

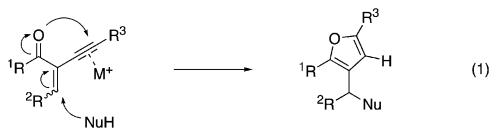
AuCl₃-Catalyzed Synthesis of Highly Substituted Furans from 2-(1-Alkynyl)-2-alken-1-ones

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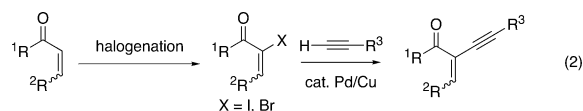
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Highly substituted furans play an important role in organic chemistry, not only as key structural units in many natural products and important pharmaceuticals,¹ but as useful building blocks in synthetic chemistry.² For this reason, the efficient synthesis of multiply substituted furans continues to attract the interest of synthetic chemists.³ Among the many different approaches to furans, the transition metal-catalyzed cyclization of allenyl ketones and 3-alkyn-1-ones is particularly attractive,⁴ although its synthetic utility is somewhat limited by a lack of general and practical routes to the starting ketones.^{4b-d,5} We envisioned that 2-(1-alkynyl)-2-alken-1-ones might also undergo a transition metal-catalyzed cyclization to highly substituted furans (eq 1).



This unique cyclization is particularly attractive, because *sequential nucleophilic domino attack onto a metal-complexed alkyne* should afford multiply substituted furans through simultaneous formation of a C–O bond and a remote carbon–nucleophile bond. Thus, the regioselective introduction of substituents about the furan ring comes down to the appropriate choice of 2-(1-alkynyl)-2-alken-1-one and nucleophile, which allows for considerable versatility, since such ketones are readily available from simple alkenones and alkynes (eq 2).



Herein, we report a highly efficient, gold-catalyzed, atom-economical approach⁶ to multiply substituted furans. Overall, ready access to a wide variety of polysubstituted furans is achieved upon reaction of various 2-(1-alkynyl)-2-alken-1-ones with an unprecedented set of nucleophiles under very mild reaction conditions. Alcohols and 1,3-diketones, as well as various electron-rich aromatics, serve as efficient nucleophiles in this new process.

Preliminary studies have been carried out on 2-phenylethynyl-2-cyclohexen-1-one (**1**) and methanol (1.5 equiv), using a series of potential transition metal catalysts (1 mol %) in CH₂Cl₂. Initial results indicated that AgO₂CCF₃ (10 h, 87%), Cu(O₃SCF₃)₂ (9 h, 81%), AuCl₃ (0.5 h, 88%), and Hg(O₂CCF₃)₂ (8 h, 86%) all afford good yields of furan **2**. Among these salts, however, AuCl₃ is the most efficient catalyst based on reaction time. This is consistent with previous work on the cyclization of 3-alkyn-1-ones to furans.^{4a} Pd(OAc)₂ provided a low yield (6 h, 30%), mainly due to the facile reduction of Pd(II) to Pd(0) in the presence of the alcohol.⁷ The addition of 2 equivs of PPh₃ to Pd(OAc)₂ did stabilize the Pd(II) salt, but slowed the reaction. Thus, AuCl₃ was chosen as the catalyst

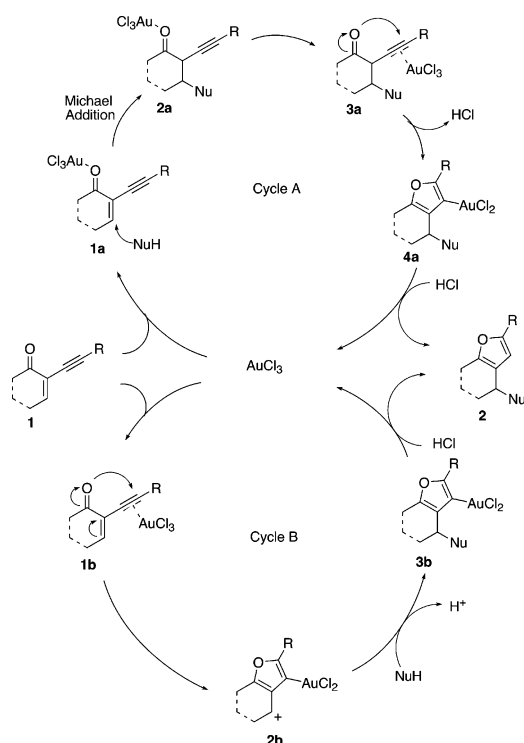
Table 1. AuCl₃-Catalyzed Synthesis of Substituted Furans by Cyclization of 2-(1-Alkynyl)-2-alken-1-ones^a

entry	alkenynone	nucleophile	product(s)	yield (%)
1	R = Ph	1 MeOH	Nu = MeO	2 88
2	Ph	1 Ph≡C-CH ₂ -OH	Ph≡C-CH ₂ -O	3 75
3	Ph	1		4 1.2:1 <i>dr</i>
4	Ph	1		5 81
5	Ph	1		6 52
6	Ph	1		7 90
7		8 MeOH	MeO	9 80
8		MeOH		10 62
9		MeOH		11 60 ^{b,c}
10		MeOH		12 66 ^b
11		MeOH		13 63 ^b
12		MeOH		14 34 + 40

^a All reactions were run under the following conditions, unless otherwise specified: a solution of 0.2 mmol of 2-(1-alkynyl)-2-alken-1-one, 1 mol % of AuCl₃, and 1.5 equiv of nucleophile in 1 mL of CH₂Cl₂ was stirred at room temperature for 1 h. ^b AuCl₃ (2 mol %) was employed and added in two equal portions. ^c The reaction took 48 h.

for the cyclization of a number of other substrates. When the reaction of **1** was performed in the absence of AuCl₃ or in the presence of a catalytic amount of HBF₄, instead of AuCl₃, no

Scheme 1



cyclization product **2** was obtained at all. These blank tests clearly indicate that AuCl₃ is required for the reaction to proceed.

The cyclization of **1** with various alcohols was first investigated (Table 1). Not only simple alcohols, such as methanol (Table 1, entry 1), but also labile alcohols, such as 3-phenyl-2-propyn-1-ol, and a protected D-pyranose are effective nucleophiles (Table 1, entries 2 and 3). The reaction of 1,3-cyclohexanedione proved quite interesting as it afforded a high yield of a product in which the new bond was formed only between the β-carbon of the α,β-unsaturated ketone and the oxygen of the diketone (Table 1, entry 4). A distinctive feature of this novel approach to complex furans is the facile introduction of electron-rich arenes, such as *N,N*-dimethylaniline and indole, as carbon-based nucleophiles (Table 1, entries 5 and 6). *N,N*-Dialkylanilines can also be employed as benzene surrogates, since the direct deamination of *N,N*-dialkylanilines has recently been reported.⁸

A range of 2-(1-alkynyl)-2-alken-1-ones readily participate in this gold-catalyzed cyclization. In addition to 2-(1-alkynyl)-cyclohexenones **1**, **8**, and **18** (Table 1, entries 1–7 and 12), chromone **10** (Table 1, entry 8) undergoes smooth cyclization. An alkyne bearing a vinylic substituent (Table 1, entry 7) is readily accommodated, but alkynes bearing H, alkyl, or TMS groups have thus far failed. Acyclic 2-alken-1-ones also afford highly substituted furans (Table 1, entries 9–11). Note that the latter acyclic substrates readily accommodate additional carbon–carbon double or triple bonds. Unfortunately, little stereoselectivity was observed in the cyclization of ketone **18** (Table 1, entry 12).

At least two conceivable mechanisms can be proposed for this gold-catalyzed cyclization (Scheme 1). In one (cycle A), gold functions as both a Lewis acid and a transition metal.⁹ AuCl₃ first acts as a Lewis acid, forming a complex with the carbonyl oxygen. This facilitates 1,4-addition of the nucleophile to the carbon–carbon double bond to produce **2a**.¹⁰ Subsequent coordination of the alkyne moiety of the alkenynone **2a** to AuCl₃ induces a cyclization of the carbonyl oxygen onto the triple bond, followed by elimination of

a proton and protonation of the resulting organogold intermediate to afford furan **2** and simultaneously regenerate the catalyst AuCl₃. An alternative mechanism in which AuCl₃ functions simply as a transition metal is also possible (Scheme 3, cycle B).^{4a} The coordination of the triple bond of **1** to AuCl₃ enhances the electrophilicity of the triple bond, and subsequent nucleophilic attack of the carbonyl oxygen on the electron-deficient triple bond generates carbocation **2b**. Intermolecular nucleophilic attack on the carbocation and subsequent protonation of the carbon–gold bond afford furan **2** and regenerate the catalyst AuCl₃. The mechanism illustrated in cycle B appears more likely since 1% AuCl₃ fails to catalyze the 1,4-addition of methanol to 2-cyclohexenone and methyl vinyl ketone under our standard reaction conditions.

In summary, a new catalytic approach to highly substituted furans has been developed through the cyclization of 2-(1-alkynyl)-2-alken-1-ones with various nucleophiles under very mild reaction conditions. The reaction is efficiently catalyzed by AuCl₃ and several other transition metal salts and likely proceeds by a novel mechanism involving cyclization to produce a gold-containing carbocationic intermediate.

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Supporting Information Available: Experimental details and characterization data for all new compounds (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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