3,3′-Bis(arylbenzofurans) via a Gold-Catalyzed Domino Process

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Abstract: A new heterogeneous gold-catalyzed system for the domino cyclization oxidative coupling of 2-alkynyl phenols for the formation of 3,3′-bisbenzofurans was developed. The substrate and the catalyst scope as well as the reaction conditions were investigated and optimized. This method provides access to this novel structural theme in two steps starting from commercially available chemicals. The molecular structure of the 3,3′-bisbenzofurans was confirmed by single-crystal X-ray analysis.

Key words: domino process, gold catalysis, 3,3′-bisbenzofurans, dimerization, oxidative coupling

Benzofurans are attractive compounds due to their interesting properties.[1] They are widespread in many molecules and natural products with important biological activities, including antitumor properties,[2] inhibition of protein phosphatase 1B,[3] 5-HT2 and 5-HT3 antagonist activity,[4] inhibition of 5-lipoxygenase,[4b] and antifungal properties.[5] Pharmaceutically, these properties are convenient in the treatment of cancers, cardiovascular diseases, type 2 diabetes, migraines, dementia, and anxiety.[2–4] Additionally, benzofurans have been reported as fluorescent markers for biomolecules.[6]

However, the bisbenzofuran scaffold is much less studied, although it is present in a number of biological active molecules, for example, in kynapcin-24. This compound, whose first total synthesis was achieved in 2009 by Yang et al.,[7] inhibits prolyl endopeptidase, an enzyme involved in Alzheimer's disease (Figure 1).[8]

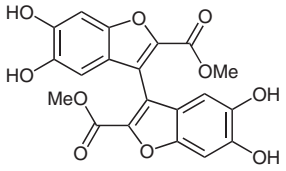
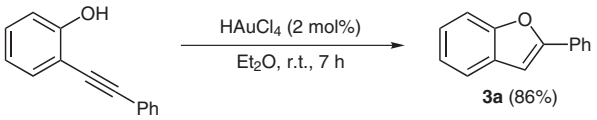


Figure 1 Kynapcin-24, a prolyl endopeptidase inhibitor

Other dimers of benzofurans, such as 2,2′-bisbenzofurans exhibit also interesting properties like antiprotozoal activities[9] or antimicrobial effects.[10] Yet, only few syntheses of bisbenzofuran derivatives have been published. Moreover, they are fastidious and multisteps demanding. They mainly involve the building of two benzofuran units which need to be activated prior to connection by metal-catalyzed coupling reaction: modified Castro reaction,[11] copper-mediated palladium-catalyzed coupling[7] or BuLi/$CuCl_2$ coupling.[12] The quick and efficient access to bisbenzofuran derivatives from easily available starting material is, therefore, a challenging field of investigations.

The gold-catalyzed formation of benzofurans from 2-alkynyl phenols is well known since a decade and proceeds through the gold activation of the alkyne (Scheme 1).[13]



Scheme 1 Gold-catalyzed 5-*endo-dig* cyclization of 2-alkynyl phenols to benzofurans reported by Belting and Krause[13c]

Besides the activation of π-systems, gold can also potentially promote oxidative coupling.[14] Recent examples were developed for the gold-catalyzed ethynylation of arenes,[15] the gold-catalyzed diamination of alkenes,[16] or the oxidative coupling of nonactivated arenes.[17] Thus, by carefully controlling the reaction conditions, a domino process can be set up to make the gold catalyst perform multiple tasks successively.[18] In our group, this approach led us to develop the gold-catalyzed domino cyclization–oxidative coupling reaction of aryl alkynyl esters for the formation of dicoumarins.[19] Such transition-metal-catalyzed domino processes are relevant to open efficient routes for C–C bond formation in complex molecules.[20]

During the 5-*endo-dig* cyclization of 2-alkynyl phenols, the interaction of the gold catalyst with the alkyne, followed by a nucleophile attack, leads to a gold complex–benzofuran intermediate. Stabilization of this intermediate should enable an oxidative coupling to obtain 3,3′-bisbenzofurans. This hypothesis was corroborated by the recent results of Hashmi.[21] Taking into account our previous work on the gold-catalyzed cyclization–oxidative coupling of aryl alkynylesters, we first examined the simple application of the reaction conditions of the dicoumarin synthesis.[19] Although *tert*-butylhydroperoxide recently showed interesting results for re-oxidation of gold in homogeneous catalysis,[22] it appeared that such transposition was not suitable for this system and led to the formation of monobenzofuran only with 61% yield (entry 1, Table 1).

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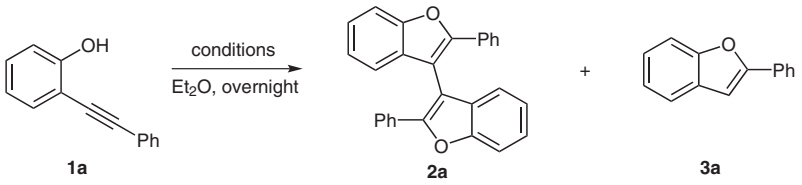
Table 1 Optimization of the Gold-Catalyzed Formation of 3,3′-Bisbenzofuran **2a**



1a **2a** **3a**

Entry	Catalyst (mol%)	Solvent	Additives (equiv)	Oxidant (equiv)	Temp	Results
1	$HAuCl_4$ (10)	1,2-DCE	–	*t*-BuOOH (5)	60 °C	**3a** 61%
2	$HAuCl_4$ (10)	1,2-DCE	–	DDQ (5)	60 °C	**2a** 4%, **3a** 29%
3	$HAuCl_4$ (10)	MeCN	–	Selectfluor® (5)	r.t.	no reaction
4	$HAuCl_4$ (10)	Me_2CO	–	Selectfluor® (5)	r.t.	ratio **2a**/**3a** 1:10[a]
5	$HAuCl_4$ (10)	Et_2O	–	$PhI(OAc)_2$ (5)	r.t.	**2a** 37%
6	$HAuCl_4$ (5)	Et_2O	–	$PhI(OAc)_2$ (5)	r.t.	**2a** 37%, **3a** 3%
7	$HAuCl_4$ (1)	Et_2O	–	$PhI(OAc)_2$ (5)	r.t.	**2a** 3%, **3a** 16%
8	$HAuCl_4$ (10)	Et_2O	K_2CO_3 (1.2)	$PhI(OAc)_2$ (5)	r.t.	**2a** 26%
9	$HAuCl_4$ (10)	Et_2O	Et_3N (1.2)	$PhI(OAc)_2$ (5)	r.t.	**2a** 33%, **3a** 15%
10	$HAuCl_4$ (10)	Et_2O	–	PhIO (5)	r.t.	**2a** 32%, **3a** 24%
11	$AuCl_3$ (10)	Et_2O	–	$PhI(OAc)_2$ (5)	r.t.	**2a** 11%, **3a** 22%
12	$AuBr_3$ (10)	Et_2O	–	$PhI(OAc)_2$ (5)	r.t.	**2a** 35%

[a] Determined by crude NMR.

Therefore, reaction conditions have been screened using **1a** as substrate. Different gold sources have been tested: gold(I) and gold(III), in combination with several solvents (1,2-dichloroethane, dichloromethane, tetrahydrofuran, acetone, acetonitrile, diethyl ether, dioxane). The regeneration of the gold catalyst by oxidation, which is a crucial point, was also a main part of the screening process: Selectfluor® ('F^+' donor reagents are well known for gold catalysts oxidation),[14a,b,g,17b] DDQ, NMO, chloranil, MnO_2, *t*-BuOOH, or Dess–Martin periodinane led only to the formation of **3a** with traces of dimer **2a** (see selection in Table 1, entries 1–4).

Finally, using (diacetoxyiodo)benzene $PhI(OAc)_2$ (5 equiv) as oxidant in anhydrous diethyl ether in presence of 10 mol% of $HAuCl_4$ (entry 5, Table 1) gave mainly dimer with small traces of the corresponding monomer. The catalyst loading can be lowered to 5 mol% although this increased the presence of monobenzofuran, generating difficulties in the purification (entry 6, Table 1). A catalyst loading of 1 mol% led to the formation of monomer mainly with traces of dimerization (entry 7, Table 1). The use of additives such as organic or inorganic bases (Et_3N or K_2CO_3), to catch the proton released during the process and avoid the formation of monomer by protodeauration, did not increase the dimerization yields (entries 8 and 9, Table 1).

Yet, $PhI(OAc)_2$ is also known to oxidize phenols to quinone derivatives.[23] We assume the occurrence of a side reaction between the 2-alkynyl phenol substrates and (diacetoxyiodo)benzene leading to the formation of benzoquinone derivatives to be responsible for lowering the dimer yield. Unfortunately, $PhI(OAc)_2$ was the only oxidant suitable to re-oxidize the gold catalyst and achieve the turnover of the catalytic domino process.

It is noteworthy that (diacetoxyiodo)benzene itself does not catalyze the dimerization nor the coupling of two monobenzofuran units. Reaction of **1a** and $PhI(OAc)_2$ in diethyl ether led to the formation of an uncharacterized orange material which we assumed to be a polymer of quinone derivatives.[23] A control experiment between monobenzofuran **3a** and $PhI(OAc)_2$ did not show any formation of **2a**.

Our attempts to avoid or reduce the side reaction (protection of the phenol, low/high temperature reactions, diluted conditions, slow addition of the substrate, reduced amount of oxidant) were not successful. Other hypervalent iodine compounds have been tested: iodosobenzene (PhIO) led to a mixture of monomer/dimer with a lower dimer yield than (diacetoxyiodo)benzene (entry 10, Table 1); bis(trifluoroacetoxy)iodobenzene (PIFA) provided no formation of monomer or dimer. The use of $PhI(OAc)_2$ with other gold catalysts did not improve the dimerization (entries 11 and 12, Table 1). A crucial finding is the use of diethyl ether as solvent. The gold catalyst and the 2-alkynyl phenols are soluble in diethyl ether while (diacetoxyiodo)benzene is only slightly soluble resulting in a het-

erogeneous system. These conditions led to the best dimer yields by limiting the side reaction with the starting material.[24] In halogenated solvents, where (diacetoxyiodo)benzene is soluble, the side reaction only occurs leading to decomposition of the starting material.

We prepared the substrates **1a–l** by known procedures (see Supporting Information). Substitution on the *para* and *meta* positions of the phenol were tolerated for the dimerization (entries 2 and 4, Table 2) provided that substituents are electron donating. Thus, the presence of electron-withdrawing group (entry 9, Table 2) prevented the dimerization process. Interestingly, the domino process took place on arylalkynyl phenols but did not occur with terminal alkynyl, silyl-alkynyl, alkyl-alkynyl phenols (entry 8, Table 2), or alkynyl cyclohexenol (entry 10, Table 2).

Table 2 Substrate Scope for the Domino Process towards the Formation of 3,3′-Bisbenzofurans **2**

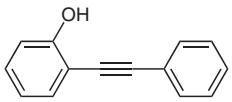
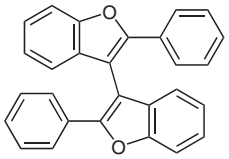
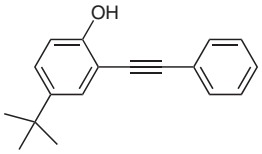
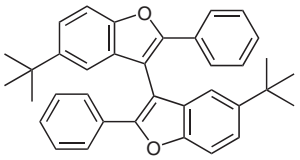
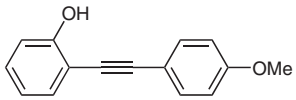
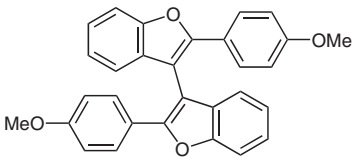
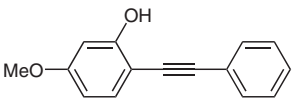
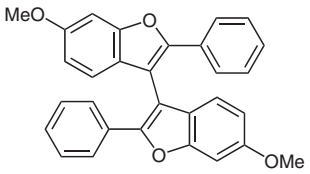
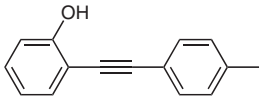
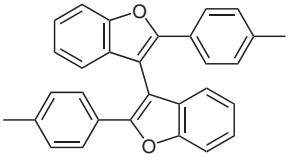
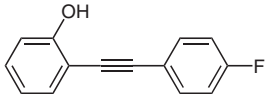
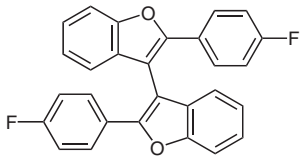
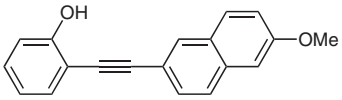
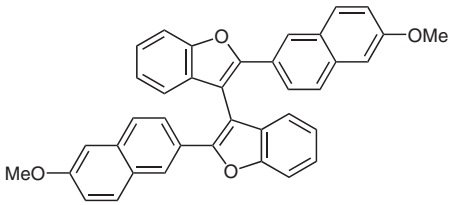
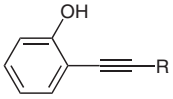
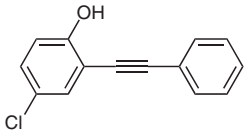
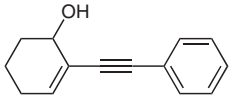
Entry	Starting material	Product	Yield (%)
1	 **1a**	 **2a**	37
2	 **1b**	 **2b**	20
3	 **1c**	 **2c**	25
4	 **1d**	 **2d**	24
5	 **1e**	 **2e**	23
6	 **1f**	 **2f**	25

Table 2 Substrate Scope for the Domino Process towards the Formation of 3,3′-Bisbenzofurans **2** (continued)

Entry	Starting material	Product	Yield (%)
7	 **1g**	 **2g**	19
8	 **1h** (R = H) **1i** (R = TMS) **1j** (R = *n*-Pr)	no dimerization	–
9	 **1k**	no dimerization	–
10	 **1l**	no dimerization	–

The cylization–oxidative coupling sequence is not affected by the nature of the substituent on the aryl alkynyl moieties since the presence of electron-withdrawing and -donating groups is suitable (entries 1–7, Table 2).

Therefore, the transformation proceeds on a very fine line of reactivity between the desired re-oxidation of the catalyst and decomposition of the starting material. Thus, despite intense efforts of optimization, the yields for this very economic transformation remained in the lower range (around 20–37%) for the main part of the substrates. However, this method opens a quick and efficient way to this novel 3,3′-bis(2-arylbenzofuran) scaffold from commercially available starting materials. It is noteworthy, that such conditions did not lead to the formation of 3,3′-bisindoles starting from 2-alkynyl anilines.

According to our preliminary results on the gold-catalyzed domino cyclization and oxidative coupling towards the formation of dicoumarins,[19] we propose a similar mechanism for the formation of 3,3′-bisbenzofurans (Scheme 2). At the beginning of the reaction the starting material can take two different ways: the 2-alkynyl phenols can be oxidized by $PhI(OAc)_2$ leading to the formation of quinone derivatives and lowering the yield of the reaction by consuming the starting material; or it can enter the domino process in which the first step is the coordination of the gold catalyst on the alkyne for activation of the cyclization. Aromatization of intermediate **B** releases the σ-complex **C**, Hashmi described a quite similar gold(I) intermediate.[21] Complex **C** can then either undergo a protodeauration step and produce the monobenzofuran or catalyze the cyclization of another molecule of substrate to lead to complex **D**. Another possibility is the formation of **D** via a ligand exchange. Complex **D** undergoes an oxidative coupling to the 3,3′-bisbenzofuran and a gold species which has to be re-oxidized to achieve the turnover of the catalytic cycle.

The structure of these novel 3,3′-bis(arylbenzofurans) has been confirmed by a single-crystal X-ray analysis of compounds **2a** and **2b**.[25]

We describe a new heterogeneous catalytic system for the gold-catalyzed domino process to convert simple 2-(arylalkynyl)phenols directly to novel 3,3′-bis(arylbenzofurans) in one step and under mild conditions (taking place in the presence of an appropriate oxidant only). Although the transformation proceeds in low yields, such C–C bond-forming reactions from nonfunctionalized starting materials are highly important for the synthesis of organic molecules. As benzofurans are interesting photochromic compounds used as dyes,[6] the photoluminescent properties of the π-system exhibited by the 3,3′-bisbenzofurans will be investigated in the future.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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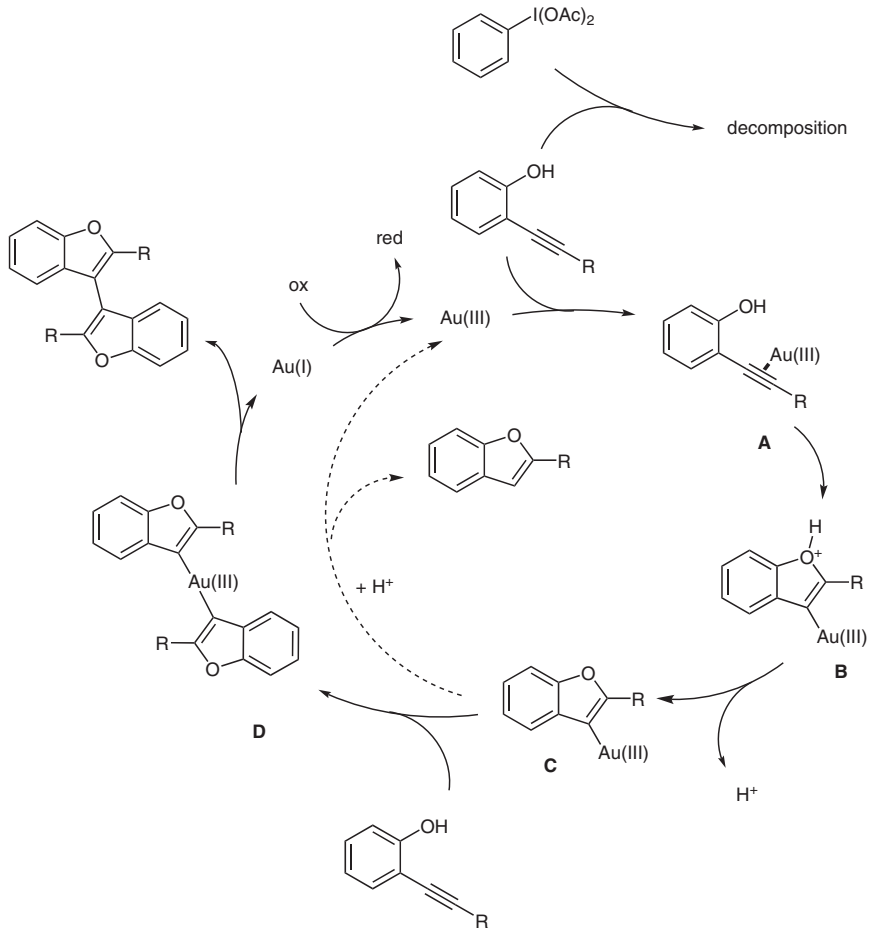

Scheme 2 Proposed mechanism for the domino process towards the formation of 3,3′-bisbenzofurans

Johnson Matthey are gratefully acknowledged for generously providing auric acid.

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(24) The procedure described for compound **2a** was applied for compounds **2b**–**g**. $HAuCl_4$ (17.5 mg, 10 mol%) was placed into a 20 mL vial (well dried), equipped with a stir bar. Et_2O (10 mL) was added, and the mixture was stirred for 5 min at r.t. Then, 2-alkynlphenol (100 mg, 1 equiv) was added first, followed by $PhI(OAc)_2$ (848 mg, 5 equiv) 5 min later. The mixture was stirred at r.t. overnight. The reaction mixture was filtered and concentrated. The crude product was purified by flash column chromatography or on preparative TLC. Compound **2a** was isolated as a white powder with a yield of 37% (37 mg); mp 179–181 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.80–7.74 (m, 4 H), 7.63 (d, *J* = 8.2 Hz, 2 H), 7.33 (m, 2 H), 7.29–7.20 (m, 6 H), 7.17–7.07 (m, 4 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 154.76 (2 C), 152.37 (2 C), 130.84 (2 C), 129.87 (2 C), 128.98 (4 C), 128.92 (2 C), 126.62 (4 C), 125.32 (2 C), 123.41 (2 C), 121.11 (2 C), 111.62 (2 C), 108.07 (2 C). ESI-HRMS: *m/z* calcd for $[C_{28}H_{18}O_2Na]^+$: 409.1204 $[M + Na]^+$; found: 409.1199. MS (EI): *m/z* (%) = 386.1 (100) $[M^+]$, 308.1 (9), 281.1 (7). IR: ν = 1600, 1588, 1486, 1470, 1454, 1439, 1338, 1288, 1254, 1203, 1109, 1063, 1026, 1008, 920 cm^{-1}.

(25) Crystallographic data for compounds **2a** and **2b** have been deposited at the Cambridge Crystallographic Data Center, the respective deposition numbers are 772967 and 772968.