Gold Catalysis

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Gold-Catalyzed Benzylic C–H Activation at Room Temperature**

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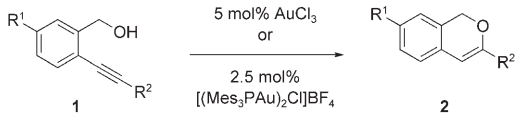
Catalytic C–H activation by metal complexes is a hot topic in organic chemistry and of growing importance for organic synthesis.[1] Only in the last few years has gold been recognized to be active in C–H activation.[2] We reported gold-catalyzed hydroarylation reactions,[3] He et al. proved that with electron-rich arenes these reactions can proceed by initial aryl-C–H activation,[4] and Li also suggested a C–H activation step for the additions of β-diketones to reactive alkenes.[5] The most remarkable gold-catalyzed activation of an unactivated C(sp^3)–H bond was achieved by Periana et al., who oxidized methane to methanol in concentrated sulfuric acid with selenic acid as the oxidizing reagent at 180 °C with a turnover number of 30. DFT studies indicated that cationic gold(I) and gold(III) species are able to mediate electrophilic C–H bond activation.[6] Here we report a gold-catalyzed C–H activation at a benzylic position that takes place in a neutral solvent at room temperature.

The starting point for our studies was the gold-catalyzed conversion of substrates **1**, which were easily available by Sonogashira coupling of 2-iodobenzyl alcohols. In a highly selective conversion (monitored by ^{1}H NMR spectroscopy) **1** (R^2 = alkyl, phenyl) underwent the expected 6-*endo*-dig cyclization to give isochromene derivatives **2** (Scheme 1, Table 1). Yamamoto et al. reported that related gold-catalyzed ring closures with carbonyl groups instead of hydroxy groups leads to carbonyl ylides.[7] We observed no reaction when R^2 = trimethylsilyl (TMS), hydrogen, or alkynyl (**1d**, **1e**, and **1f**, respectively).

Since products **2** are very sensitive, the yields were diminished and **2** could also not be stored for extended periods. Table 2 shows that when $AuCl_3$ served as catalyst, the initially obtained **2** undergoes significant decomposition (**2a** and **2c**) or conversion was low (**2b**, 55% of the substrate was recovered). In contrast, the Au^I catalyst[8] led to good conversion and good yields when the substituent R was sterically shielding (**2b** and **2c** but not **2a**).

When the substrates bore additional nucleophilic groups like ester or amide functionalities (**1g**–**1k**), not only product **2** but also the unexpected dimer **3** was obtained with both the gold(I) and the gold(III) catalyst (Table 2). The eight (!) new bonds formed in this unprecedented dimerization are shown in bold (Scheme 2).

The structure eludication of the products **3** was quite difficult, and efforts to obtain single crystals failed even for the nitroaryl compound **3k**. Mass spectrometry showed **3** to be a dimer of substrate **1**. A combination of ^{1}H NMR, ^{13}C NMR, H,H-COSY, and HMBC spectra finally made an unambiguous assignment possible.[9] The good solubility,



Scheme 1. Gold-catalyzed conversion of **1** into **2**. Mes = 2,4,6-trimethylphenyl.

Table 1: Conversion of substrates **1** into products **2** (R^1 = H).

1	Catalyst	Conv. to 2 [%][a]	Yield of 2 [%]
1a, R^2 = *n*Pr	$AuCl_3$[b]	95	27
	$[(Mes_3PAu)_2Cl]BF_4$	n.d.[c]	31
1b, R^2 = Ph	$AuCl_3$[d]	40	36
	$[(Mes_3PAu)_2Cl]BF_4$[e]	n.d.[c]	75
1c, R^2 = *t*Bu	$AuCl_3$	87	24
	$[(Mes_3PAu)_2Cl]BF_4$	n.d.[c]	95
1d, R^2 = TMS	$AuCl_3$	–	–
	$[(Mes_3PAu)_2Cl]BF_4$	–	–
1e, R^2 = H	$AuCl_3$	–	–
	$[(Mes_3PAu)_2Cl]BF_4$	–	–
1f, R^2 = ethynyl(2-hydroxymethylphenyl)	$AuCl_3$	–	–
	$[(Mes_3PAu)_2Cl]BF_4$	–	–

[a] Determined by ^{1}H NMR spectroscopy. [b] 4.3 mol% catalyst. [c] Not determined. [d] 7.5 mol% catalyst [e] 5 mol% catalyst.

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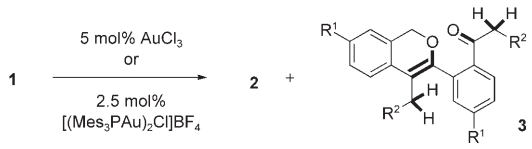
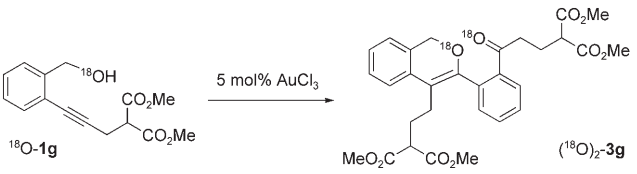
Table 2: Conversion of substrate **1** into **2** and dimer **3**.

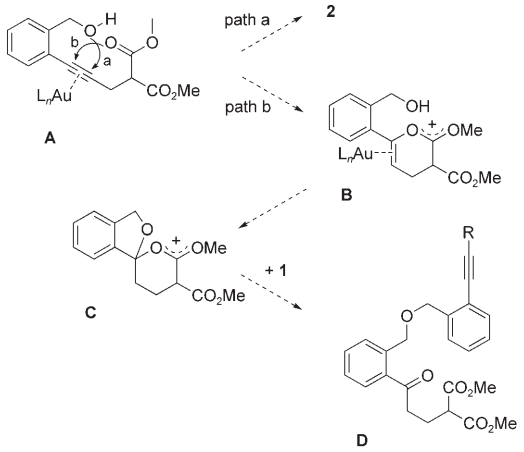
1	Catalyst	Yield of **2** [%]	Yield of **3** [%]
1g $R^1 = H$, $R^2 = CH_2CH(CO_2Me)_2$	$AuCl_3$	20	78
	$[(Mes_3PAu)_2Cl]BF_4$	36	35
1h $R^1 = H$, $R^2 = CH_2C(Me)(CO_2Me)_2$	$AuCl_3$	32	29
	$[(Mes_3PAu)_2Cl]BF_4$	37	33
1i $R^1 = H$, $R^2 = CH_2CH_2CO_2Me$	$AuCl_3$	37	56
	$[(Mes_3PAu)_2Cl]BF_4$	48	37
1j $R^1 = H$, $R^2 = CH_2CH_2CONMe_2$	$AuCl_3$	16	73
	$[(Mes_3PAu)_2Cl]BF_4$	39	–
1k $R^1 = NO_2$, $R^2 = CH_2CH_2CONMe_2$	$AuCl_3$	21	26
	$[(Mes_3PAu)_2Cl]BF_4$	34	–



Scheme 2. An unprecedented dimerization was observed with **1g**–**1k**.



Scheme 3. Intramolecular migration of the oxygen atom of the benzylic alcohol.



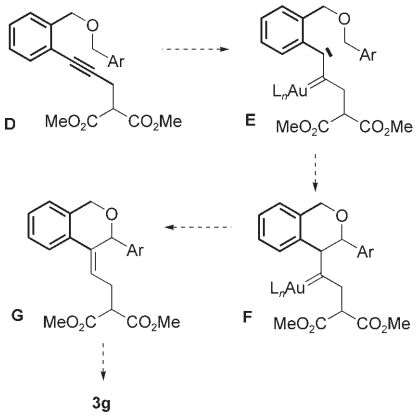
Scheme 4. Proposed mechanism for the formation of the ether bridge between the two substrate units and the intramolecular oxygen transfer.

which prevented crystallization of **3**, was finally utilized and an INADEQUATE spectrum of a concentrated solution of **3g** confirmed the structural assignment. Most striking are the conversion of one arylalkynyl group into an aryl ketone and the formation of two new C–C bonds at a benzylic position; the latter can be explained only by activation the benzylic C–H bonds by the gold catalyst. The dimers are not of the type Echavarren and Nevado obtained in Ag^I-catalyzed reactions,[10] and radical reactions like those in related work of Li and Li[11] can be excluded—our reaction readily proceeded in the presence of the radical inhibitor di(tert-butyl)hydroxytoluene (BHT).

An isotopic-labeling experiment with ^{18}O-**1g** proved an intramolecular oxygen shift. In the mass spectrum the molecular-ion peak of $(^{18}O)_2$-**3g** appeared as the base peak, indicating that the ^{18}O atoms of both substrate molecules were incorporated in the dimer (Scheme 3).

A mechanistic proposal for the formation of **3** must consider that the dimer **3** is formed only in the presence of the additional nucleophilic groups. After coordination of the alkyne to the gold catalyst (Scheme 4, intermediate **A**),[12] either the hydroxy group can attack as a nucleophile (path a), or the second nucleophilic group can attack (path b). The latter competing reaction is more effective, when the group is more nucleophilic (better for amide **1j** than for ester **1i**) or when two of these groups are present (less effective for **1i** with one ester group than for **1g** with two ester groups). The regioselectivity of these competing pathways would be different. The nucleophilic attack of the carbonyl group and a subsequent protodemetalation would lead to the olefin complex **B**, which then could deliver **C** by an intramolecular addition of the hydroxy group. Intermediate **C** represents an activated derivative of the benzyl alcohol. Attack of a second molecule of **1** would then form the dibenzyl ether bond and explain the intramolecular oxygen transfer from the benzylic position to the ketone.

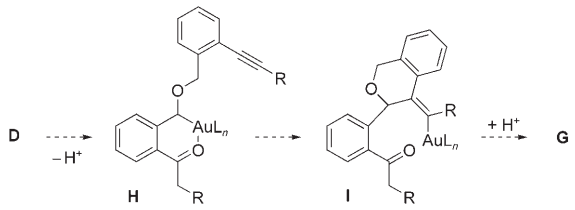
Intermediate **D** could again coordinate a gold species at the alkyne (Scheme 5), and the resulting carbenoid **E**[10,13,14] could insert[15] into the benzylic C–H bond to form **F**. Migration of the benzylic hydrogen would lead to olefin **G**,



Scheme 5. Conceivable transformation of **D** to **3g**.

and migration of the double bond would form an extended conjugated system (**3g**).[16]

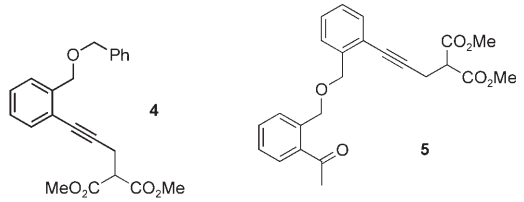
A second conceivable mechanism for the conversion of intermediate **D** into **3g** could proceed by electrophilic C–H activation (Scheme 6),[6] possibly assisted by the carbonyl



Scheme 6. Conceivable alternative route from **D** to **G**.

group as an additional ligand (**H**). Insertion of the alkyne to give **I** and protodemetalation would deliver **G**. From this point the mechanism would be the same as above. Recently, Li et al. suggested a similar (chelate-like) assistance of a neighboring phenolic hydroxy group for the C–H activation of a formyl group.[17]

Control experiments with substrates **4** and **5**, which both represent substructures of **D**, gave no conversion even in the



presence of **1g**. Since **1g** reacted as usual, the catalytic activity of an intermediate gold species differing from the precatalyst can be excluded for **4** and **5** as well. This proves the importance of the additional coordinating groups: they seem to be involved not only in the first step as the nucleophile (**A**→**B**) but also as additional chelating ligands.

Crucial information regarding the mechanism then came from attempts to recrystallize a [(Mes_3P)AuX] catalyst from acetone. In this situation the carbonyl compound was present in high concentration, and a direct α-auration was observed.[18] Single crystals of [(Mes_3P)$AuCH_2COCH_3$] for a crystal structure analysis were obtained (Figure 1).[19] In the X-ray crystal structure the distinction between an acetate and an acetone enolate was not possible, but the ESI mass spectrum of the crystals in the positive-ion mode clearly shows the protonated molecular ion at *m*/*z* 643 (acetate would lead to *m*/*z* 645) and its fragmentation by loss of C_3H_6O (58) to *m*/*z* 585 (with acetic acid 60 rather than 58 would be lost). Since in **D** a vinylogous α position of a ketone is present, the observation of the direct auration of acetone (which in fact is the microscopic reverse of the proto-deauration, the last step in many gold-catalyzed reactions)[2b] links the reactivity of **1** to the Ito–Sawamura–Hayashi aldol reaction.[20] But in **D**, because of the assistance of the carbonyl group of the

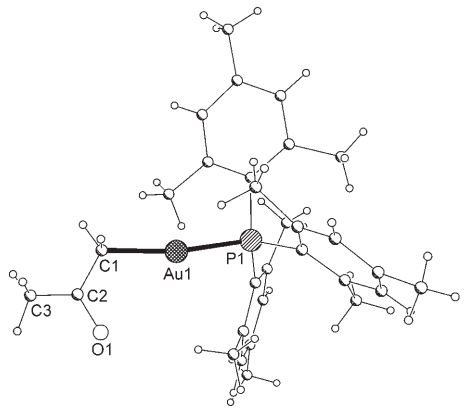
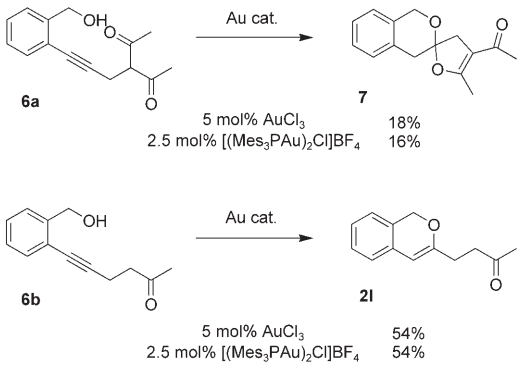


Figure 1. Solid-state structure of [(Mes_3P)$AuCH_2COCH_3$].

ketone and the ester or amide as chelating ligands, no additional base is needed.

The importance of these chelating groups is further underlined by the substrates **6a** and **6b**, which contain keto groups as less nucleophilic carbonyl groups (in comparison to esters and amides in **1g–k**). Reaction of the β-diketone **6a** led to the spiroketal **7**;[21] With **6b** only the isochromene derivative **2l** was obtained (Scheme 7). No dimers related to **3** were observed in either case.



Scheme 7. Products obtained when there are keto groups in the side chain.

Overall, we have described the unexpected and unprecedented reaction of **1** to give **3**, which must involve C–H activation, and we have presented experimental proof of the direct auration of acetone. In the light of previous reports on C–H activation assisted by coordinating groups at higher temperatures,[17] this indicates that gold-catalyzed C–H activation, when directed by proper coordination/chelation, should generally proceed under very mild conditions. Future work will address the further exploitation of this principle in highly functionalized substrates.

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