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A Gold-Catalyzed A3 Coupling/Cyclization/Elimination Sequence as Versatile Tool for the Synthesis of Furfuryl Alcohol Derivatives from Glyceraldehyde and Alkynes

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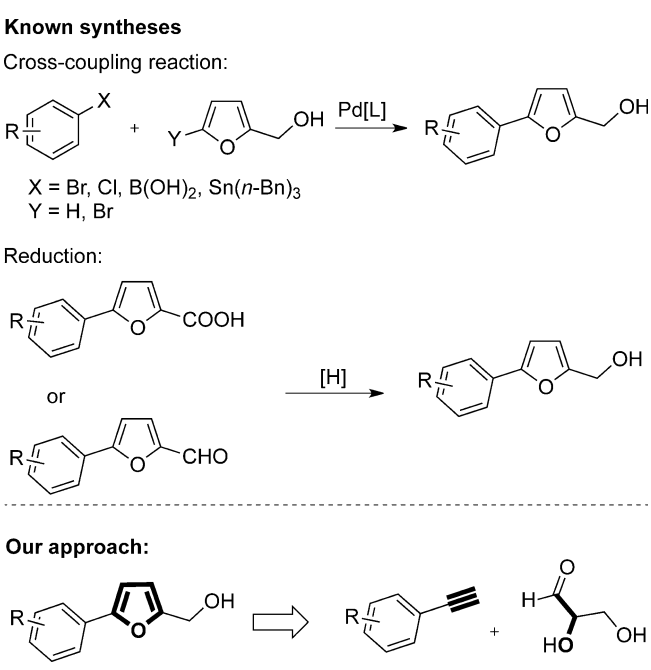
Abstract: The reaction of glyceraldehyde with alkynes delivers furfuryl alcohol derivatives within only one reaction step in the presence of a gold(III) catalyst. The reaction cascade is initiated by an intermolecular gold-catalyzed A3 coupling sequence in which morpholine is used as additive. Intramolecular cyclization and subsequent aromatization under elimination of the amine then deliver the target molecules. The protocol offers a valuable alternative to the common routes that are based on functionalization of already existing furan cores.

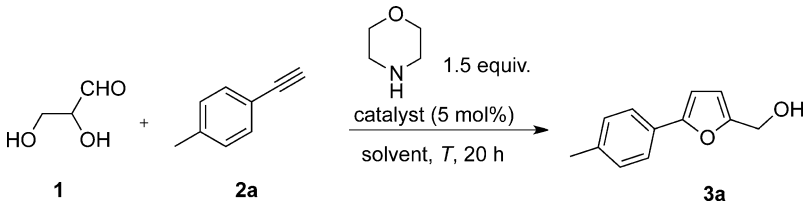
Keywords: alcohols; aldehydes; alkynes; amines; furans; gold

Furan derivatives are important structural motifs that are found in a wide range of natural products,[1] pharmaceuticals[2] and functional materials.[3] As a result, numerous efficient synthetic methods for the synthesis of substituted furan derivatives have been developed.[4] However, only limited protocols are reported for the assembly of (5-arylfuran-2-yl)methanol, which is an important building block in organic synthesis; traditional methods are Pd-catalyzed reactions, such as the Suzuki–Miyaura coupling,[5] the Stille coupling reaction[6] and direct arylations of furfuryl alcohols[7] (Scheme 1). However, due to the required prefunctionalization of the applied starting substrates (such as halides, arylboronic acids or other organometallic reagents), these approaches can be challenging. An alternative method to access (5-arylfuran-2-yl)methanol derivatives is the reduction of 2-furanyl aldehydes, acids or esters, but these precursors often also have to be prepared by several reaction steps.[8] Despite the impressive progress made in this area, the exploration of new methods for the preparation of (5-arylfuran-2-yl)methanols from readily available starting materials is still highly desirable. While all these protocols are based on chemical modifications of an already existing furan core, we envisioned that a completely different disconnection might be possible.



Scheme 1. Synthetic strategies for the synthesis of 2-furanmethanol.

Table 1. Screening of the reaction conditions.[a]



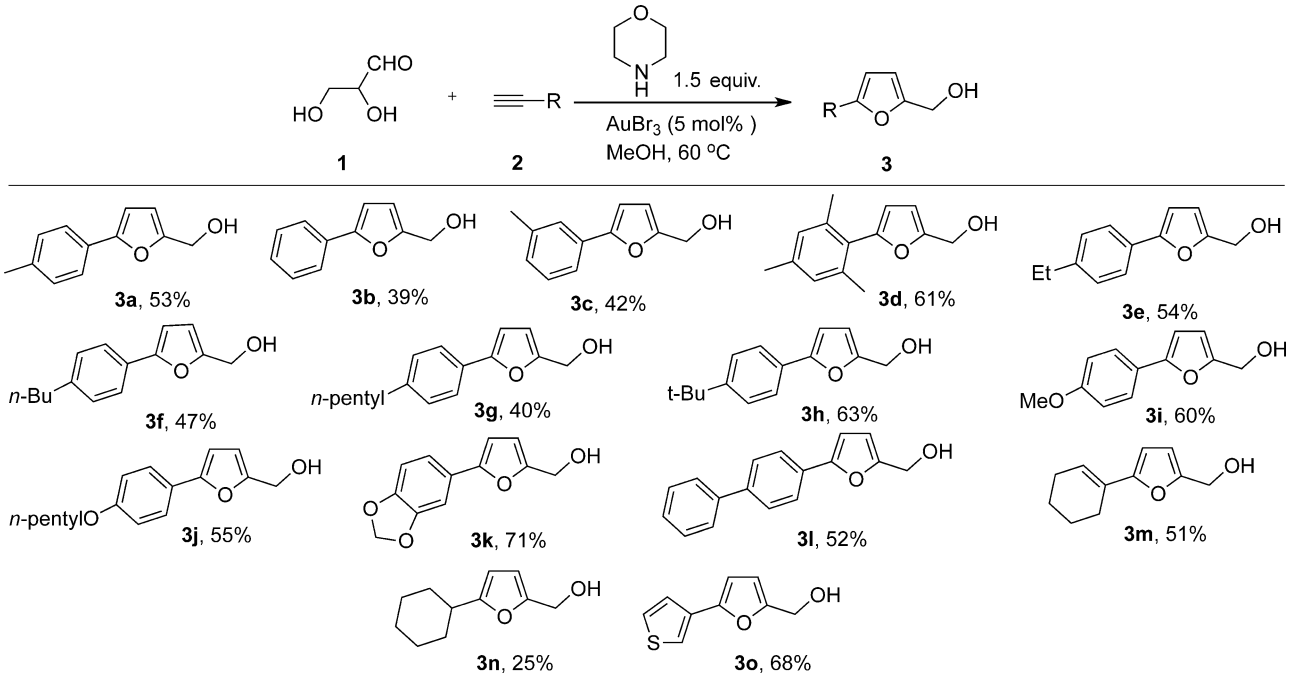
Entry	Catalyst	Solvent	Temperature [°C]	Yield [%] of **3a**
1	$AuBr_3$	MeOH	r.t.	17
2	$AuBr_3$	MeOH	60	53
3	$AuBr_3$	MeOH	80	20
4[b]	$AuBr_3$	MeOH	60	39
5[c]	$AuBr_3$	MeOH	60	0
6	$AuCl_3$	MeOH	60	31
7	AuCl	MeOH	60	19
8	CuI	MeOH	60	0
9	$PtCl_2$	MeOH	60	0
10	$PtCl_4$	MeOH	60	0
11	TfOH	MeOH	60	0
12	Ph_3PAuCl	MeOH	60	15
13	$Ph_3PAuCl/AgOTf$	MeOH	60	13
14	IPrAuCl	MeOH	60	0
15	IPrAuCl/AgOTf	MeOH	60	0
16	IPrAuCl/AgNTf	MeOH	60	0
17	$AuBr_3$	DCE	60	trace
18	$AuBr_3$	DCM	60	17
19	$AuBr_3$	DMF	60	0
20	$AuBr_3$	DMSO	60	0
21	$AuBr_3$	MeCN	60	trace
22	$AuBr_3$	toluene	60	23
23	$AuBr_3$	$MeOH/H_2O$ (9/1)	60	41

[a] *Reaction conditions:* a solution of **1** (0.3 mmol), **2a** (0.45 mmol), morpholine (0.45 mmol) and catalyst (5 mol%) was stirred in the specified solvent (1.0 mL) and at the specified temperature for 20 h.
[b] 20 mol% of morpholine was employed.
[c] Morpholine was absent.

We regarded the $AuBr_3$-catalyzed A3-coupling reaction[9] of terminal alkynes, aldehydes, and amines as ideal as it has already proven to be a powerful tool for the access to complex compounds from simple starting materials.[10] By using an alkyne and glyceraldehyde as building blocks, an addition/condensation/cyclization strategy might deliver the desired product in only one step. In continuation of our interest in gold-catalyzed syntheses of furans,[11] we herein disclose a divergent approach for the construction of (5-arylfuran-2-yl)methanol through a gold(III)-catalyzed A3-coupling/cyclization cascade.

Glyceraldehyde **1**, morpholine and 1-ethynyl-4-methylbenzene **2a** were selected as substrates for the first model reaction. Our optimization studies are summarized in Table 1. With $AuBr_3$ as catalyst at room temperature in MeOH, minor amounts of furfuryl alcohol **3a** were collected (entry 1). Temperature variation (entries 2 and 3) showed that a higher yield of **3a** is achievable by a moderate raise of the temperature. At 60 °C, 53% of furan was obtained. As no morpholine is incorporated in the final product, we tested the reaction in the absence of morpholine, but no reaction took place (entry 5). Even with only 20 mol% of morpholine, 39% of the target compound were collected which demonstrates that morpholine acts as a kind of co-catalyst but still the results with stoichiometric amounts of this additive were higher (entry 4). A brief screening of different catalysts revealed $AuBr_3$ to be optimal for the A3-coupling reaction to furfuryl alcohols. Other counter ions at the gold(III) center reduced the yield (entry 6) while no conversion at all was obtained with Cu and Pt salts, as well as by the use of TfOH (entries 8–11). Gold(I) salts were also not suitable and only a minor conversion was obtained with phosphane ligands (entry 12), while no reactivity was detected with NHC ligands (entry 14). In order to study the effect of solvent, the reaction with the best catalyst ($AuBr_3$) was carried out in a variety of different solvents. In all cases

Table 2. Synthesis of 5-subsititued furfuryl alcohols.[a]

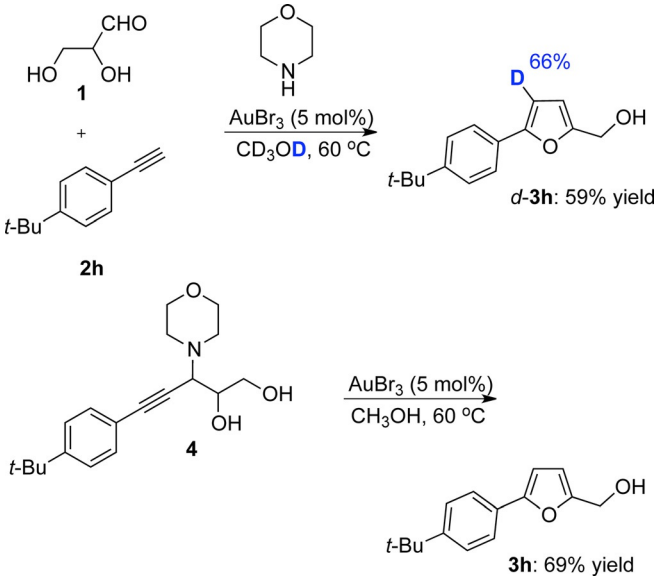


[a] *Reaction conditions:* a solution of **1** (0.3 mmol), **3** (0.45 mmol), morpholine (0.45 mmol), and $AuBr_3$ (5 mol%) was stirred in MeOH (1.0 mL) at 60 °C for 20 h.

(even in a mixture of MeOH and H_2O) the reaction only led to **3a** in low yield (entries 17–23).

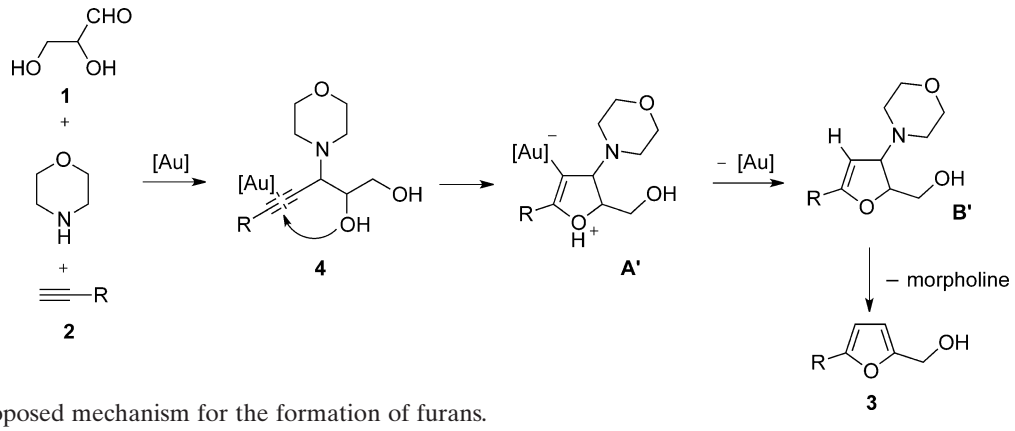
Under the optimized conditions for the formation of furfuryl alcohol derivative **3a**, we explored the substrate scope of this synthetic concept. As outlined in Table 2, 2,5-disubstituted furan products **3** could be obtained in good to moderate yields. The scope of the reaction with respect to the alkyne was investigated. The reaction of glyceraldehyde **1** with various alkynes **2** gave the corresponding products **3** in 25–71% isolated yields. Regarding the substrate scope, terminal alkynes with an electron-donating group attached to the aromatic part, such as methyl (**3a**, **3c**, **3d**), ethyl (**3e**), butyl (**3f**), amyl (**3g**), *tert*-butyl (**3h**) and alkoxy (**3i–k**) are beneficial for an effective transformation. In addition vinyl (**3m**), aliphatic (**3n**) and heterocyclic substitutents (**3o**) at the alkyne part turned out to be suitable starting materials as well. Finally, it should be mentioned that electron-withdrawing substituents at the arene core showed no reactivity under the optimized conditions. As a consequence methyl 1-ethynyl-4-(trifluoromethyl)benzene, 4-ethynylbenzoate, 4-ethynylbenzonitrile and 1-bromo-4-ethynylbenzene did not yield the desired furans.

To gain mechanistic insight, isotope labelling experiments using glyceraldehyde **1**, morpholine and 1-*tert*-butyl-4-ethynylbenzene **2h** as the model reaction under standard conditions were conducted (Scheme 2). As the solvent property significantly affected the reaction outcome, CD_3OD was first utilized



Scheme 2. Mechanistic experiments.

as the solvent and *d*-**3h** was obtained, *d*-**3h** showed deuterium incorporation in the C-4 position of the furan product. It is reasonable to assume that this deuterium is derived from a protodemetallation step by the solvent. This indicates that a 4-aurated furan is an intermediate in the catalytic cycle. Next, the possible intermediate propargylamine **4** (that would be formed by an initial A3 coupling reaction) was pre-



Scheme 3. Proposed mechanism for the formation of furans.

pared and isolated by using a copper catalyst and then treated under the standard reaction condition with the gold catalyst. Indeed the target compound **3h** was collected in 69% yield. This strongly suggests that an A3-coupling reaction of the substrates **1**, **2g** and morpholine stands at the beginning of the reaction cascade.

Based on these experiments, we propose[12] the mechanism illustrated in Scheme 3 for the formation of the furans **3**. An initial $AuBr_3$-catalyzed A3-coupling of **1** with **2** and morpholine generates the intermediate **4**. This homopropargylic alcohol **4** then undergoes an intramolecular cyclization[13] which after protodemetallation delivers dihydrofuran intermediate **B′**. Aromatization by elimination of the amine then leads to the final product **3**.[14]

In summary, we have established a new Au(III)-catalyzed A3-coupling/cyclization cascade to afford furan-2-ylmethanol derivatives. This versatile protocol enables easy access towards the target products from abundantly available alkynes and aldehydes as starting materials and is operated under mild reaction conditions. With regard to the synthetic efficiency it is important to note that the functionalized furfuryl alcohols are formed in one synthetic step and not by post-functionalizations of a preformed furan system. Three new bonds are formed overall, thus a yield of 51% is equivalent to an average efficiency of 80% for each bond formation, the best yield of 71% even to an average of 91%. Therefore we believe that this protocol offers an attractive alternative to existing protocols for the synthesis of these valuable building blocks.

Experimental Section

General Procedure; Synthesis of 5-Subsititued Furan-2-ylmethanol 3

In a one-necked flask, a solution ofglyceraldehyde **1** (0.3 mmol), morpholine (4.5 mmol), alkyne **2** (4.5 mmol) and $AuBr_3$ (5 mol%) in methanol (2 mL) was stirred at 60 °C for 20 h. After completion of the reaction (observed on TLC), the solvent was evaporated under reduced pressure to obtain the crude mixture. The residue was purified by silica-gel column chromatography (ethyl acetate/petroleum ether = 1/10–1/4) to afford the pure product **3**. The obtained product was analyzed by ^{1}H NMR, ^{13}C NMR and HR-MS.

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