Gold Catalysis

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Gold-Catalyzed Regioselective Synthesis of 2- and 3-Alkynyl Furans**

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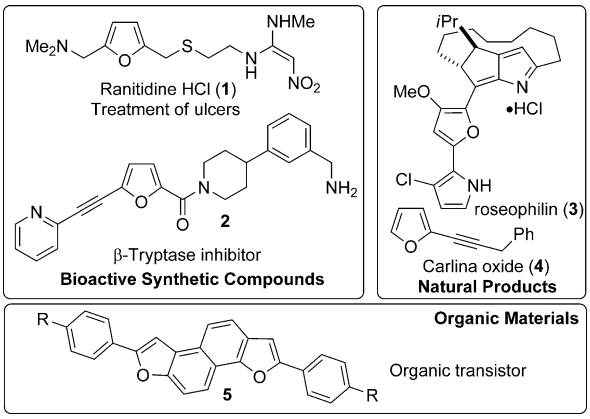
Furans are omnipresent in synthetic bioactive compounds, natural products, and innovative organic materials (Scheme 1).[1] They also give access to equally important



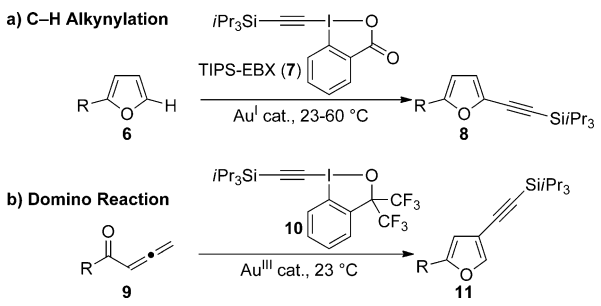
Scheme 1. Examples of furans and alkynyl furans in synthetic bioactive compounds, natural products, and organic materials.

tetrahydrofurans through reduction or dihydropyrans through oxidation. It is consequently not surprising that the development of new methods to synthesize and functionalize furans is an area of intense research in modern organic chemistry.[2] In particular, direct metal-catalyzed methods based on C–H functionalization or domino cyclization reactions constitute promising efficient approaches.[3]

The efficient synthesis of alkyne-substituted furans would be highly desirable, because these compounds are present in bioactive molecules and natural products (Scheme 1). They also constitute ideal building blocks for the elaboration of more complex scaffolds, owing to the versatile chemistry of the triple bond.[4] Recently, efficient direct C–H alkynylation reactions have emerged for the functionalization of a broad range of (hetero)aromatic compounds.[5] In the case of furans, only two examples of direct alkynylation occurring in 45–53% yield have been reported very recently by Su and co-workers.[5m] Alkynylated furans are usually accessed from prefunctionalized heterocycles, with the Sonogashira reaction of halogenated precursors being the most frequently used. New catalytic methods giving a more direct and regioselective access to alkynylated furans need consequently to be developed.

The exceptional properties of gold for the activation of π systems and the functionalization of C–H bonds have been investigated intensively in the last 15 years.[6] Nevertheless, most gold-catalyzed processes were terminated by protonation or halogenation until very recently. In the last five years, important breakthroughs towards more efficient domino processes have been realized by using two approaches: the transmetalation of the gold intermediate to another metal[7] and the in situ oxidation to a Au^{III} intermediate by using a strong oxidant, followed by reductive elimination.[8] Despite this progress, there are currently only two examples of Au-catalyzed alkynylation through in situ oxidation: the C–H functionalization of arenes developed by Nevado and de Haro[5g] and a domino cyclization/alkynylation of allenoates to give butenolides introduced by Gouverneur and co-workers.[8d]

To develop more general oxidative electrophilic alkynylation methods, we have turned towards well-defined hypervalent ethynylbenziodoxolone (EBX) reagents.[9] The unique possibility to tightly modulate the electrophilicity and oxidation potential of these reagents allowed us to develop the Au-catalyzed C–H alkynylation of electron-rich arenes,[9a–e] the metal-free α-alkynylation of carbonyl compounds[9f] and the Pd-catalyzed oxy- and amino-alkynylation of olefins.[9g–h] Herein, we report the first example of direct alkynylation of furans by using a Au^{I} catalyst and 1-[(tri*iso*propylsilyl)-ethynyl]-1,2-benziodoxol-3(1*H*)-one (TIPS-EBX, **7**). This reaction proceeds at low temperature (23 to 60 °C) and is highly selective for the most electron-rich C2 position of furans (Scheme 2a). To access C3-alkynylated furans, we envisaged a domino process based on the well-established Au-catalyzed cyclization of allenic ketones.[6f,10] However, we had shown before that TIPS-EBX (**7**) is not able to intercept Au–C_{sp^2} intermediates in domino processes.[9c] Herein, we dem-



Scheme 2. Selective Au-catalyzed synthesis of 2- and 3-ethynylated furans through C–H alkynylation and domino cyclization/alkynylation.

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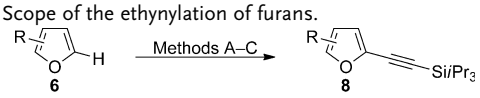
onstrate that the modified ethynylbenziodoxole reagent **10** is exceptionally efficient in this domino process, leading to C3-alkynylated furans in high yields at room temperature (Scheme 2b). The availability of a well-defined reagent for alkynylation in gold-catalyzed domino processes represents a major breakthrough and is expected to find broad application beyond the synthesis of alkynyl furans.

We started our investigations with the C2-alkynylation of 2-hexylfuran (**6a**) as substrate. When this substrate was treated under the standard conditions for thiophene alkynylation (TIPS-EBX (**7**, 1.2 equiv),[11] trifluoroacetic acid (TFA, 1.2 equiv) in acetonitrile),[9b] only decomposition of the starting material was observed. This was probably due to the acid sensitivity of furans. In fact, the C2-alkynylation product was isolated in 90% yield in the absence of TFA, thereby allowing us to proceed directly with the examination of the scope of the reaction (Table 1).

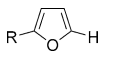
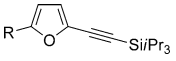
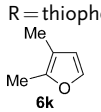
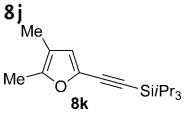
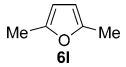
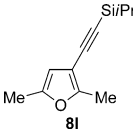
The reaction worked well for 2-alkyl-substituted furans (Table 1, entries 1–5) and furan (**6f**) itself (entry 6). For volatile substrates, it was more convenient to run the reaction in the furan itself as solvent. The alkynylation of 2-aryl furans was slower, but the products could be obtained in 56–71% yield by running the reaction at 60°C (Table 1, entries 7–10). Finally, disubstituted furans could also be used in the reaction (Table 1, entries 11 and 12). In case of 2,5-disubstituted furan **6l**, 3-alkynylation product **8l** was obtained in 45% yield (Table 1, entry 12).

After having developed a C–H functionalization method for the 2-alkynylation of furans, we turned to the synthesis of

Table 1: Scope of the ethynylation of furans.



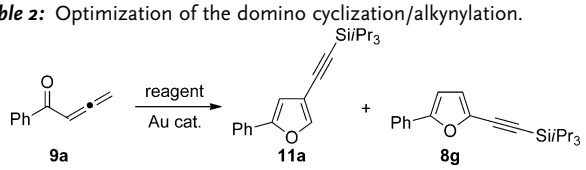
A: TIPS-EBX (**7**, 1.2 equiv), CH_3CN, 23 °C[a]
B: Neat, 23 °C[b]
C: TIPS-EBX (**7**, 1.2 equiv), CH_3CN, 60 °C[c]

Entry	Substrate	Product	Method	Yield [%][d]
				
1	R = hexyl **6a**	**8a**	A	90
2	R = methyl **6b**	**8b**	B	78
3	R = ethyl **6c**	**8c**	B	79
4	R = *t*Bu **6d**	**8d**	A	56
5	R = CH_2OBn **6e**	**8e**	C	55
6	R = H **6f**	**8f**	B	61
7	R = phenyl **6g**	**8g**	C	68
8	R = tolyl **6h**	**8h**	C	66
9	R = 4-$MeOC_6H_4$ **6i**	**8i**	C	71
10	R = thiophenyl **6j**	**8j**	C	56
11	 **6k**	 **8k**	A	65
12	 **6l**	 **8l**	B	45

[a] Reaction conditions: **6** (0.40 mmol), **7** (0.48 mmol), AuCl (5 mol%), 0.2 M, RT, 26 h. [b] Furan **6** (1 mL), **7** (0.40 mmol), RT, 26 h. [c] As [a] but at 60°C. [d] Yields of isolated products after column chromatography.

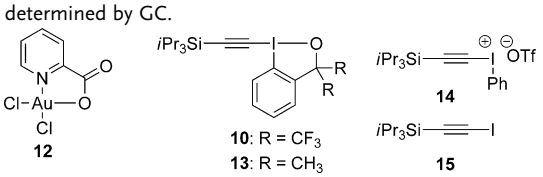
the 3-substituted regioisomers based on a domino cyclization/alkynylation process (Table 2). The first results were not promising: a Au^I catalyst (AuCl) did not promote the cyclization of allene **9a**[12] (Table 2, entry 1), whereas a Au^{III}

Table 2: Optimization of the domino cyclization/alkynylation.



Entry	Catalyst	Equivalents (reagent)	Base	Solvent	Yield [%] **11a**/**8g**[a]
1	AuCl	1.2 (**7**)	–	CH_3CN	< 5
2	$AuCl_3$	1.2 (**7**)	–	CH_3CN	< 5[b]
3	**12**	1.2 (**7**)	–	CH_3CN	24:7
4	**12**	1.2 (**7**)	NEt_3	CH_3CN	< 5
5	**12**	1.2 (**7**)	K_2CO_3	CH_3CN	10:0
6	**12**	1.2 (**7**)	Na_2CO_3	CH_3CN	31:0
7	**12**	1.2 (**10**)	–	CH_3CN	50:0[c]
8	**12**	1.2 (**13**)	–	CH_3CN	< 5
9	**12**	1.2 (**14**)	–	CH_3CN	< 5
10	**12**	1.2 (**15**)	–	CH_3CN	< 5
11	**12**	1.2 (**10**)	Na_2CO_3	CH_3CN	33:0[d]
12	**12**	2.0 (**10**)	Na_2CO_3	CH_3CN	73:0[d]
13	**12**	2.0 (**10**)	Na_2CO_3	CH_2Cl_2	11:0[d]
14	**12**	2.0 (**10**)	Na_2CO_3	THF	6:0[d]
15	**12**	2.0 (**10**)	Na_2CO_3	EtOH	23:0[d]
16	**12**	2.0 (**10**)	Na_2CO_3	*i*PrOH	93:0[d]

[a] Reaction conditions: **9a** (0.1 mmol), Au catalyst (5 mol%), 0.02 M, RT, 72 h, yield of isolated product. [b] Formation of cyclization product **6g** was observed. [c] Furan **6g** was isolated in 14% yield. [d] Yield was determined by GC.



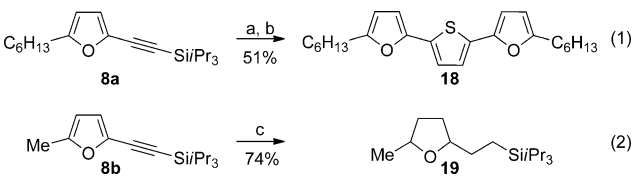
catalyst ($AuCl_3$) led to cyclization as reported,[10a] but no alkynylation was observed (entry 2). We consequently extended our search to a broad range of other Au^I and Au^{III} catalysts, and a promising result was obtained with pyridine-2-carboxylato-gold(III) dichloride (**12**), which gave 24% of the desired 3-alkynylation product **11a** together with 7% of 2-alkynylation product (Table 2, entry 3).[13] In principle, 2-alkynylation could have occurred after premature protonation of the formed gold intermediate. Indeed, furan **8g** was obtained exclusively in 23% yield when catalyst **12** was used with 2-phenyl-furan (**6g**) under the conditions of Table 1. We speculated that a base could prevent protonation of the intermediate Au–C bond and avoid 2-alkynylation. In fact, 3-alkynylation was observed exclusively in presence of bases, with the best result (31%) obtained with sodium carbonate (Table 2, entries 4–6). However, when using TIPS-EBX (**7**), we were not able to further increase the yield of **11a**, despite extensive optimization of the reaction conditions.

For the domino process to be successful, fine-tuning of the reactivity of the alkynylation reagent is expected to be an

essential factor. We therefore decided to examine other hypervalent iodine reagents for the reaction. Indeed, the domino process was more efficient when using bistrifluoromethyl benziodoxole reagent **10**,[11a] which gave 50% of **11a** together with 14% of 2-phenyl furan (**6g**), resulting probably from protonation of the putative organogold intermediate (Table 2, entry 7). The fact that no 2-alkynylation product was obtained in this case is probably due to the lower efficiency of reagent **10** in direct C–H alkynylation.[9d,14] In contrast, no product was observed with the dimethyl-substituted reagent **13** or alkynyl iodonium salt **14**, with a more or less basic oxygen atom bound to the iodine, respectively (Table 2, entries 8 and 9). On the other hand, no product was observed when alkynyl iodide **15** was used (Table 2, entry 10). These results further demonstrated that success in this challenging domino process can be achieved only for a very narrow window of electronic density at the iodine atom. In presence of sodium carbonate, the formation of 2-phenyl furan (**6g**) was suppressed, albeit at the cost of the yield of **11a** (Table 2, entry 11). Fortunately in this case, a larger excess of hypervalent iodine reagent **10** allowed increasing the yield substantially to 73% (Table 2, entry 12). Finally, reinvestigation of the solvent led to the use of isopropanol, for which the 3-alkynylated product **11a** was obtained in 93% yield determined by using GC (Table 2, entries 13–16). On a 0.3 mmol scale, furan **11a** could finally be isolated in 68% yield (Table 3, entry 1).

Investigation of the scope of the reaction showed that substitution of the benzene ring by a methyl group led to nearly quantitative yields (94–95%), independently of its position (Table 3, entries 2–4). A *para*-methoxy or a phenyl group were also well-tolerated in the reaction (Table 3, entries 5 and 6), as well as a furyl substituent (entry 7). A current limitation of the method is that electron-withdrawing groups were not tolerated, because in this case Michael addition of the solvent on the allene was observed in isopropanol and decomposition was obtained in other solvents. The reaction was not limited to aromatic substituents, and excellent yields were obtained with both primary (Table 3, entries 8–9) and a secondary (entry 10) aliphatic substituent. A more sensitive benzyl group was also well tolerated, giving the alkynylation product **11k** in 77% yield (Table 3, entry 11). Finally, an important preliminary result was obtained for the synthesis of polysubstituted furans: Starting from allene ketone **16**, trisubstituted furan **17** was obtained in 94% yield (Table 3, entry 12). The synthesis of such a product would be very challenging through C–H functionalization, owing to serious issues of reactivity and regioselectivity.

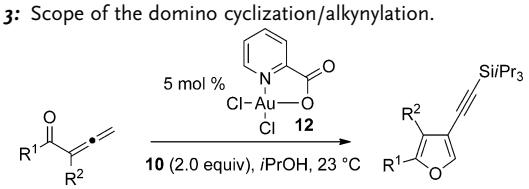
The obtained silylated alkynyl furan **8a** was easily deprotected to give the corresponding free acetylene. By using a methodology developed previously in our group,[9b] one-pot dimerization and thiophene formation then resulted in the formation of alternating heterocyclic oligomer **18** (Scheme 3, (1)). Heterocyclic oligomers are important in organic materials, but are usually composed of a single class of heterocycles. New properties can be expected to emerge with an easier access to more-complex oligomers. Furthermore, hydrogenation gave access to tetrahydrofurans, which are important building blocks for the synthesis of bioactive synthetic and natural products (Scheme 3, (2)).

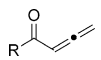
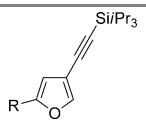
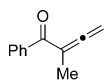
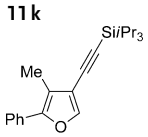


Scheme 3. Functionalization of alkynyl furans **8a** and **8b**. Reaction conditions: a) tetrabutylammonium fluoride, THF, 0°C, 1 h, 78%; b) $Cu(OAc)_2$, CH_3CN, 80°C, 12 h; then $Na_2S{\cdot}3H_2O$, 80°C, 24 h, 65%; c) 10 wt% Pd/C, H_2, pentane/EtOH, 12 h, 74%, 5:1 d.r.

The results obtained for the C2-alkynylation of furans are in line with our previous work on the alkynylation of heterocycles.[9a–d] In particular, we had shown that AuCl reacts instantaneously with TIPS-EBX (**7**) to form bis(triisopropylsilyl)diyne as major product. This led us to propose a catalytic cycle involving first oxidative addition of a Au^I species on the reagent, followed by C–H auration and reductive elimination as one of the most probable mechanisms for this transformation. In this context, the fact that the new domino cyclization/alkynylation process is catalyzed by a Au^{III} catalyst is mechanistically intriguing. In fact, the only domino cyclization/alkynylation process reported to date has been proposed to proceed through a Au^I–Au^{III} catalytic cycle.[8d] To explain our results, an unprecedented electro-

Table 3: Scope of the domino cyclization/alkynylation.



Entry	Substrate	Product	Yield [%][a]
			
1	R^1 = Phenyl **9a**	**11a**	68
2	R^1 = 4-MeC_6H_4 **9b**	**11b**	94
3	R^1 = 3-MeC_6H_4 **9c**	**11c**	95
4	R^1 = 2-MeC_6H_4 **9d**	**11d**	94
5	R^1 = 4-$MeOC_6H_4$ **9e**	**11e**	83
6	R^1 = 4-PhC_6H_4 **9f**	**11f**	53
7	R^1 = 2-furyl **9g**	**11g**	75
8	R^1 = hexyl **9h**	**11h**	93
9	R^1 = ethyl **9i**	**11i**	96
10	R^1 = cyclohexyl **9j**	**11j**	97
11	R^1 = benzyl **9k**	**11k**	77
12	 **16**	 **17**	94

[a] Reaction conditions: **9a** (0.3 mmol), Au catalyst **12** (5 mol%), isopropanol (15 mL), RT, 5–72 h, yields of isolated products after column chromatography are given.

philic alkynylation of a Au^{III} intermediate has to be postulated. To better understand the unique properties of catalyst **12** in the domino process, several control experiments were done:

1) Product **11a** was obtained in 81% yield (determined by using GC) when the catalyst was formed in situ from $AuCl_3$ and picolinic acid.
2) No product was obtained with $AuCl_3$/pyridine, $AuCl_3$/benzoic acid, or $AuCl_3$(pyridine)/benzoic acid as catalyst.
3) The use of $AuCl_3$ together with 4-carboxy-pyridine (isonicotinic acid) did also not lead to product formation.
4) Stoichiometric reaction of **12** with **9a** led to the immediate formation of furan **6g**. In contrast to what had been observed with AuCl, no reaction was observed when mixing **12** with benziodoxole **10**.

These experiments demonstrated that a gold(III) picolinic acid complex was required for the domino process, and that the first step in the reaction most probably involved cyclization of the allene. Obviously, further work will be required to better understand the mechanism of the reaction and the exact role of the picolinic acid ligand.

In summary, we have reported the first selective synthesis of 2- and 3-alkynylated furans based on gold catalysis. An unprecedented Au-catalyzed C–H functionalization with the hypervalent iodine reagent TIPS-EBX (**7**) was first applied to access 2-ethynylated furans. By using a conceptually different domino cyclization/alkynylation approach, we were able to develop the first Au-catalyzed synthesis of 3-alkynylated furans. Key for success was a unique combination of a Au^{III} catalyst and a modified benziodoxole reagent **10**. The clean interception of an Au–C intermediate with a well-defined alkynylation reagent constitute an important breakthrough in the field, and future work will be focused on further applications in Au-catalyzed C–H functionalization and domino processes, as well as to the investigation of the mechanism of the reaction.

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Keywords: C–H functionalization · domino reactions · furans · gold · hypervalent iodine

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