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Highly Efficient Gold-Catalyzed Atom-Economical Annulation of Phenols with Dienes

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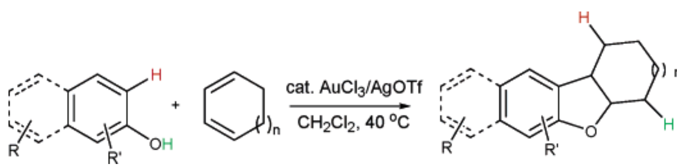
ABSTRACT



A highly efficient annulation of phenols and naphthols with dienes was developed by using a combination of $AuCl_3$/AgOTf as catalyst. The annulation generated various benzofuran derivatives under mild conditions rapidly.

Recently, gold catalysis has emerged as a powerful tool to construct highly complex molecules.[1] For example, heterobicyclic molecules,[2] cyclopentenone,[3] highly substituted pyrroles,[4] furans,[5] and chromanols[6] have been expediently synthesized by gold-based catalysis. Strained bicyclic systems can be accessed by gold-catalyzed cycloisomerizations.[7] The gold-catalyzed reaction also provided a key step in the total synthesis of angucyclinone antibiotics.[8] On the other hand, we have reported efficient gold(III)-catalyzed multicomponent couplings leading to propargylamines[9] and benzylamines.[10] More recently, an interesting nucleophilic substitution of propargyl alcohol has been described.[11] Direct addition of acidic O−H bonds to alkenes[12] and aromatic C−H bonds to alkynes[13] can also be catalyzed by gold. We have also reported the direct addition of activated C−H bonds to alkenes[14] and dienes[15] catalyzed by gold(III).[16] On the other hand, dihydrobenzofurans are the key structural feature of many biologically important compounds and natural products.[17] Recently, we reported an atom-economical[18] consecutive C−C/C−O bond formation between β-keto esters and dienes to generate bicyclic lactones.[19] The success

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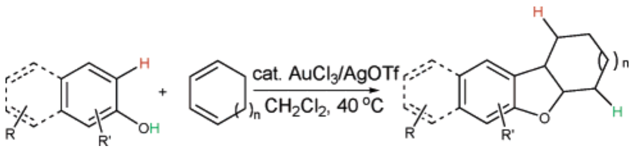
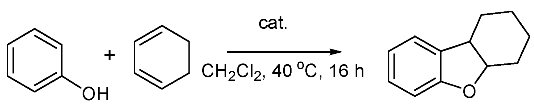
of this approach led us to consider the direct annulation of phenols and naphthols with dienes, which would lead to a highly efficient and completely atom-economical synthesis of dihydrobenzofurans (Scheme 1). Herein, we wish to describe such an annulation catalyzed by a combination of $AuCl_3$/AgOTf.

Scheme 1. Annulation of Phenols and Naphthols with Dienes



Initial studies were conducted using phenol and cyclohexadiene as a prototype reaction in CH_2Cl_2 at 40 °C (oil bath temperature) for 16 h (Table 1). The use of gold(I) as a catalyst led to very low conversions of the starting materials, whereas a cationic gold(I) triphenylphosphine complex did not lead to any desired product at all (Table 1, entries 1 and 2). However, a combination of $AuCl_3$ and AgOTf as catalyst afforded the dihydrobenzofuran **1a** in 74% yield as shown by NMR in the crude reaction mixture (with an internal standard) (Table 1, entry 3). On the other hand, either $AuCl_3$ or AgOTf alone did not catalyze the reaction at all (Table 1, entries 4 and 5), and the use of $AgSbF_6$ instead of AgOTf as the cocatalyst did not improve the product yield (Table 1, entry 6). Finally, the use of an excess amount of diene led to 85% (NMR) yield of the desired product.

Table 1. Annulation of Phenol with Cyclohexadiene Catalyzed by Gold and Silver



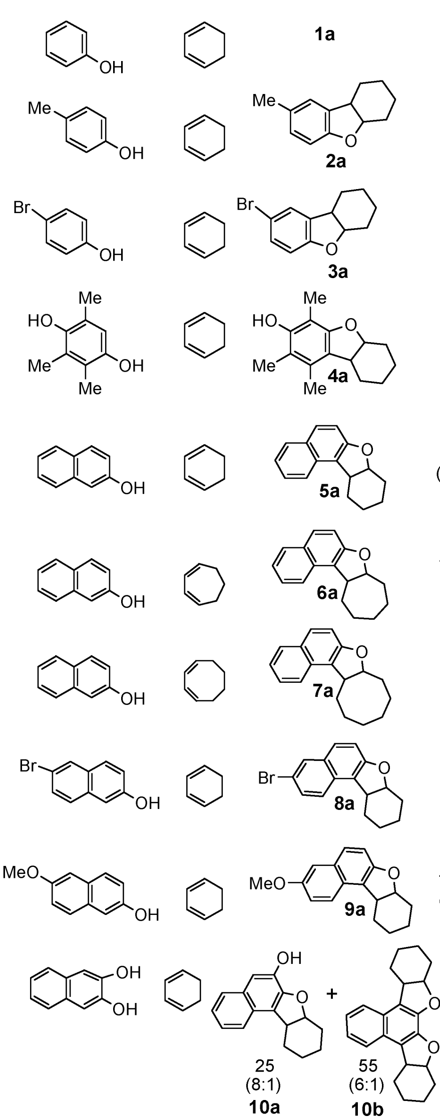
1a

entry[a]	catalyst	yield (%)[b]
1	5% AuCl/5% AgOTf	trace
2	5% $AuCl(PPh)_3$/5% AgOTf	–
3	5% $AuCl_3$/15% AgOTf	74
4	5% $AuCl_3$	0
5	15% AgOTf	0
6	5% $AuCl_3$/15% $AgSbF_6$	74
7	5% $AuCl_3$/15% AgOTf	85[c]

[a] Phenol (1 mmol), diene (0.5 mmol), $AuCl_3$ (0.025 mmol), and AgOTf (0.075 mmol). [b] NMR yield using nitromethane as an internal standard. [c] Phenol (0.5 mmol), diene (1 mmol), $AuCl_3$ (0.025 mmol), and AgOTf (0.075 mmol).

Subsequently, various phenols and naphthols were coupled with a range of dienes to generate various benzofuran products in good yields (Table 2). The presence of electron-donating groups on the aromatic ring seems to promote the reaction; however, lower product yields were observed when an electron-withdrawing group was present (Table 2, entries 2−5). The use of strong electron-withdrawing groups (such as nitro) led to very low conversions under the present conditions. Similar electronic effects were observed with naphthol derivatives: the presence of electron-donating groups (Table 3, entries 9 and 10) is more beneficial than the presence of electron-withdrawing groups (Table 2, entry 8). Furthermore, the use of a large diene ring seems to decrease the yield (Table 2, entry 7). On the other hand, the

Table 2. Gold-Catalyzed Reaction of Phenols/Naphthols with Dienes



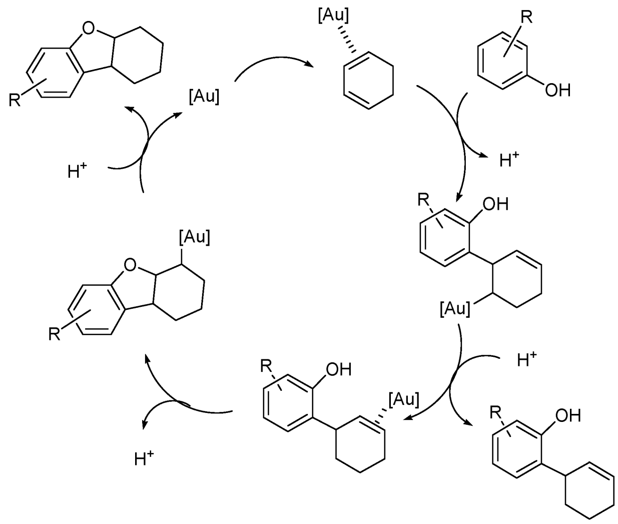
entry[a]	phenol/naphthol	diene[b]	product	yield (%)[c] (syn:anti)[d]
1			**1a**	71(85) (3:1)
2			**2a**	74 (4:1)
3			**3a**	53 (3:1)
4			**4a**	72(88) (12:1)
5			**5a**	80(96) (11:1)
6			**6a**	77(88) (8:1)
7			**7a**	49 (5:1)
8			**8a**	58 (11:1)
9			**9a**	71(89) (11:1)
10[e]			**10a** 25 (8:1) + **10b** 55 (6:1)	80

[a] The oil bath was kept between 40 and 45 °C for 16 h. [b] Conditions: phenol/naphthol (0.5 mmol), diene (1 mmol), $AuCl_3$ (0.025 mmol), AgOTf (0.075 mmol). [c] NMR yields are given in parentheses using an internal standard. [d] The ratio of two diastereoisomers was determined by NMR. [e] Conditions: naphthol (1 mmol), diene (2 mmol), $AuCl_3$ (0.025 mmol), AgOTf (0.075 mmol).

use of acyclic dienes led to a complicated mixture that is still under investigation.

Interestingly, the reaction of aniline with diene did not give any annulation product under the present conditions.[20]

Scheme 2. Tentative Mechanism for the Gold(III)-Catalyzed Phenol−Diene Annulation



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On the basis of our results, a tentative mechanism is proposed in Scheme 2. The first step of the annulation involves the coordination of the double bond with Au(III) followed by an intermolecular addition of the C−H bond to generate a gold intermediate. Protonolysis of the C−Au bond generates intermediate **2**. Then, Au(III) (or triflic acid) recoordinates to the remaining double bond, which is followed by the intramolecular addition of the phenol O−H bond to generate another gold intermediate. Protonolysis of the C−Au bond generates the product and regenerates the Au(III) for further catalysis. Alternatively, the same process can occur in the reverse order: intermolecular allylation on oxygen followed by intramolecular hydroarylation.

In conclusion, we have developed a highly efficient gold-catalyzed annulation of phenols and naphthols with dienes to generate various dihydrobenzofuran derivatives efficiently. The scope, mechanism, and applications of the method in natural product synthesis are under investigation in our laboratories.

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Supporting Information Available: Representative experimental procedures and characterization of all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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