribution itself. But if one compared the H/D ratios of products **7b** and **9b**, the lower H/D ratios for **9b** should result from an acid-catalyzed isomerization rather than a spontaneous isomerization.[7] It was obvious that the isomerization of the arene oxide to the phenols follows general acid catalysis (the metal might only play a role in Lewis catalysis, but the selectivity is determined by the substrate itself). Indeed, the addition of 5 mol% of *p*TsOH (*p*Ts: *p*-toluenesulfonyl) to the enriched arene oxide **G** (R = methyl) led immediately to the corresponding phenol. Concerning the mechanistic aspects, it is very interesting that product **9a** showed two deuterated positions and, furthermore, the 5-position was strongly favored. If pathway I (Scheme 2) would be passed, intermediate **B** should consequently, in analogy to the NIH-shifts as observed for the deuterium labels (pathway Ia), also transfer the R group by means of Wagner–Meerwein shifts (especially for the easily migrating aryl substituent in **3**, but only phenol **2** (R = 4-bromophenyl) was observed), which would lead to products **M** and **N** in about a 2:1 ratio. As this was not observed at all, the only explanation was that the intermediate Wheland-type arenium ion **B** is not passed before a regioselective formation of the arene oxide occurs, which was only in accord with pathway II. The selectivity of the ring opening of the arene oxide seemed to be determined by the intrinsic stability of the pentadienyl cation formed.

To support this assumption, we investigated the $AuCl_3$-catalyzed reaction of substrate **10a** (Scheme 3), the latter bearing a methyl group at the 3-position but as in **6**, possessing no substituent at the 5-position of the



Scheme 3. Competing pathways for **10a/b**.

furan ring. After column chromatography, 90% of **11b** (X-ray structure:[8] Figure 4) and only 4% of the other regioisomer **11a** [conversion of **10b** (X-ray structure:[8] Figure 4) yielded 88% of **11c** as the only product] could be isolated!

This inversion of the chemoselectivity by introduction of a methyl group far away from the reaction center must be an electronic and not a steric effect, the stabilizing effect of

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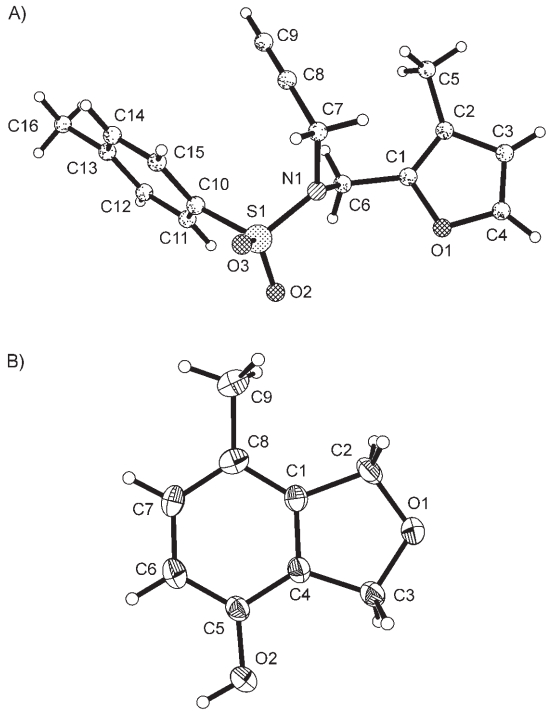


Figure 4. X-ray structures of A) **10b** and B) **11b**.[8]

the methyl group being only effective in the pentadienyl cation **10d** and not in **10c**.

In addition to these experimental results, the energy differences between the two possible intermediates and products (Figure 5, further computational details can be found in the Supporting Information) were quantified by using quantum chemical calculations (HF/6-31G*).[9] Table 1 shows the energy differences between isomeric structures of type I and II for the intermediates and products (Figure 5). The energy differences of the products (ΔE_{pr}) are less than 1 kcal mol^{-1}, while the energy differences of the intermediates (ΔE_{int}) are relatively large, up to 5 kcal mol^{-1} for the methyl-substituted intermediates (Y = CH_3). The intermediate structures of type II are more stable than the intermediate structures of type I. The larger energy difference (ΔE_{int}) for the methyl-substituted compounds (Y = CH_3) as compared to those with Y = H is a result of the charge-stabilizing substituent effect of the CH_3 group in the intermediate structure of type II. The calculated energy difference of the intermediates determines the regioselectivity of the reaction and leads to kinetically controlled product formation. Thus, our calculations support the experimentally observed product ratio, the excess yield of **11b** (Y = CH_3, structure of type II) over **11a**.

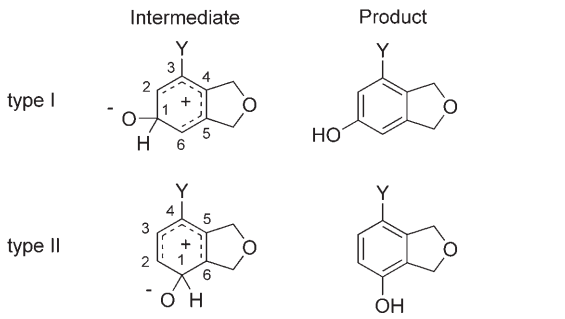


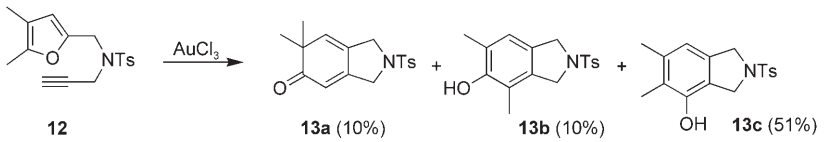
Figure 5. Molecular structures of the intermediates and products (Y = H, CH_3).

Table 1. Comparison of energy differences[a] of the intermediates (ΔE_{int}) and the products (ΔE_{pr}) between structures of type I and II in Figure 5.

	Y = H		Y = CH_3	
	ΔE_{int}[b]	ΔE_{pr}[b]	ΔE_{int}[b]	ΔE_{pr}[b]
gas phase	−2.03 (−1.89)	−0.82 (−0.69)	−5.13 (−4.68)	−0.07 (0.05)
PCM[c]	−0.59 (−0.41)	−0.42 (−0.36)	−4.17 (−3.97)	0.82 (0.93)

[a] Energy differences are shown in kcal mol^{-1}. Relative energies with ZPE corrected are shown in parentheses. [b] $\Delta E = E$(structure of type II) − E(structure of type I). [c] PCM model calculation with $\varepsilon = 78.6$ (water).

As one could argue that a methyl oxirane ring might undergo an oxygen migration rather than a NIH shift of the methyl group, we finally used substrate **12** that contains methyl groups at the 4- and 5-positions of the furan ring (Scheme 4).



12 **13a** (10%) **13b** (10%) **13c** (51%)

Scheme 4. Product distribution in the conversion of **12**.

Here a ring opening of the arene oxide in both directions was observed and for the first opening mode the two possible NIH-shifts of the methyl group led to ketone **13a** (10%) and phenol **13b** (10%) besides the other expected phenol **13c** (51%), which resulted from a ring opening at the higher substituted carbon–oxygen bond (structure determination of **13b**/**13c** is based on HSQC-, HMQC- and ROESY-NMR spectra). In addition, the crystal structures of the penta-substituted phenol **13c** and the ketone **13a** (Figure 6A and B, respectively)[8] could be determined.

Having learned all this, in a retrospective view even product **15b** as a side product in the Jungianol synthesis[1d] could be explained by this theory—there the electron-withdrawing substituent in the tether destabilized the usually formed pentadienyl cation and induced a less-selective ring opening of the arene oxide in both directions and a subsequent NIH-shift of the methyl group in the reaction leading to **15b** (Scheme 5).

Finally, our interest focused on the influence of a sterically demanding substituent at the propargylic position of the starting material. Conversion of substrate **16** (Scheme 6)

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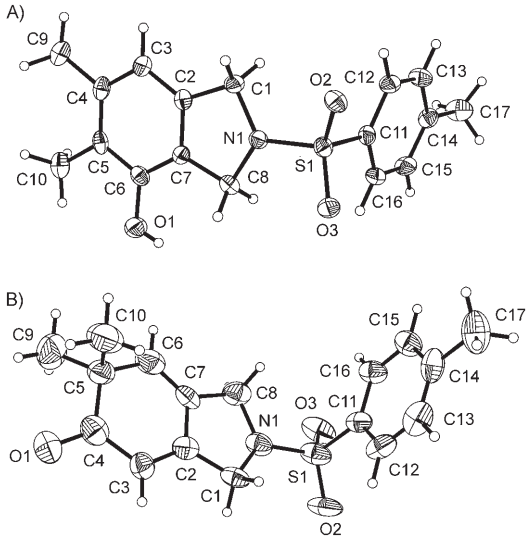
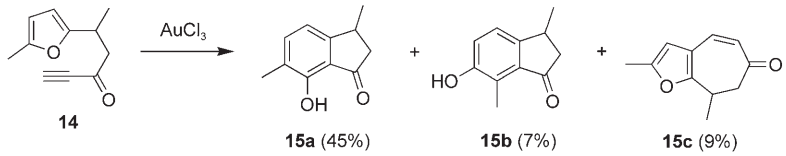
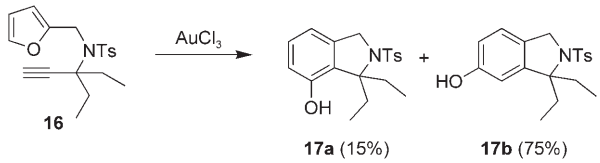


Figure 6. X-ray structures of A) **13c** and B) **13a**.[8]

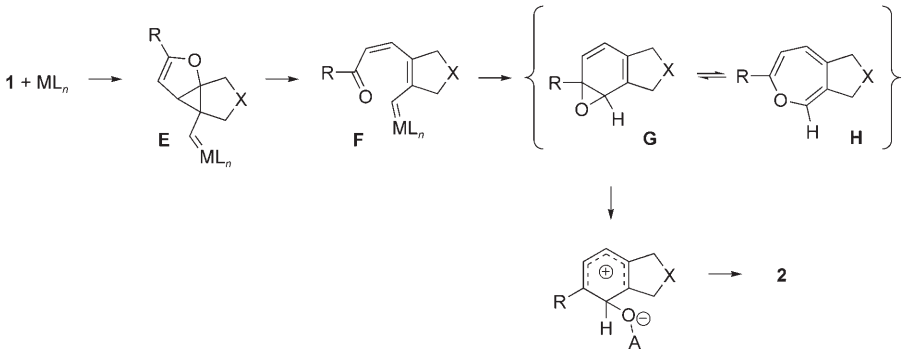
shifted the product distribution from the 1:1.6 ratio observed with the substrate lacking the diethyl substitution to a 1:4 ratio of **17a**/**17b**, controlled by ring opening to the pentadienyl-cation with decreased steric interaction.



Scheme 5. Product distribution in the key step of the Jungianol synthesis.



Scheme 6. Influencing the product distribution by steric interactions.



Scheme 7. Pathway supported by the experimental findings (A = Lewis or Brønsted acid). The intrinsic stability of the cation determines the regioselectivity of the epoxide ring opening and, therefore, the product selectivity.

All these results are in accordance with the mechanism depicted in Scheme 7.

Conclusion

Overall, we could provide a direct experimental proof that the reaction does not proceed via an alkynyl or a vinylidene complex. Furthermore, the observed distribution of deuterium labels or aryl substituents is in accord with the pentadienyl cation formed only after the arene oxide/oxepine intermediate and not before (see pathway I; Scheme 2); the selectivity is intrinsic to the substrate and not to the Lewis/Brønsted acid catalyst, the ring opening leading to the more stable pentadienyl cation being preferred.

Acknowledgement

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