Gold Catalysis

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Gold(I)-Catalyzed Formation of Benzo[*b*]furans from 3-Silyloxy-1,5-enynes**

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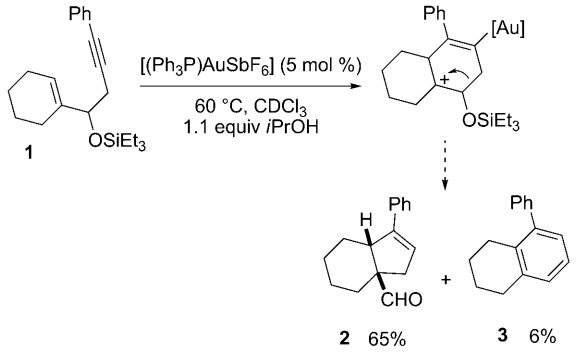
Gold-catalyzed[1] cyclizations of aromatic and heteroaromatic compounds with alkynes offer new ways for the efficient construction of bioactive compounds, and have attracted much attention in the last decade.

Recently, Kirsch et al.[2] developed an interesting method for the synthesis of bicyclic formyl compounds. It is based on the cyclization of 3-silyloxy-1,5-enynes under mild conditions with gold(I) catalysts and *i*PrOH as an additive in a process that involves a 6-*endo-dig* cyclization to the distal position of the double bond and a pinacol rearrangement (Scheme 1). The biphenyl derivative **3** is observed as a side product.



Scheme 1. Gold-catalyzed cyclization/pinacol rearrangement and the competing reaction according to Kirsch et al.

Inspired by this intriguing study and in continuation of our work on the application of furan substrates in synthesis,[3] we investigated the reaction of compounds of type **4** (Figure 1). As a consequence of both the short two-carbon tether between the furan ring and the alkyne and the aryl substituent on the alkyne, neither the gold-catalyzed synthesis of phenols[4] nor related known reactions are possible.[5]

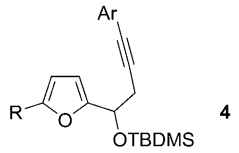
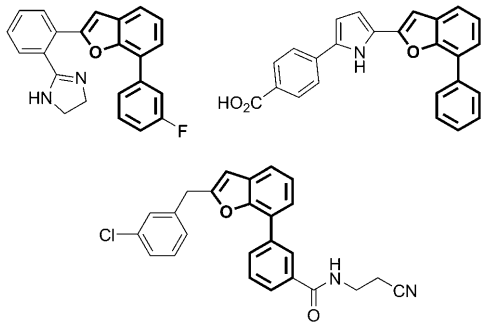


Figure 1. Furan derivatives **4** are structurally related to Kirsch's substrate **1**. Ar = aryl, hetaryl; R = alkyl, aryl; TBDMS = *tert*-butyldimethylsilyl.

First experiments conducted with substrate **4a** indicated that a benzo[*b*]furan is formed in this conversion when Gagosz's[6] catalyst is used. Benzofurans represent an important structural motif frequently found in a variety of bioactive compounds (Scheme 2);[7] for example, 2-substituted benzofurans and their derivatives exhibit a broad range of biological activities, such as their antineoplastic, antiviral, antioxidative, and anti-inflammatory properties. As a result, a number of routes leading to 2-substituted benzo[*b*]furans have been described in the literature;[8] however, currently no general synthetic methodology for the 7-substituted benzo[*b*]furans exists, especially for 7-aryl benzofurans. Herein we report our findings on how to gain access to the desirable 7-aryl benzofurans by an unexpected substitutent "castling" procedure.



Scheme 2. Bioactive compounds with a 7-aryl benzofuran core structure.[9]

Since the reaction time of 42 h and the yield of 87% were not satisfactory, we optimized the catalysis conditions (Table 1). While the new NAC–gold catalysts[10] (NAC = nitrogen acyclic carbene) gave no significant improvement (Table 1, entries 2 and 3) and simple gold chlorides delivered very low yields (Table 1, entries 4 and 5), the N-heterocyclic carbene (NHC) ligand 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene (IPr) afforded an improved yield of 91% after only 1 h reaction time (Table 1, entry 6). Decreasing the

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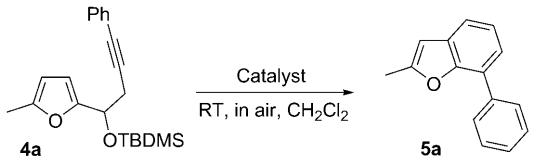
Table 1: Optimization studies on the rearrangement of **4a**.[a]



Entry	Catalyst	*t* [h]	Yield [%]
1[b]	$[Ph_3PAuNTf_2]$	42	87
2[c]	$[NACAuCl]/AgSbF_6$	3	58
3	$[NACAuCl]/AgNTf_2$	48	68
4	AuCl	42	19
5	$AuCl_3$	42	23
6	**$[IPrAuCl]/AgNTf_2$**	1	91
7[d]	$[IPrAuCl]/AgNTf_2$	8	93
8[e]	$[IPrAuCl]/AgNTf_2$	48	18
9[f]	$[IPrAuCl]/AgNTf_2$	1	85
10	$[MePhosAuCl]/AgNTf_2$	24	92
11	$AgNTf_2$	42	n.r.
12	*p*-TsOH	48	decomposition of the substrate

[a] Reaction conditions: Substrate (200 μmol), [Au] (2 mol%), [Ag] (2 mol%), 1.1 equiv *i*PrOH, CH_2Cl_2 (3 mL), RT, in air. The reaction was monitored by TLC. [b] Substrate (300 μmol). [c] Substrate (100 μmol). [d] 0.5 mol% of catalyst. [e] 0.1 mol% of catalyst. [f] Without *i*PrOH. Tf = trifluoromethanesulfonyl, n.r. = no reaction.

catalyst loading to 0.5 mol% gave a respectable 93% yield of the product after 8 h (Table 1, entry 7). With only 0.1 mol% of catalyst, the yield dropped to 18% after 48 h, no more conversion was observed after that time (Table 1, entry 8). Without *i*PrOH as the additive, the yield was reduced by 6% (Table 1, entry 9). An even better yield of 92% was obtained with the phosphane ligand MePhos, but the reaction needed 24 h (Table 1, entry 10). Control experiments with silver(I) gave no conversion (Table 1, entry 11), while with *p*-toluenesulfonic acid (*p*-TsOH) the usual slow decomposition of the furan was observed (Table 1, entry 12).

Initially one could have expected the benzofuran to be the product of a normal hydroarylation of the furan ring in the 3-position[3b] and a subsequent aromatization by elimination of silanol.[11] This would deliver the 2,4-disubstituted benzofuran **6a**. A safe assignment of the structure of anellated disubstituted benzofurans by NMR spectroscopy is difficult, but more reliable results were obtained by X-ray crystal structure analysis of the benzofuran product.[12] Thus, the 2,7-disubstituted structure of **5a** was proven unambiguously (Figure 2).

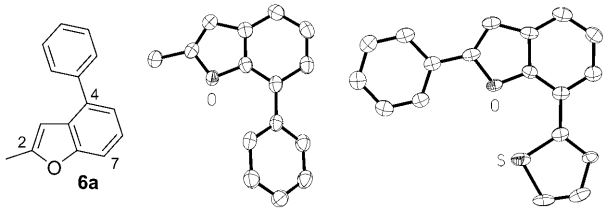
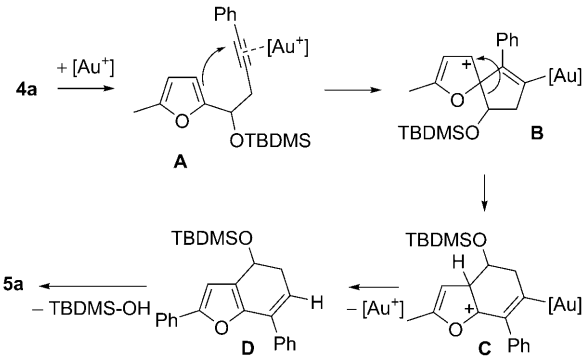


Figure 2. Left: Conceivable structure of benzofuran **6a**. Middle: Solid-state molecular structure of **5a**. Right: Solid-state molecular structure of the sulfur-containing product **5i**. Thermal ellipsoids at 50% probability.

The connectivity of **5a** can easily be explained by the mechanism[13] depicted in Scheme 3. After coordination to the triple bond (**A**),[14] the gold catalyst induces an electrophilic

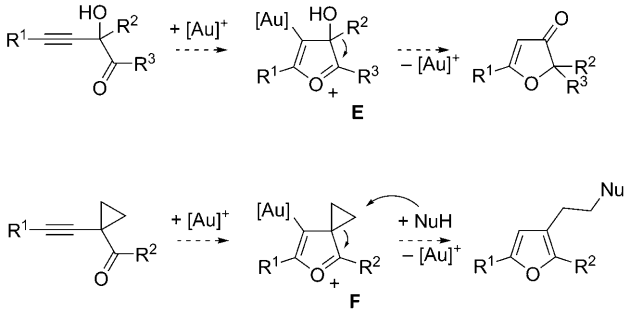


Scheme 3. Proposed mechanism for the gold(I)-catalyzed rearrangement of the substrate **4a** to the 2,7-disubstituted benzo[*b*]furan **5a**.

attack at the most nucleophilic position of the furan ring, the 2-position (**B**). After this 5-*endo-dig* cyclization, a Wagner–Meerwein shift delivers the intermediate **C** with a more stable carboxonium ion. Rearomatization of the furan by deprotonation and protodeauration delivers **D**, and a subsequent aromatization by elimination of silanol affords the final product **5a**.

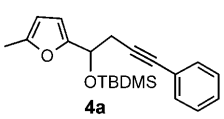
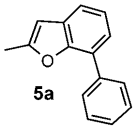
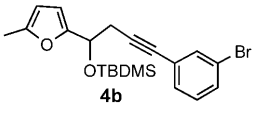
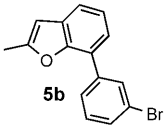
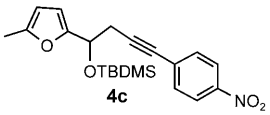
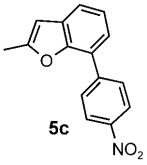
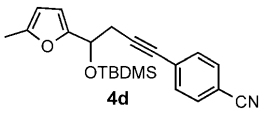
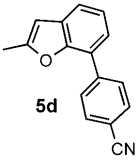
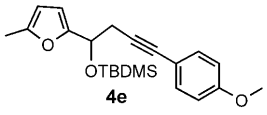
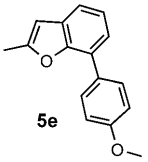
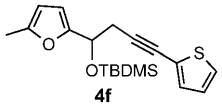
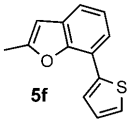
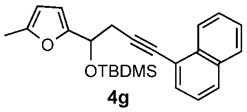
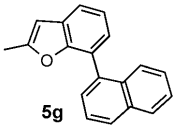
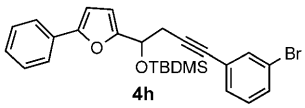
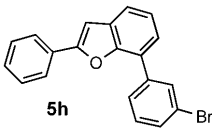
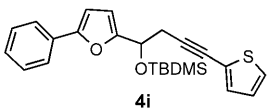
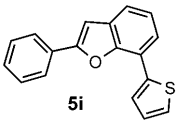
Crucial for the substituent "castling" is the selective migration of the sp^3-carbon atom rather than the sp^2-carbon atom in the spiro intermediate **B**, which probably originates from stabilization of the positive charge in the transition state of the 1,2-shift of the oxygen atom from the 2- to the 3-position (carboxonium-like stabilization). Other gold-catalyzed conversions involving furan-derived arenium intermediates have so far only shown a 1,2-shift from the 3- to the 2-position in **E**[15] or a rearomatization by opening of a three-membered ring in the spiro intermediate of type **F** (Scheme 4).[16]

Apart from the intriguing mechanism, we were also interested in the scope of this conversion. A series of substrates **4a**–**4i** was easily available by the reaction of furfurals with propargyl bromide and zinc, silyl protection of



Scheme 4. Furyl-derived Wheland-type intermediates according to Kirsch et al. and Schmalz and co-workers. Top: R^1 = aryl, alkyl; R^2 = alkyl; R^3 = aryl, alkyl; bottom: R^1 = aryl, alkyl; R^2 = aryl, alkyl; Nu = R^3O.

Table 2: Scope and limitations of the gold(I)-catalyzed rearrangement of 3-silyloxy-1,5-enynes.[a]

Entry	Substrate	Product	*t* [min]	Yield [%]
1	 **4a**	 **5a**	60	91
2	 **4b**	 **5b**	40	92
3	 **4c**	 **5c**	120	93
4	 **4d**	 **5d**	240	91
5	 **4e**	 **5e**	180	81
6	 **4f**	 **5f**	12	95
7	 **4g**	 **5g**	180	86
8	 **4h**	 **5h**	60	94
9	 **4i**	 **5i**	12	95

[a] Reaction conditions: Substrate (200 μmol), [IPrAuCl] (2 mol%), [$AgNTf_2$] (2 mol%), 1.1 equiv *i*PrOH, CH_2Cl_2 (3 mL), RT, in air. The conversion was monitored by TLC.

the alcohol, and subsequent Sonogashira coupling of the terminal alkynes with an aryl iodide. We further explored the generality of the rearrangement of the 3-silyloxy-1,5-enynes using [IPrAuNTf$_2$] in dichloromethane at room temperature under the optimized conditions. The results are shown in Table 2. The reaction is highly tolerant of various substituents at both the alkyne and the 2-position of the furan ring. For example, reactions with substrates bearing either electron-rich or electron-poor aryl-functional groups on the alkyne moiety proceeded smoothly and delivered the products in high yields (Table 2, entries 1–5). Noticeably, even the sulfur-containing thiophene substituent on the alkyne could be perfectly converted after 12 minutes without any sign of catalyst deactivation (Table 2, entries 6 and 9). This is one of the few conversions of a low-valent sulfur-containing compound by gold catalysis.[5a,17] The X-ray crystal structure of **5i** again confirms the migration of the substituent of the furan ring from position 2 to 3 (Figure 2).[12] Extended π systems such as the naphthyl substituent are tolerated and don't influence the relative migration aptitude (Table 2, entry 7). The two examples containing bromoarenes (Table 2, entries 2 and 8) highlight the high functional-group tolerance of the gold catalyst and the orthogonality to palladium catalysts.[18]

In conclusion, we have developed a novel gold(I)-catalyzed rearrangement reaction under mild conditions, which provides a rapid and efficient access to benzo[*b*]furans from the simple, readily available 3-silyloxy-1,5-enynes. Further studies to probe the mechanism of this transformation and extensions of this chemistry towards thiophene and other heterocycles can be easily envisioned, and are being currently explored in our laboratory.

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