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## Silver-Catalyzed Highly Regioselective Synthesis of a-Carbonyl Furans from Enynones

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# SILVER-CATALYZED HIGHLY REGIOSELECTIVE SYNTHESIS OF $\alpha$ -CARBONYL FURANS FROM ENYNONES

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#### **GRAPHICAL ABSTRACT**



**Abstract** A general and efficient method for the synthesis of a wide range of  $\alpha$ -carbonyl furans is described here. The cyclization of enynone is catalyzed by  $AgBF_4$  in a fluorous biphasic system of perfluorodecalin and N,N-dimethylformamide. A variety of chain ketone and cyclic ketone substrates were used to investigate the scope of the reactions.

Keywords α-Carbonyl furans; enynone; ketone; molecular oxygen; perfluorodecalin

#### INTRODUCTION

The synthesis of furans has been the subject of intense research, because they are wildly used as key structural units in many bioactive natural products and important pharmaceuticals. Moreover, they are useful intermediates for the preparation of varieties of acyclic and heterocyclic compounds.<sup>[11]</sup> The search for efficient routes to multiply substituted furans is an important, continuing goal of organic synthesis. Recently, several studies have focused on the development of metal-catalyzed synthesis of furans employing acyclic precursors. These include the cyclization of allenyl,<sup>[2]</sup> alkynyl,<sup>[3]</sup> cyclopropenyl,<sup>[4]</sup> and cyclopropyl<sup>[5]</sup> ketone derivatives. Alternative strategies involve the cyclization of alkynols,<sup>[6]</sup> substituted propargyl vinyl ethers,<sup>[7]</sup> functionalized oxiranes,<sup>[8]</sup> 1,3-diynes,<sup>[9]</sup> and other substrates.<sup>[10]</sup> Those methodologies are convenient for constructing polysubstituted furans; however, only few examples have been reported on the synthesis of  $\alpha$ -carbonyl furans.<sup>[11]</sup>

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The fluorous biphase system (FBS), first reported by Horváth and Rábai in 1994,<sup>[12]</sup> has attracted considerable interest. It bears some potential advantages over classical homogenous systems, including easy separation and recycling of the catalyst. Moreover, the perfluorinated hydrocarbons are ideal solvents for organic transformation; for example, they have exceptionally high affinity for dioxygen in the catalytic oxidation of hydrocarbons.<sup>[13]</sup> Indeed, a number of organic reactions have achieved in fluorous media.<sup>[14]</sup> Very recently, carbonyl ene-yne compounds have been used for efficient synthesis of multisubstituted furans.<sup>[15]</sup> Inspired by these results, here we present a silver-catalyzed highly regioselective synthesis of  $\alpha$ -carbonyl furans from enynones in fluorous media with molecular oxygen as the oxidant.

#### **RESULTS AND DISCUSSION**

Table 1 summarizes the results of the reaction of ene-yne-diketone (1a) with molecular oxygen in the presence of a catalytic amount of silver salts and

Table 1. Optimization of reaction conditions for the synthesis of multisubstituted furan<sup>a</sup>



Entry	Catalyst	Cosolvent	Yield $(\%)^b$
1	AgCl	DCE	16
2	AgNO <sub>3</sub>	DCE	25
3	AgOAc	DCE	29
4	AgOTf	DCE	47
5	AgF	DCE	8
6	Ag <sub>2</sub> CO <sub>3</sub>	DCE	26
7	AgSbF <sub>6</sub>	DCE	39
8	AgBF <sub>4</sub>	DCE	56
9	<b>C</b> .	DCE	n.r
10	$AgBF_4$	EtOH	41
11	AgBF <sub>4</sub>	Toluene	53
12	AgBF <sub>4</sub>	1,4-Dioxane	84.
13	AgBF <sub>4</sub>	DMSO	77
14	$AgBF_4$	CH <sub>3</sub> CN	63
15	AgBF <sub>4</sub>	DMF	87 (83)
16 <sup>c</sup>	$AgBF_4$	DMF	56
$17^d$	AgBF <sub>4</sub>	DMF	n.p
18 <sup>e</sup>	AgBF <sub>4</sub>	DMF	43

<sup>*a*</sup>Reaction conditions: **1a** (0.25 mmol), catalyst (10 mol%),  $O_2$  (1 atm), cosolvent (0.5 mL), and perfluor-odecalin (0.5 mL) at 60 °C for 16 h.

<sup>b</sup>Determined by GC. Number in parentheses is isolated yield.

<sup>c</sup>DMF (1 mL) without perfluorodecalin.

<sup>d</sup>Under anaerobic conditions.

<sup>e</sup>AgBF<sub>4</sub> (3 mol%).









perfluorodecalin as solvent to screen the best reaction conditions. First, different commonly used metal silver salts were used as the catalyst to conduct this reaction. As can be seen, all silver salts had some effects on the reaction and AgBF<sub>4</sub> could afford the corresponding product in 56% gas chromatographic (GC) yield (Table 1, entries 1–8). The reaction did not proceed without catalyst (Table 1, entry 9). Then AgBF<sub>4</sub> was used as the catalyst of choice. The reaction showed strong cosolvent dependence. Among the cosolvents used, dimethylsulfoxide (DMSO), 1,4-dioxane, and dimethylformamide (DMF) proved appropriate (Table 1, entries 10–15). Control experiments revealed that perfluorodecalin was important to this transformation (Table 1, entry 16). It is noteworthy that the reaction did not work without molecular oxygen (Table 1, entry 17). A decrease of the catalyst dosage led to less satisfactory results (Table 1, entry 18).

With the optimized conditions in hand (Table 1, entry 15), we next investigated the scope of the formation of  $\alpha$ -carbonyl furans by using a variety of substituted enynones. As shown in Table 2, almost all substrates could afford corresponding products with satisfactory yields. Initially, substituents R<sup>1</sup> and R<sup>2</sup> at the carbonyl moiety were evaluated under the standardized conditions. For example, the cyclic substrates could afford  $\alpha$ -carbonyl furans in good yields (**2b**-**f**). The cyclization reactions showed high functional group tolerance, and the functional groups such as keto, ester, or amido group were suitable substrates for the transformation (**2f**-**r**). It is noteworthy that the steric hindrance of the *tert*-butyl group was compatible to the conditions (**2i**). Gratifyingly, the challenging substrates **1s**-**y** were also compatible in the standard conditions and afforded the corresponding products in moderate to good yields (**2s**-**y**). The substituents at the terminal alkyne moiety were subsequently examined. It was pleasing to discover that both the aryl and the alkyl substrates provided the  $\alpha$ -carbonyl furans in similar isolated yields.



Scheme 1. Plausible mechanism for the synthesis of  $\alpha$ -carbonyl furan.

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The possible mechanism was proposed (Scheme 1) on the basis of the previous mechanism studies and our reaction results.<sup>[11]</sup> First, the AgBF<sub>4</sub> coordinated to the triple bond of the alkyne moiety and the carbonyl group. Then the carbonyl oxygen attacked the silver-activated alkyne and the silver carbene intermediate **B** was formed. Finally, the carbene intermediate **B** was oxidized to  $\alpha$ -carbonyl furan **2a** with molecular oxygen.

#### CONCLUSION

In summary, we have developed a highly efficient catalytic system for the synthesis of multisubstituted  $\alpha$ -carbonyl furans via cyclization of enynones with molecular oxygen in a fluorous biphasic system of perfluorodecalin and *N*,*N*-dimethylformamide. Both the chain ketones and the cyclic ketones are suitable substrates for the transformations. Further synthetic applications and studies of the reaction mechanism are in progress.

#### EXPERIMENTAL

#### Typical Procedure for the Preparation of the $\alpha$ -Carbonyl Furans

Enynone (0.25 mmol) and AgBF<sub>4</sub> (10 mol%) were added to an oven-dried Schlenk tube. The septum-sealed tube was evacuated and refilled with O<sub>2</sub> three times. DMF (0.5 mL) and perfluorodecalin (0.5 mL) were added via syringe. The samples were vigorously stirred at 60 °C for 16 h. After the reaction completed, the resulting mixture was cooled with an ice bath. Then the fluorous layer on the bottom was separated for the next reaction. The reaction mixture (organic phase) was diluted with water (6 mL) and extracted with ether ( $3 \times 5$  mL). The combined organic extracts were dried with anhydrous MgSO<sub>4</sub>. The solvent was removed and the crude product was separated by column chromatography to give the pure sample.

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#### SUPPORTING INFORMATION

Typical experimental procedure and characterization for all products can be found in the supplemental data for this article, which can be accessed on the publisher's website.

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