Reactive Intermediates

Gold Catalysis: Proof of Arene Oxides as Intermediates in the Phenol Synthesis**

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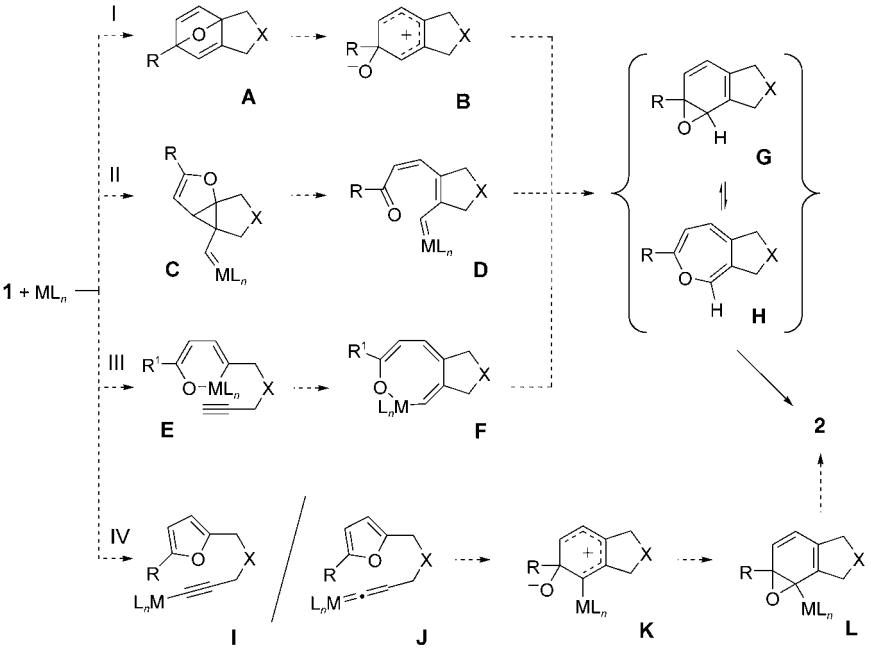
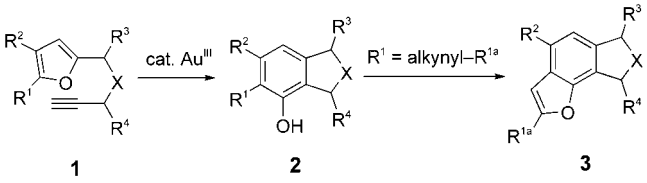
The gold-catalyzed synthesis of highly substituted arenes **2** or benzofurans **3** from furans **1** has proved to be a powerful tool for organic synthesis (Scheme 1).[1] As reported previously, a number of other transition metals with a d^8 configuration also catalyze this transformation,[1b,2] but all are significantly less active than gold(III).[1b] We had obtained experimental evidence for an intramolecular migration of the furan oxygen atom (which becomes the phenol oxygen atom).[1a] Such a 1,2-transposition suggested the intermediacy of an arene oxide, but in our initial publication we only dared to propose a simple, organic-type mechanism (pathway I via **A** and **B**, Scheme 2).[1a]

Subsequently, Echavarren and co-workers conducted theoretical studies in which they compared pathways I and II (Scheme 2). According to their calculations, pathway II is favored, and side products observed in Pt^{II}-catalyzed reactions would also correspond to the hydrolysis of intermediate **D** of pathway II.[2] However, such side products do not necessarily stem from the catalytic cycle but can be generated in a competing side reaction. Furthermore, the gold-catalyzed reactions were highly selective, and such side products were never observed. Other conceivable pathways would proceed through alkynyl or vinylidene complexes (**I** or **J**, pathway IV), or, if the d^8 precatalyst was reduced in situ, the insertion of a d^{10} species into the $C(sp^2)$–O bond (as in the Felkin/Wenkert reaction;[3] pathway III), followed by insertion of the alkyne to give **F**.



Scheme 2. Possible pathways for the transformation of **1** into **2**.



Scheme 1. The gold-catalyzed phenol synthesis. R^1–R^4 = alkyl, aryl, alkynyl; X = CR^5_2, NR^5, O (three atoms in the linker), $-CR^5_2NR^6-$ (four atoms in the linker).

Herein we describe how the arene oxides/oxepins **G**/**H** can be enriched and detected readily in the reaction mixture after modification of the energy profile of the reaction by variation of the ligand in the gold complex. Our efforts to gain further experimental mechanistic insight formed the starting point of these studies. Even experiments with substoichiometric amounts of $AuCl_3$ (30 mol%) led to no detectable concentration of an intermediate. When a mixture at −20 °C of $AuCl_3$ (5 mol%) and the substrate was warmed up gradually, either no reaction was observed by ^{1}H NMR spectroscopy, or the slow formation of **2** at 0 °C. The breaking of four bonds and the formation of four new bonds during the reaction is clearly not a single-transition-state elementary reaction, and thus the failure to detect any intermediates with $AuCl_3$ simply meant that the first step was the rate-limiting step. If the reaction proceeded by pathway IV, a primary kinetic isotope effect should be observable with **1** deuterated at the alkyne, but this effect was not observed.

To detect intermediates, it is necessary to change the energy profile of the whole reaction; a later step must have

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[**] This work was supported by the Fonds der Chemischen Industrie, in particular through a Chemiefonds-Doktoranden-Stipendium to J.P.W., and by the AURICAT EU-RTN (HPRN-CT-2002-00174).

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

  DOI: 10.1002/anie.200462672

the highest energy of activation. When we used **1a** (R^1 = Me, R^2–R^4 = H, X = NTs; Ts = *p*-toluenesulfonyl) and the complex **4**[4] (X-ray crystal structure shown in Figure 1),[5] we indeed observed an additional species **5a**/**6a** (Figure 2).

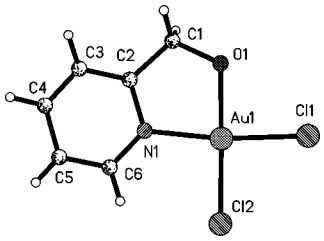


Figure 1. Crystal structure of **4**.

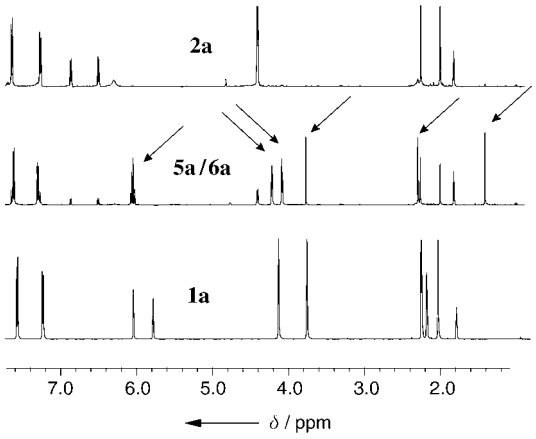


Figure 2. ^{1}H NMR spectrum of the transient species.

Under optimized conditions, **5a**/**6a** can be enriched to account for 80% of the material in the reaction mixture at room temperature (Figure 3) and shows long-term stability when cooled to −20°C. At room temperature **5a**/**6a** converts directly into **2a** (Scheme 3).

Two-dimensional NMR spectroscopy (H,H-COSY, HMQC) of the reaction mixture at −20°C strongly pointed towards the presence of an arene oxide structure **5a**. The direct isolation of **5a** failed, as the compound always

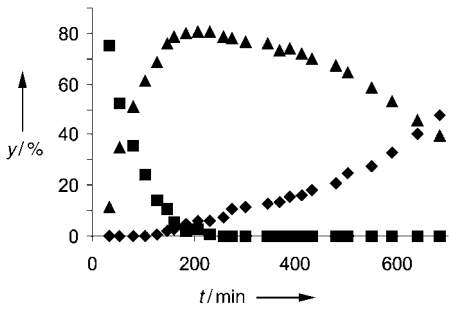
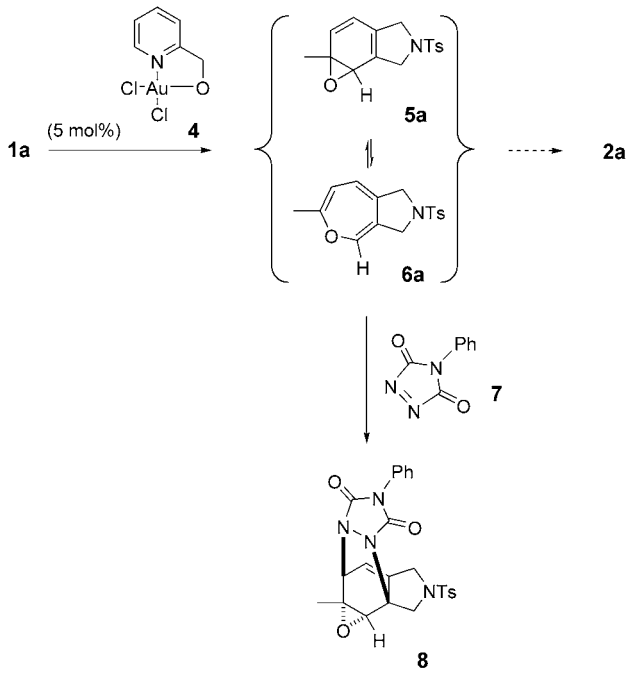


Figure 3. The amount *y* of the transient species as a percentage of the material present in the reaction mixture is plotted against time. The transient species can be accumulated to 80%. ◆ **2a**, ■ **1a**, ▲ **5a**/**6a**.



Scheme 3. Diels–Alder reaction of the transient species.

rearranged to **2a**. From the literature it was known that the 1,3-diene substructure of arene oxides can undergo Diels–Alder reactions with dienophiles such as **7** to provide stable derivatives.[6] By following this concept, **8** was isolated as a single diastereomer and could even be characterized by X-ray crystal-structure analysis (Scheme 3, Figure 4).[5]

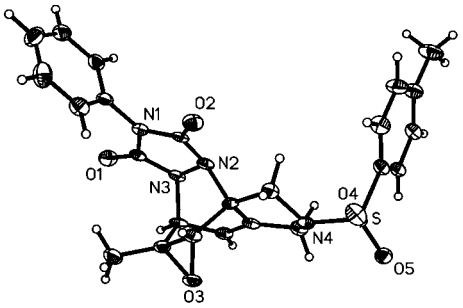
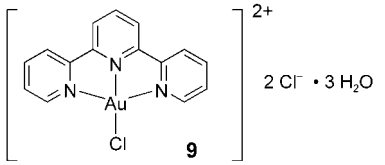
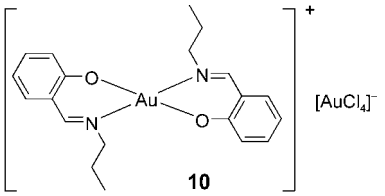


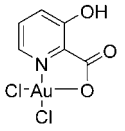
Figure 4. Crystal structure of **8**.

When other complexes, such as **9**,[7] **10**[8] (X-ray crystal structure shown in Figure 5),[5] **11**,[8] and even $PtCl_2$ or $[\{(cod)IrCl\}_2]$ (cod = cyclooctadiene), were used, small transient peaks of **5a** were also observed in the ^{1}H NMR spectra recorded during the reaction.

It is clear that **2a** is much lower in energy than **1a**. Density functional calculations (B3LYP/6-31G** including zero-point-energy (ZPE) correction) showed that even **5a** and **6a** are both 19 kcal mol^{-1} lower in energy than **1a**, and the reaction to give **2a** then sets free another 42 kcal mol^{-1}. On the other hand, the experimentally observed relative energies of **5a** and **6a** could not be reproduced at this level of theory: In the NMR spectra, the signals for the diastereotopic hydrogen atoms of both CH_2 groups adjacent to the tosyl-







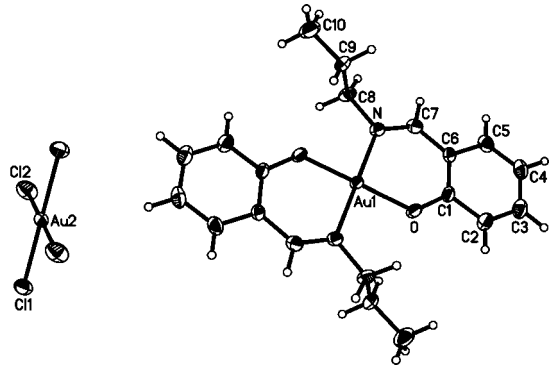


Figure 5. Crystal strucuture of **10**.

amide group suggest that **5a** is lower in energy than **6a** and that a possible equilibrium with low concentrations of **6a** must be slow on the NMR timescale; however, calculations with different basis sets (B3LYP/6-31G**, BLYP/6-31G**, or LMP2/6-31G**, each including ZPE correction) gave identical energies within the error of the method (a difference of less than 1 kcal mol^{-1}).[9,10]

Further support for an arene oxide structure was provided by the following characteristic ^{1}H NMR and ^{13}C NMR spectroscopic data, which are in good agreement with literature values for a substituted epoxide: The signal for the hydrogen atom on the epoxide is a singlet at $\delta =$ 3.87 ppm[11] with $^1J_{CH} = 184$ Hz;[12] the tertiary and quaternary carbon atoms of the oxirane ring give rise to signals at $\delta = 66.1$ and 69.5 ppm, respectively;[13] the signal for the hydrogen atoms on the methyl group is shifted to high field at $\delta =$ 1.52 ppm, thus indicating an sp^3-hybridized neighboring group.

Under the reaction conditions **5a** does not undergo interconversion into other constitutionally isomeric arene oxides, as is known from the "oxygen walk"[14] in the NIH shift reaction.[15] The possibility of enriching the intermediate seems to be quite general; other substrates, such as **2b** ($R^1 =$ mesityl, R^2–$R^4 =$ H, X = NTs), **2c** ($R^1 =$ Me, R^2–$R^4 =$ H, X = NNs; Ns = nosyl), **2d** ($R^1 =$ Me, R^2–$R^4 =$ H, X = O), **2e** ($R^1 =$ 4-Br-Ph, R^2–$R^4 =$ H, X = O), and **2f** ($R^1 =$ Me, R^2–$R^4 =$ H, X = $^-$CH(CH$_2$O–allyl)O$^-$) show the same chemical behavior.

In conclusion, we have provided the first direct experimental evidence for the formation of **2** via **5**. The lack of a primary kinetic isotope effect in the $AuCl_3$-catalyzed reactions is an argument against pathway IV, by which, furthermore, the isomerization of the metalated arene oxide **L** to the phenolate should be faster than a possible protodemetalation of **L**. Thus, of the many conceivable pathways, only those that proceed via **5**, such as pathways I–III, can be responsible for product formation. With a workup appropriate to the sensitivity of **5**, complex **4** might open a new entry to the entire chemistry[11] of **5** from simple, readily available starting materials. A further modification of the energy profile of the reaction by ligand variation might reveal even more details of the reaction mechanism.

Experimental Section

Synthesis of **8**: **1a** (45.0 mg, 150 μmol) was dissolved in CD_3CN, and **4** (2.70 mg, 7.50 μmol, 5 mol %) was added. The reaction was monitored at room temperature by NMR spectroscopy. After five hours, the solution was cooled to −40 °C, and **7** (26.4 mg, 150 μmol) was added. The red solution was stored in the freezer at −25 °C for four days; during this time it became colorless. After column chromatography of the crude material (petroleum ether/ethyl acetate (PE/EA) 3:1), **8** (31.3 mg, 44 % from **1a**) was obtained as a colorless solid. m.p. 158 °C; R_f (PE/EA 2:1): 0.23; ^{1}H NMR (500 MHz, CD_2Cl_2): $\delta = 1.55$ (s, 3H), 2.38 (s, 3H), 3.32 (s, 1H), 3.55 (d, $^2J = 11.6$ Hz, 1H), 3.70 (dd, $^2J =$ 14.6 Hz, 2.5 Hz, 1H), 4.00 (dd, $^2J = 14.6$ Hz, $^4J = 2.0$ Hz, 1H), 4.81 (d, $^2J = 11.6$ Hz, 1H), 4.92 (d, $^3J = 5.9$ Hz, 1H), 5.96 (dt, $^3J = 5.9$ Hz, $^4J =$ 2.25 Hz,[a] 1H), 7.32–7.36 (m, 5H), 7.40–7.43 (m, 2H), 7.68 ppm (d, $^3J = 8.2$ Hz, 2H); [a] only a mean coupling constant could be determined; ^{13}C NMR (126 MHz, CD_2Cl_2): $\delta = 16.35$ (q), 21.69 (q), 49.12 (t), 51.22 (d), 51.59 (t), 52.09 (q), 59.39 (d), 71.07 (s), 116.35 (d), 125.97 (d, 2C), 128.41 (d, 2C), 128.81 (d), 129.36 (d, 2C), 130.28 (d, 2C), 131.57 (s), 132.37 (s), 138.96 (s), 144.96 (s), 154.64 (s), 155.36 ppm (s); IR (neat): $\tilde{\nu} = 1767$, 1710, 1596, 1497, 1415, 1361, 1319, 1248, 1161, 1095, 1076, 1063, 1025, 993, 811, 782, 760, 712, 693, 666 cm^{-1}; MS (FAB(+), 3-nitrobenzyl alcohol): *m/z*: 479 $[M+H]^+$; MS (EI(−), 70 eV): *m/z* (%): 177 (42), 119 (64), 91 (100), 65 (22); $C_{24}H_{22}N_4O_5S$ (478.52).

Received: November 19, 2004
Revised: January 19, 2005
Published online: March 30, 2005

Keywords: arene oxides · density functional calculations · gold · homogeneous catalysis · N ligands

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