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Gold catalysis: Experimental mechanistic insights into the anellation of phenols with 1,3-dienes

Sarah Bay [a], Alexandra Englert [a], Kumara Swamy Nalivela [a], A. Stephen K. Hashmi [a, b, *], Mie Højer Larsen [a, *]

[a] Organisch-Chemisches Institut, Universität Heidelberg, Im Neuenheimer Feld 270, 69120 Heidelberg, Germany
[b] Chemistry Department, Faculty of Science, King Abdulaziz University, Jeddah 21589, Saudi Arabia

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ABSTRACT

An intermediate of the anellation reaction of phenols and 1,3-dienes could be detected, isolated and characterized as the hydroarylation product. The other conceivable intermediate, the hydroaryloxylation product, was prepared *via* Pd-catalysis and converted under the conditions of the gold catalysis, too. Under exactly the same conditions a very fast Claisen rearrangement took place delivering the formal hydroarylation product as well. After this fast *intermolecular* formation of the intermediate (formed either directly *via* the hydroarylation pathway or *via* a hydroaryloxylation/Claisen rearrangement sequence) the subsequent *intramolecular* reaction leading to the product turned out to be significantly slower. The major product is the *cis*-diastereomer (*cis*-**3**/*trans*-**3** = 12:1).

1. Introduction

Since 2000 the exponential growth of homogeneous gold catalysis [1] is based on the development of many new synthetic methods. In the recent past this innovative methodology increasingly has been applied in total synthesis [2]. On the other hand, the experimental insight into the detailed mechanism of many of these reactions is still limited [3].

While alkynes, allenes and alkenes have been studied in some detail, 1,3-dienes have been used in homogeneous gold catalysis in only a few examples [4]. Thus experimental studies of the reaction mechanisms of this class of unsaturated substrates are scarce, an important theoretical study has just been highlighted [5]. Most of the gold-catalyzed conversions of 1,3-dienes either involve C–X bond formation *or* a C–C bond formation. The only gold-catalyzed reactions of 1,3-dienes involving both a C–X *and* a C–C bond formation is the anellation of phenols **1** with cyclic, cisoid dienes **2** developed by C.-J. Li et al. (Scheme 1) [4a].

With regard to the mechanism, this raises an interesting question. The formation of the product **3** obviously involves two gold-catalyzed steps, one hydroaryloxylation [6] and one hydroarylation [7] of the double bonds of the diene. But it is unknown whether the first step is an intermolecular hydroarylation and the second step an intramolecular hydroaryloxylation or, as the authors state, “alternatively, the same process can occur in the reverse order: intermolecular allylation on oxygen followed by intramolecular hydroarylation” [4a].

For the future exploitation of 1,3-dienes as interesting building blocks for gold catalysis, we now investigated their intrinsic reactivity with the ambident nucleophile phenol in detail. Here we report our results on the chemoselectivity of the 1,3-diene **2** in the anellation reaction.

2. Results and discussion

In addition to the published $AuCl_3$/3AgOTf catalyst system, we first tested the IPrAuCl/AgOTf catalyst, too. No NHC ligand had been included in the catalyst screening of the initial investigation [4a], but the best results were still obtained with the published 2.5 mol%

* Corresponding authors. Organisch-Chemisches Institut, Universität Heidelberg, Im Neuenheimer Feld 270, 69120 Heidelberg, Germany.
E-mail addresses: hashmi@hashmi.de (A.S.K. Hashmi), mhv@kiku.dk (M.H. Larsen).

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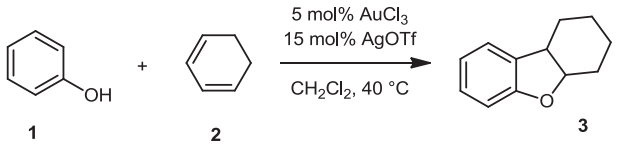
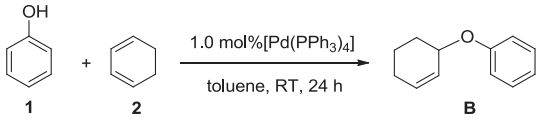
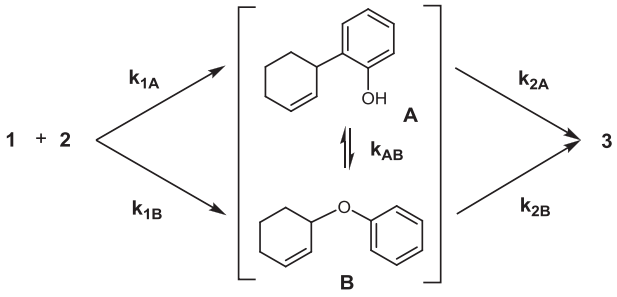


Scheme 1. Li's anellation method.



Scheme 3. Synthesis of the possible intermediate **B** by an "orthogonal" palladium(0)-catalyzed route.



Scheme 2. Different pathways may deliver the product **3**.

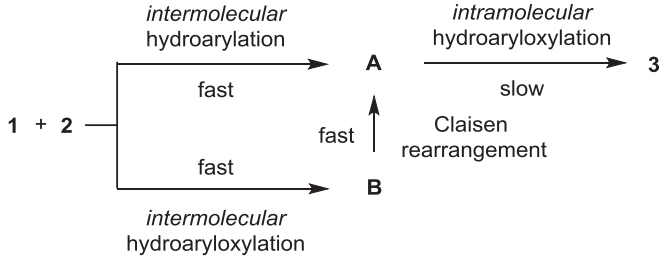
Table 1
GC–MS monitoring of the gold-catalyzed conversion of **1** and **2**.

Entry	Temperature	Time	GC–MS
1	0 °C	30 min	No conversion
2	0 °C	60 min	No conversion
3	30 °C	30 min	**3** (t_R = 11.13 min) **X** (t_R = 11.83 min)

Table 2
Retention times of **A**, **B** and **3**.

Compound	t_R [min][a]	Molecular Mass by GC–MS [g/mol]
A	11.83	174.1
B	11.02	174.1
3	11.13	174.1

[a] GC–MS: agilent, MSD: 5975C, GC: 7890A; column: HP5, carrier gas: helium; 60 °C, 15 min, 20 °C/min, 250 °C.



Scheme 4. Possible reaction pathways.

$AuCl_3$/7.5 mol% AgOTf and like with phosphane gold(I) complexes, with the NHC ligand no conversion was observed. Control experiments with triflic acid, which potentially could be formed under the reaction conditions [8], gave only polymeric material.

Then we turned to the details of the reaction. Depending on the reaction pathway, two different intermediates are conceivable (Scheme 2). Either the initial step is the hydroarylation, then **3** would be formed *via* intermediate **A**. Or the initial step is the hydroaryloxylation, then **B** would be the intermediate. If the barriers of activation for the rate-limiting step of both pathways would be similar, both pathways would contribute to the product formation. In addition a Claisen type rearrangement between **A** and **B** must be considered. A fast Au(III)-catalyzed Claisen rearrangement has already been observed with a closely related system [9,10].

Different efforts to identify any intermediates by GC–MS are shown in Table 1 (due to a strong signal overlap, in situ ^{1}H NMR spectroscopy could not be used). At 0 °C no conversion is observed (entries 1 and 2). At 30 °C after 30 min both the product **3** (t_R = 11.13 min, *m/z* = 174.1 $[M]^{+\cdot}$), as well as a second compound **X** with the identical molecular mass (t_R = 11.83 min, *m/z* = 174.1 $[M]^{+\cdot}$) could be detected. Monitoring the reaction at 30 °C shows that initially the portion of that second compound is higher, with increasing conversion that species is consumed and the portion of **3** increases. This indicated that the new compound is one of the two conceivable intermediates.

By separating **X** from the crude reaction mixture after short reaction times and stopping the catalysis reaction by the addition of 2.5 mol% triethylamine, indeed 15% of **X** could be obtained and a full characterization was possible. It clearly indicated that **X** is the intermediate **A**. Only four arene protons are detectable in the ^{1}H NMR, only four CH in the ^{13}C NMR; NMR clearly shows only one olefin in the product. IR shows the phenolic hydroxyl group.

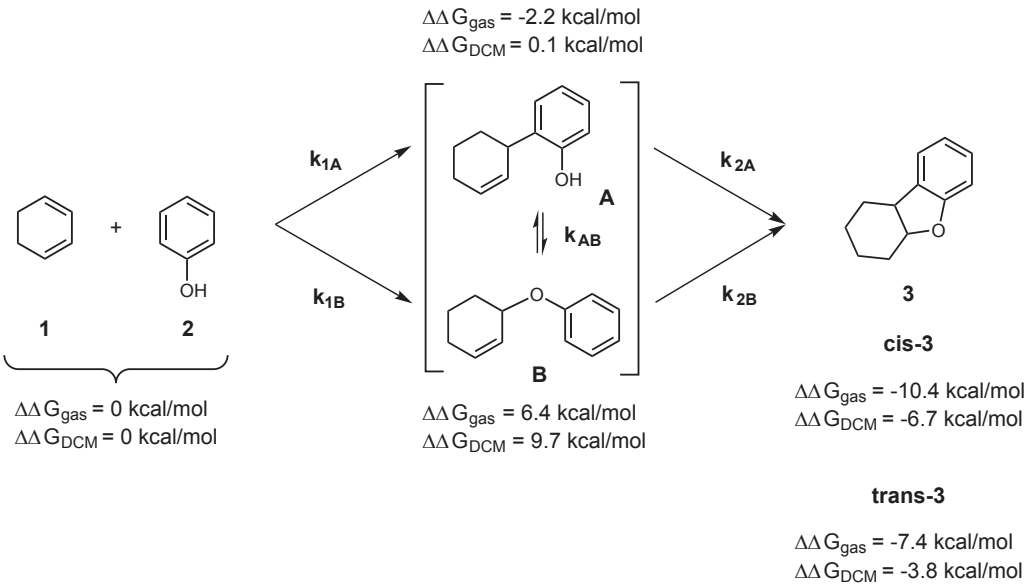
When **A** was subjected to the catalyst, product **3** was formed selectively, and the dominating diastereomer was *cis*-**3** (*cis*-**3**/*trans*-**3** = 12:1 for both the conversion of the mixture of **1** and **2** and for the conversion of **A**).

At this point it was clear that **A** was involved in the formation of **3**. The observation of **A** only meant that $k_{1A} > k_{2A}$, which causes the build-up of a stationary concentration of **A** during the conversion. Not detecting **B** might mean that $k_{1B} << k_{2B}$. This would prevent a detectable stationary concentration of **B**. If in addition $k_{1B} > k_{1A}$, most of **3** could still be formed *via* **B**. Furthermore, an equilibrium between **A** and **B** could deliver the same intermediate **A** *via* an addition/rearrangement pathway.

Thus, in order to investigate the possible participation of **B** in detail, we prepared **B** by a palladium-catalyzed route according to Kawatsura and Hartwig [11]. A palladium(0)-catalyzed hydroaryloxylation of **2** delivers **B** (Scheme 3). This once more demonstrates the difference in reactivity of the d^{10} systems palladium(0) and gold(I) [12].

An initial measurement of the individual retention times of **A**, **B** and **3** (Table 2) shows that no signal overlap is responsible for the failure to detect **B** in the crude reaction mixture.

Then we subjected **B** to the catalyst $AuCl_3$/3AgOTf (same catalyst loading as shown in Scheme 1) monitoring the reaction by gas chromatography. Within less than a minute **B** was completely consumed and only intermediate **A** was detected. At this early stage of the reaction no product was found. This indeed demonstrates that the Claisen rearrangement from **B** to **A** is a very fast process even at room temperature. As expected after longer reaction times intermediate **A** was then converted to the final product.



Scheme 5. Computed relative energies of the different species involved.

In this context, it is also important to look at the relative energy of the species involved. This was addressed by a computational study. Scheme 4 shows these relative energies for both the gas phase and in DCM (B3LYP/cc-pVDZ level, solvation as single point calculation using the SMD model with dichloromethane as the solvent at the reaction temperature, 40 °C). Looking at the two diastereomers of the product, it becomes evident that *cis*-**3** is the thermodynamic product of the reaction. The intermediate **B** clearly is higher in energy than the starting materials, while **A** is almost at the energy of the starting materials.

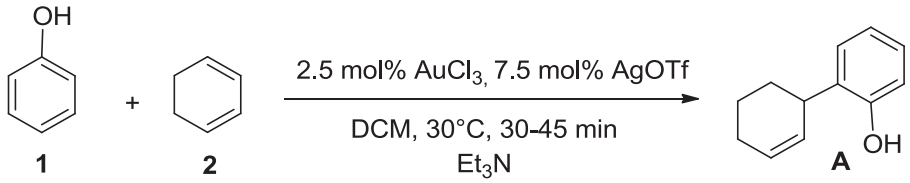
3. Conclusions

Overall, with that experimental data still two pathways have to be considered (Scheme 5). Pathway 1 consists of an intermolecular hydroarylation/intramolecular hydroaryloxylation sequence, while pathway 2 comprises a three step sequence namely intermolecular hydroaryloxylation/Claisen rearrangement/intramolecular hydroaryloxylation. It is noteworthy that the first intermolecular step is faster than the final intramolecular step towards the product. This can either be explained by the higher reactivity of the diene system compared to the alkene intermediate or the hydroarylation is always a faster process than a hydroaryloxylation process which could be the case if the reaction would proceed *via* pathway 1.

4. Experimental section

The assignment of the ^{13}C NMR signals is based on DEPT135 and HSQC spectra.

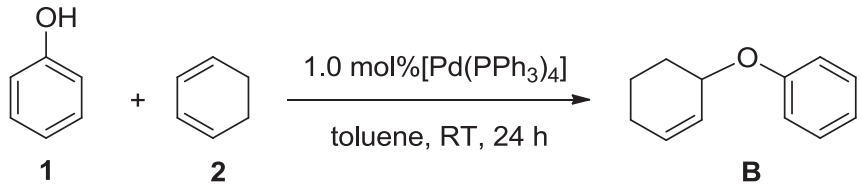
1. Gold-catalyzed synthesis of 3-(2-hydroxyphenyl)cyclohexene (**A**)



In a dry Schlek flask under an atmosphere of dinitrogen 300 mg (3.20 mmol) phenol **1** and 250 mg (3.20 mmol) 1,3-cyclohexadiene **2** were added to a stirred mixture of 24.0 mg (80.0 μmol) $AuCl_3$ and 60.0 mg (200 mmol) AgOTf in 1.5 mL dry DCM. The mixture is warmed to 30 °C. After 30–45 min the catalysis is stopped by the addition of triethylamine. The crude mixture is filtered over celite and purified by column chromatography (SiO_2, petroleum ether/ethyl acetate 200:1). The product **A** could be obtained as a colorless liquid (86.0 mg, 15%).

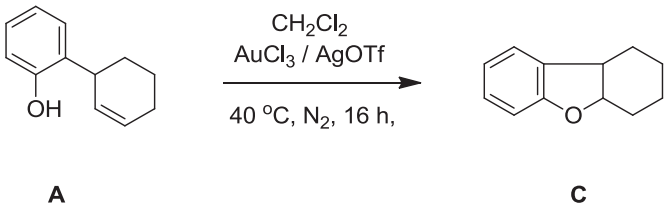
R_f (petroleum ether/ethyl acetate 200:1) = 0.5; ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.36–2.24 (m, 6H), 3.60 (m, 1H), 5.32 (s, 1H), 5.97 (m, 2H), 6.73–7.16 (m, 4H); ^{13}C NMR (CD_2Cl_2, 75 MHz): δ = 22.32 (CH_2), 25.94 (CH_2), 30.96 (CH_2), 38.36 (CH), 116.8 (CH), 121.4 (CH), 128.3 (C_{quart}), 130.3 (CH), 130.6 (CH), 131.4 (CH), 132.3 (CH), 154.9 (s); GC–MS: t_R = 11.83 min, *m/z* = 174.1 $[M]^*$, 159.0, 145.0, 131.0, 115.0, 97.0, 84.0, 70.1, 51.0; MS (EI^+, 70 eV): *m/z* (%) = 174 (100.0) $[M^+]$, 159 (26), 145 (49), 131 (35), 120 (42), 107 (22), 91 (12); HRMS (EI^+, 70 eV): $[C_{12}H_{14}O]$: calcd. 174.1045, found 174.1034; IR (film, cm^{-1}): $\tilde{\nu}$ = 3464, 3020, 2927, 2857, 2109, 1647, 1488, 1453, 1265, 1218, 1095, 1046, 881, 817, 754, 740, 706, 664, 413. The data correspond to the data in Ref. [13].

2. Synthesis of cyclohex-2-enylphenylether (**B**)



In a dry Schlenk flask under an atmosphere of dinitrogen $Pd(PPh_3)_4$ (62.0 mg, 53.6 μmol) in 3 mL of dry toluene are stirred under an atmosphere of dinitrogen 500 mg (5.31 mmol) anhydrous phenol and 1.70 g (21.2 mmol) 1,3-cyclohexadiene are added. The mixture is stirred for 2 d at room temperature. Then GC–MS does not show any more 1,3-cyclohexadiene. The solvent is removed in vacuo and the residue is purified by column chromatography (SiO_2, petroleum ether/ethyl acetate 300:1) yielding a colorless oil (301 mg, 33%). ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.51–2.68 (m, 1H), 1.70–2.17 (m, 5H), 4.66–4.81 (m, 1H), 5.78–5.85 (m, 1H), 5.87–5.96 (m, 1H), 6.78 6.94 (m, 3H), 7.17–7.25 (m, 2H). The ^1H NMR spectrum is in accordance with previous reports for this compound [11].

3. Synthesis of 1,2,3,4,4a,9b-hexahydro-dibenzofuran (**C**)



A solution of $AuCl_3$ (3.45 mg, 0.011 mmol) and AgOTf (8.82 mg, 0.034 mmol) was stirred in dry CH_2Cl_2 (1.0 mL) at room temperature for 2 h under N_2 atmosphere. Cyclohexene **A** (40 mg, 0.23 mmol) was added in dry CH_2Cl_2 (1.0 mL) and the resulting solution was stirred for 16 h at 40 °C under an atmosphere of dinitrogen. The crude reaction mixture was filtered through celite and purified by column chromatography on silica gel (ethyl acetate: petroleum = 0.1: 100) to afford the product **C** (0.03 g, 75%) as a colorless oil.

The ratio of the two diastereoisomers of **C** is 12: 1 = *syn*: *anti*. (assignment of the major diastereomer by NOESY):

syn-Isomer: ^1H NMR ($CDCl_3$, 600 MHz): δ = 1.53–2.02 (m, 8H), 3.21 (q, J = 7.2 Hz, 1H), 4.70 (q, J = 5.2 Hz, 1H), 6.83–7.16 (m, 4H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ = 20.5 (s), 22.0 (s), 27.5 (s), 28.2 (s), 40.6 (s), 82.5 (s), 110.0 (s), 120.4 (s), 123.5 (s), 127.7 (s), 133.4 (s), 159.4 (s); ^1H NMR (CD_2Cl_2, 300 MHz): δ = 1.21–2.29 (m, 6H), 4.79 (m, 1H), 5.85 (m, 1H), 5.96 (ddt, J = 3.0 Hz, 4.5 Hz, 9.0 Hz, 1H), 6.91 (m, 3H), 7.26 (m, 2H).

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jorganchem.2015.05.034.

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