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Benzofuran Synthesis

Au–Ag Bimetallic Catalysis: 3-Alkynyl Benzofurans from Phenols via Tandem C–H Alkynylation/Oxy-Alkynylation

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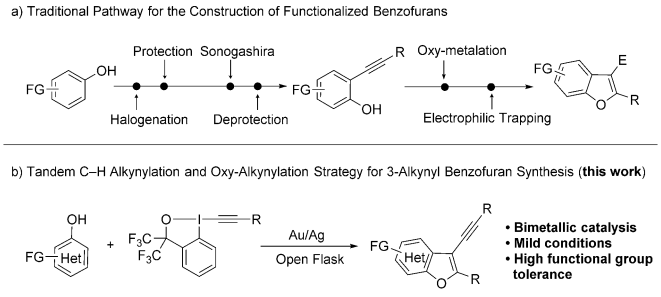
Abstract: *The development of new methodologies enabling a facile access to valuable heterocyclic frameworks still is an important subject of research. In this context, we describe a dual catalytic cycle merging C–H alkynylation of phenols and oxy-alkynylation of the newly introduced triple bond by using a unique redox property and the carbophilic π acidity of gold. Mechanistic studies support the participation of a bimetallic gold–silver species. The one-pot protocol offers a direct, simple, and regio-specific approach to 3-alkynyl benzofurans from readily available phenols. A broad range of substrates, including heterocycles, is transferred with excellent functional group tolerance. Thus, this methodology can be used for the late-stage incorporation of benzofurans.*



Scheme 1. Metal-catalyzed synthesis of functionalized benzofurans; a) common strategies; b) this work.

Benzofuran, as a privileged structure, can be found in many natural products and biologically active molecules.[1] In addition, highly substituted benzofurans are also prevalent in many leading drug candidates[2] and organic materials.[3] Due to the immense importance of this target, several efficient strategies have already been developed.[4,5] One of the most successful modular strategies, which was established over the past decades, is based on a tandem Sonogashira coupling/5-*endo*-*dig* cyclization and a subsequent trapping of the intermediate alkenyl–metal species by various electrophiles (Scheme 1 a).[6] The requirement of functionalized precursors, such as *ortho*-halo or -alkynyl phenols, is a drawback. For example, in 2005, Fürstner and Yamamoto independently reported an elegant example of a platinum-catalyzed cyclization reaction of *ortho*-alkynyl phenols to produce 3-(α-alkoxyalkyl)benzofurans.[6a,g] In 2014, Blum's group reported an intramolecular gold-catalyzed alkoxyboration of C–C multiple bonds, an impressive method for the preparation of benzofuran boronic acid derivatives, ideal precursors for downstream transformations.[6b] Recently, Fensterbank et al. developed a dual gold- and photo-induced alkynylative *ortho*-cyclization to achieve 3-alkynyl benzofurans via a photosensitized oxidative addition.[6i] Despite the efficiency and the synthetic potential of these strategies, the requirement of pre-functionalized substrates is still disadvantageous in these specialized protocols involving multistep procedures. Consequently, there is still a high demand to develop efficient and simple methods for the direct synthesis of functionalized benzofurans.

Gold catalysis serves as a powerful tool in synthetic organic chemistry,[7] in particular in the fields of heterocyclic chemistry[8] and complex molecule synthesis.[9] Recently, the potential of alkynyl gold(III) species to introduce alkyne moieties as useful synthetic handles for further manipulations was reported.[10] As part of our continuing efforts in gold redox chemistry, we recently developed a ligand-enabled oxidative addition of alkynylbenziodoxole as key to alkynyl gold(III) complexes.[11] Based on this, we envisioned that an intermolecular tandem process starting from simple phenols might directly afford functionalized benzofurans, enabled by a reactive alkynyl gold(III) species. To the best of our knowledge, the direct synthesis of valuable 3-alkynyl benzofurans from readily available phenols is yet unknown. Two challenges in a reaction of phenols with alkynyl gold(III) complexes are: a) the sensitivity of phenols towards strong oxidants, which can lead to homocoupling (as known for other transition metals);[12] b) tailoring the conditions for the generation of a reactive alkynyl gold(III) species in a catalytic fashion. Herein, we report the development of an unprecedented direct synthesis of 3-alkynyl benzofurans by an Au–Ag

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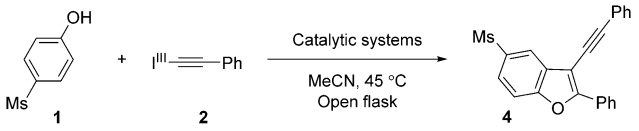
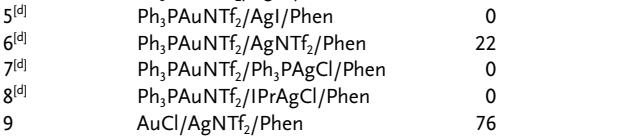
bimetallic-catalyzed cascade reaction from readily accessible phenols and alkynylbenziodoxole reagents (Scheme 1b).

We started our evaluation of the reaction parameters by using the phenol **1** and alkynylbenziodoxole **2** as model substrates to examine the feasibility of the approach and to optimize the reaction conditions (Table 1). After the adjustment of various reaction parameters, the desired 3-alkynyl benzofuran **4** was isolated in 94% yield in the presence of 5 mol% $Ph_3PAuCl/AgNTf_2$ and 20 mol% Phen in MeCN under open-flask conditions at 45°C. Control experiments showed that gold, silver, and Phen all are essential for the reaction. No reaction was observed with pre-activated $Ph_3PAuNTf_2$ (by Celite filtration of the $Ph_3PAuCl/AgNTf_2$ mixtures) instead of an in situ activation ($Ph_3PAuCl/AgNTf_2$; Table 1, entries 1 and 2). The need for the presence of silver salts indicated a decisive role of silver, it was not only a simple halide scavenger[13] (Table 1, entries 3–6). However, AgCl in combination with a ligand (PPh_3, IPr) as additive was not able to promote the reaction, which indicated that free coordination sites at the silver are necessary to coordinate the Phen ligand (Table 1, entries 7 and 8). Various gold(I) and gold(III) complexes were also tested (Table 1, entries 9–11). Among them, AuCl led to formation of **4** in 76% yield, and the commonly used $AuCl_3$ or IPrAuCl in the presence of $AgNTf_2$ showed no catalytic activity. Other Phen-type ligands **L1** and **L2** did not improve the reaction efficiency (Table 1, entries 12–14). When the alkynylbenziodoxolone **3** was used instead of **2**, no conversion to **4** was observed (Table 1, entry 15).

Table 1: Optimization of the reaction conditions.[a]



Entry	Catalytic system	Yield [%][b]
1	**$Ph_3PAuCl/AgNTf_2$/Phen**	**94** (0)[c]
2	$Ph_3PAuNTf_2$/Phen	0
3	$Ph_3PAuNTf_2/AgCl$/Phen	85
4	$Ph_3PAuNTf_2/AgBr$/Phen	64
5[d]	$Ph_3PAuNTf_2/AgI$/Phen	0
6[d]	$Ph_3PAuNTf_2/AgNTf_2$/Phen	22
7[d]	$Ph_3PAuNTf_2/Ph_3PAgCl$/Phen	0
8[d]	$Ph_3PAuNTf_2$/IPrAgCl/Phen	0
9	$AuCl/AgNTf_2$/Phen	76
10	$IPrAuCl/AgNTf_2$/Phen	0
11	$AuCl_3/AgNTf_2$/Phen	0
12	$Ph_3PAuCl/AgNTf_2$/bpy	0
13	$Ph_3PAuCl/AgNTf_2$/L1	61
14	$Ph_3PAuCl/AgNTf_2$/L2	82
15[e]	$Ph_3PAuCl/AgNTf_2$/Phen	0



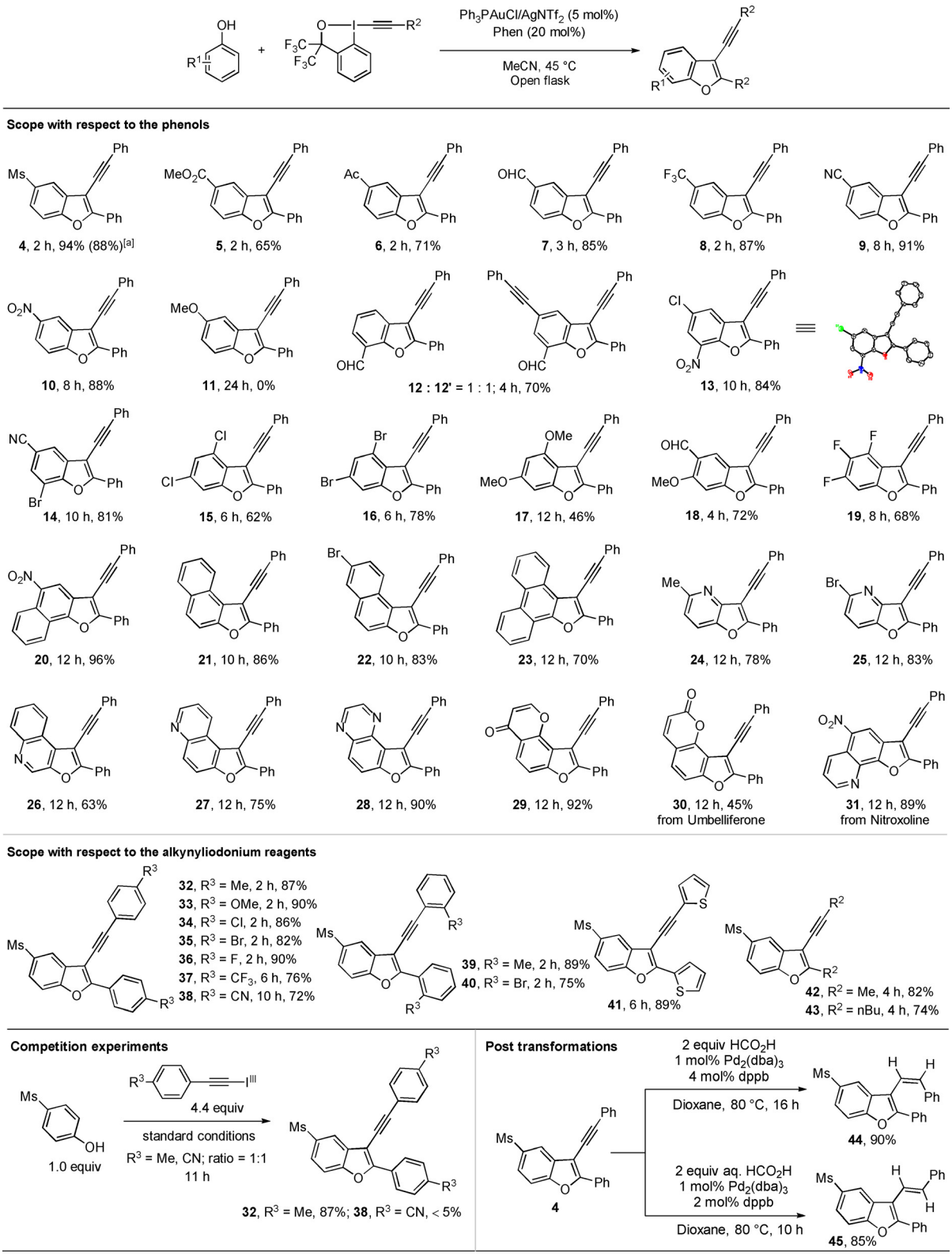
[a] **1** (0.10 mmol), **2** (0.22 mmol), $Ph_3PAuCl/AgNTf_2$ (5 mol%), Phen (20 mol%) in CH_3CN (2 mL) at 45°C under open flask conditions. [b] Isolated yields. [c] No Ph_3PAuCl, or $AgNTf_2$, or Phen. [d] 24 h for the reaction. [e] **3** instead of **2**. Phen = 1,10-phenanthroline.

Under the optimized reaction conditions from Table 1 we investigated the substrate scope of this tandem reaction. First, we explored the scope with regard to the phenol moiety. A variety of phenols smoothly reacted with alkynylbenziodoxole **2** providing the corresponding 3-alkynyl benzofurans in good to excellent yields. As illustrated in Scheme 2, various types of functional groups, for example, sulfonyl, carboxyl, acyl, formyl, nitro, and cyano as well as F, Br, and Cl substituents, were tolerated (**4–10; 13–19**).[14] Moreover, disubstituted and trisubstituted phenols smoothly delivered the products in excellent positional selectivity; only for an *ortho*-substituted phenol a product mixture of **12** and **12′** was obtained. Naphthols and 9-phenanthrol also delivered the corresponding π-extended products in good yield and with very good selectivity (**20–23**). Notably, hydroxy-substituted heterocyclic systems were also compatible, providing the products in good to excellent yields (**24–28**). Only some electron-rich phenols, such as 4-methoxyphenol, were not compatible (**11**); instead, a reductive homocoupling to 1,4-diphenylbutadiyne was observed. A possible reason is that 4-methoxyphenol due to the high pK_a value (19.1 in DMSO) cannot regenerate the bimetallic catalyst **C** (Scheme 5), while the lower pK_a value of *ortho*-$C_6H_4IC(CF_3)_2OH$ allows the catalyst regeneration (there is only a literature-known value for hexafluoro-2-propanol, $CH(CF_3)_2OH$, which has a pK_a of 17.9 in DMSO; due to the H substitutent it should be higher than the pK_a of *ortho*-$C_6H_4IC(CF_3)_2OH$ with a sp^2-C substitutent). And with the electron-withdrawing effect of two *meta*-methoxy groups on the phenol, the pK_a value of phenol is increased. Therefore, product **17** was obtained in decent yield. Various complex phenol derivatives of pharmaceutical importance were examined next to prove the synthetic potential of this strategy (**29–31**). A moderate amount of the desired benzofuran product **30** was obtained from Umbelliferone and **2**, without affecting the lactone functionality of the coumarin moiety. Pleasingly, Nitroxoline, an antibiotic that has been used by humans for many years, reacted smoothly with **2** to provide **31** in excellent yield.

The scope with regard to the alkynylbenziodoxoles reagents was studied with both aliphatic and (hetero)aromatic ethynylbenziodoxole derivatives. These could successfully be employed as precursors, providing a variety of 3-alkynyl benzofurans in good to excellent yield (**32–43**).[15] In a one-pot competition experiment of two different alkynylbenziodoxoles, mainly the product **32** was obtained, in addition to a small amount of **38**; GC/MS shows only a trace of a heterocoupling.

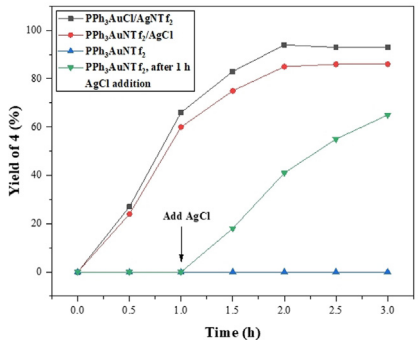
The obtained benzofurans still possess functional groups, the alkynyl benzofuran was hydrogenated by formic acid under palladium catalysis. Depending on the conditions either the *Z*-alkene **44** or the *E*-isomer **45** was generated in excellent yield.

Mechanistic evidence for the role of AgCl was gathered by monitoring the conversion rates for different catalyst combinations. As shown in Figure 1, equimolar amounts of $Ph_3PAuCl/AgNTf_2$ or $Ph_3PAuNTf_2/AgCl$ smoothly promoted the reaction, while $Ph_3PAuNTf_2$ as single catalyst was inactive. Notably, the addition of an equimolar amount of AgCl to the mixture turned on the catalytic activity again and the reaction



Scheme 2. General substrate scope with respect to phenols and alkynylbenziodoxoles. Reaction conditions: **1** (0.1 mmol), **2** (0.22 mmol), $Ph_3PAuCl/AgNTf_2$ (5 mol%), and Phen (20 mol%) were stirred in CH_3CN under open flask conditions at 45 °C; Yields refer to isolated product. [a] 4 mmol scale.

proceeded smoothly in a good yield. As the solubility of AgCl in acetonitrile at 25 °C is low (0.05 mg L^{-1}),[16] a coordination by the Phen ligand must take place. Thus, the active catalyst is formed, probably a heterobimetallic complex. The lack of reactivity with AgCl bearing an additional ligand (PPh_3 or IPr) can be explained by the missing free coordination site for



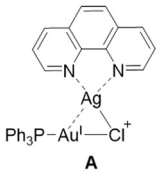
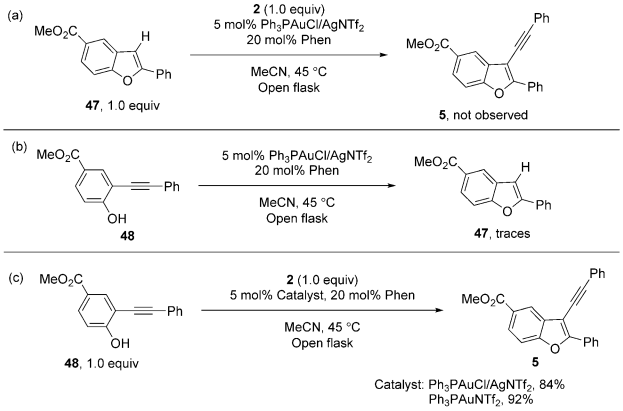
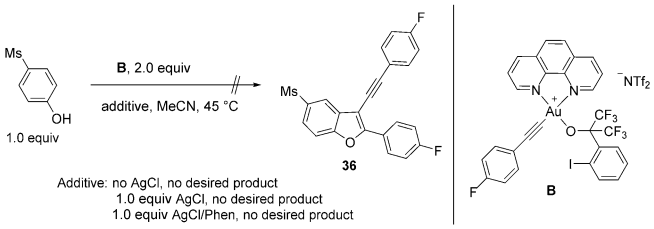


Figure 1. ^{1}H NMR monitoring of the reaction course with different catalytic systems. Conditions: **1** (0.1 mmol), **2** (0.22 mmol), the catalytic system (5 mol%), and Phen (20 mol%) were stirred in CH_3CN under open-flask conditions at 45 °C.



Scheme 4. Control experiments.

the Phen ligand in these complexes. This further underlines that a PhenAgCl species is a crucial structural element in the actually operating catalytic species. By ESI-MS measurements of the $Ph_3PAuCl/AgNTf_2$/Phen system, an ion with $m/z = 781.0009$ was detectable. A computational study of different possible isomers originating from these components was carried out. Complex **A** is the most stable of all calculated species (see the Supporting Information). An analysis of this led us to the proposal of a heterobimetallic species $Ph_3PAuClAg(Phen)$ **A** as active catalytic species (Figure 1, right side). In analogy to previous studies,[11a] we assumed that an alkynyl gold(III) species might be a crucial intermediate in the catalytic cycle as well. To verify this hypothesis, stoichiometric reactions with the preformed (Phen)gold(III) alkynyl species **B** and **1** were conducted. But neither with nor without AgCl, the desired product was detected (Scheme 3). This indicated that the reaction is not proceeding through intermediate **B**, which is then activated by the effect of AgCl, but instead via the in situ-generated heterobimetallic Au/Ag species **A** (introducing the Ag already at the Au^I stage), which serves as the active catalyst.



Scheme 3. Stoichiometric reactions with alkynyl gold(III) species **B**.

Next we reacted C3-unsubstituted benzofuran **47** and **2**, but the reaction failed to deliver any 3-alkynyl benzofuran **5** under the standard reaction conditions (Scheme 4a). In addition, 2-alkynyl phenol **48** failed to afford the C3-unsubstituted benzofuran (Scheme 4b); no conversion was observed. In contrast, with or without AgCl, the reaction of 2-alkynyl phenols **48** with **2** afforded the desired 3-alkynyl benzofuran **5** in excellent yield (Scheme 4c). This indicates that silver only is essential in the *ortho*-alkynylation of phenol, which is the first step of the overall reaction, the step leading to intermediates like **48** (Table 1, entry 2). It also shows nicely that silver is not needed in the oxy-alkynylation step and not needed in the benzofuran alkynylation. In the absence of silver it is the $[PhenAuPPh_3]^+$ complex which is able to undergo oxidative addition of **2**, as previously shown.[11a] This strongly indicates that the cascade starts with the alkynylation of the phenol in the first step. It excludes a scenario in which a C3-unsubstituted benzofuran and gold(I) 3-benzofuryl complex are first formed which is then alkynylated in the final step;[10a–c] instead, the oxy-alkynylation is triggered by a bimetallic gold(III)-acetylide-Ag complex followed by a subsequent reductive elimination.

Then the thermochemistry of the oxidative addition of the used hypervalent iodo species to **A** was calculated (Figure 2). Two reaction pathways were taken into consideration. On the one hand the two-step oxidative addition starting from **I** formed transition state **II** ($\Delta H = 15.1$ kcal mol^{-1}; $\Delta G = 14.8$ kcal mol^{-1}). Afterwards species **III** ($\Delta H = 1.51$ kcal mol^{-1}; $\Delta G = 0.93$ kcal mol^{-1}) was obtained as an ionic pair of a Au^{III}-complex with the alkyne from the hypervalent iodo species and the corresponding benzylic alcoholate anion. Ultimately, species **IV** ($\Delta H = -28.3$ kcal mol^{-1}; $\Delta G = -27.6$ kcal mol^{-1}) was obtained as the final product of the oxidative addition. Furthermore, a barrier-free concerted pathway was found, which led to the same product **IV**. The

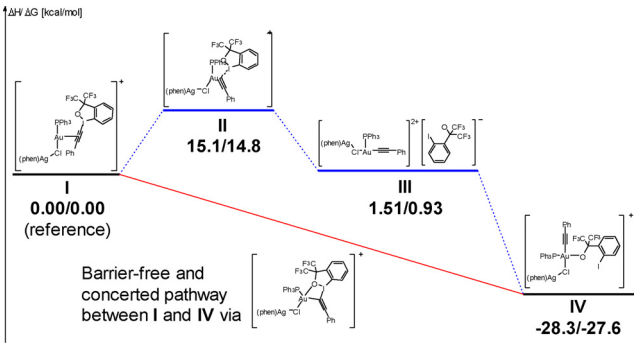


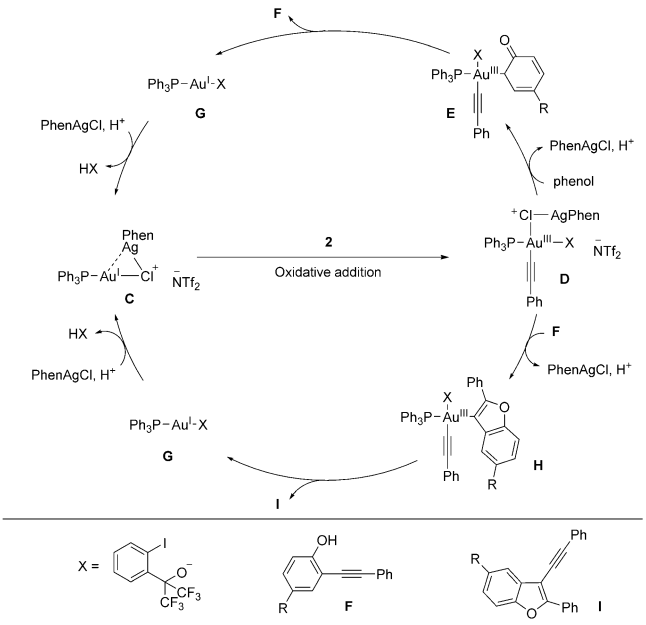
Figure 2. DFT-computed free energies of the oxidative addition of the hypervalent iodo species to heterobimetallic Au–Ag species **A**. Red: concerted pathway; blue: stepwise pathway.

same reaction was also calculated with Ph_3PAuCl. This system did neither undergo *cis* nor *trans* oxidative addition of the hypervalent iodo reagent towards a Au^{III}-species.

Geometry optimizations of the postulated active complex **A** show a distance of of 3.17 Å between gold and silver. Given the van der Waals radii of both metals ($r(Au) = 1.66$ Å and $r(Ag) = 1.72$ Å), this indicates a metallophilic interaction between the two metal centers. This and the ligation of the Ag(Phen) fragment lead to the increased reactivity of complex **A**.[17]

On the basis of these observations and DFT calculations, a plausible mechanism[18] is outlined in Scheme 5. First the active heterobimetallic species $Ph_3PAu^{I}ClAg(Phen)$ (**C**) is formed. This species then undergoes *cis*-oxidative addition with **2** to afford alkynyl gold(III) compound **D**. At this stage, attack of the phenol at the alkynyl Au^{III} species **D,** with liberation of PhenAgCl and H^+, delivers the quinone-type intermediate **E**. Reductive elimination then affords the alkynyl phenol **F** after tautomerization. In the second cycle the alkyne in **F** is activated by Au^{III}-acetylide species **D**, which triggers the intramolecular oxyauration to afford the gold(III) complex **H**. Upon reductive elimination of **H**, the desired product **I** is formed.[19] The reaction of the released catalyst **G** then regenerates **C** with liberation of $C_6H_4IC(CF_3)_2OH$ (which leads to a low proton activity in the reaction mixture and thus avoids proto-deauration processes).

In summary, by taking advantage of the unique redox property and carbophilic π acidity of gold, we have developed a novel direct synthesis of 3-alkynyl benzofurans involving a Au–Ag bimetallic-catalyzed tandem reaction of commercially available phenols with alkynylbenziodoxole reagents. The available mechanistic data are consistent with the proposed oxidative addition of alkynyl hypervalent iodine reagent onto the Au–Ag bimetallic active catalyst. This study also enhances our understanding of the gold catalytic reaction and draws attention to the actual role of AgCl in organic transformations.[17]



Scheme 5. Proposed mechanism.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: Alkynylation · Au–Ag bimetallic catalysis · Benzofurans · Phenols

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