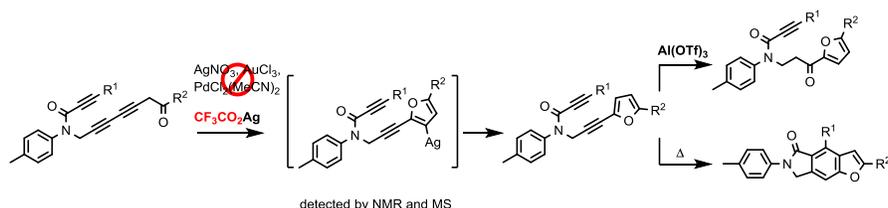


# Silver Trifluoroacetate Promoted Cycloisomerization of 3,5-diyn-1-ones: the direct observation of Ag intermediate and their application in synthesis

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Supporting Information Placeholder



**ABSTRACT:** A simple and mild method for silver trifluoroacetate promoted cycloisomerization of 3,5-diyn-1-ones provided 2-alkynyl furans, which can be further transformed into alkyne hydration or furan-based polycyclic products was developed. It was found that trifluoroacetate anion plays a crucial role in the cycloisomerization reaction, and the intermediate Ag-furan complex was first directly observed by  $^1\text{H-NMR}$  spectroscopy and mass spectrometry.

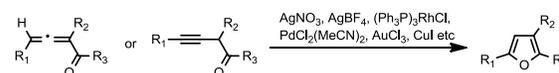
The field of furan synthesis is rapidly developing over the past century, and a variety of inter- and intramolecular strategies have been developed for constructing furan scaffolds.<sup>1</sup> The Paal–Knorr synthesis<sup>2</sup> and the Feist–Benary synthesis<sup>3</sup> have proven very useful for the synthesis of furan derivatives, and transition metal catalyzed furan synthesis has also attracted considerable interest from synthetic chemists.<sup>4</sup> Since Marshall discovered allenyl ketones can selectively be rearranged into furans by  $\text{AgNO}_3$ ,  $\text{AgBF}_4$  and  $(\text{Ph}_3\text{P})_3\text{RhCl}$  (**Scheme 1, a**),<sup>5</sup> It is reported that the cycloisomerization is also feasible under catalysis by  $\text{PdCl}_2(\text{MeCN})_2$ ,  $\text{AuCl}_3$  and  $\text{CuI}$  (**Scheme 1, a**)<sup>6–8</sup>. Although lots of transition metal complex have proven to be effective in furan synthesis, to the best of our knowledge, there are no reports of conversion of conjugated alkynyl propargyl ketones to corresponding furans.

On the other hand, although the plausible mechanism of the cyclization reaction was investigated by deuterium labeling experiments.<sup>6a,9</sup> However, due to the short life and low concentration of reaction intermediates, the attempt to directly observe reaction intermediates by spectroscopic methods was unsuccessful,<sup>6a,7a,10</sup> which can provide deep perception into reaction mechanisms.

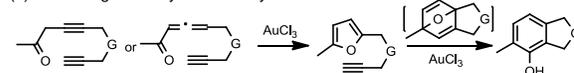
Herein, we report silver trifluoroacetate could selectively activate specific triple bond, thus smoothly promote conversion of 3,5-diyn-1-ones to 2-alkynyl furans. And the reaction intermediate was successfully observed by  $^1\text{H-NMR}$  spectroscopy and mass spectrometry. It is found that trifluoroacetate anion plays an important role in the selectively activation of alkynes. Compare to Hashmi's gold-catalyzed arene synthesis (**Scheme 1, b**)<sup>10</sup>, the extra alkyne moiety requires the catalyst to recognize and activate specific alkynyl group in the substrate, thus result in significant difference.

## Scheme 1. Metal-Catalyzed Furans Synthesis and Intramolecular Dehydro Diels-Alder Reactions of Diarylacetylenes

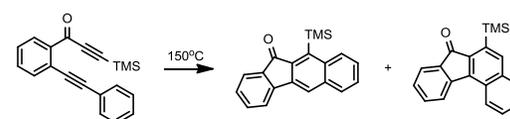
(a) Metal-catalyzed allenone or propargyl ketone cycloisomerization leading to furans<sup>5–8</sup>



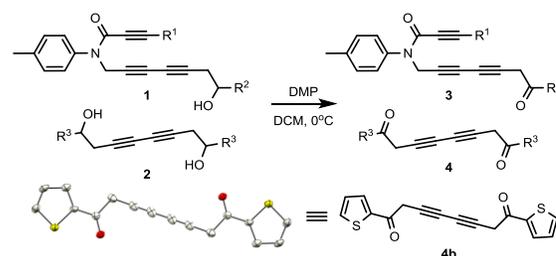
(b) Hashmi's gold-catalyzed arene synthesis<sup>10</sup>



(c) Intramolecular dehydro Diels-Alder reactions of diarylacetylenes<sup>12</sup>



## Scheme 2. Representative of Synthesis of Propargyl Ketones

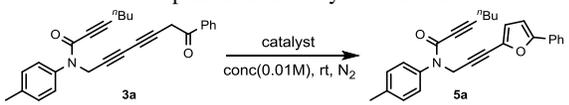


Oxidation of homopropargylic alcohols **1** and **2** with Dess-Martin periodinane afforded the less stable propargyl ketones **3**<sup>11</sup> and **4** (**Scheme 2**), but no isomerization<sup>13</sup> to allenyl ketones were observed after chromatographic workup on silica gel (see Supporting information for NMR spectra, and X-ray structure of **4b**). The propargyl ketones should be used as soon as possible after prepared because of their instability, especially those propargyl ketones bearing the electron-withdrawing groups at

R<sup>2</sup>. Propargyl aldehyde substrate (R<sup>2</sup>=H) was too unstable to obtain.

At the outset, **3a** was chosen as the substrate for reaction discovery and optimization (Table 1). To our surprise, initial tests of the reactivity by mixing **3a** and AuCl<sub>3</sub> under reported conditions<sup>7a</sup> did not provide any desired furan products **5a**, only decomposition ensued (entry 1). Exploring the reaction with the Ag(I) salts, however, AgNO<sub>3</sub><sup>9c</sup> and AgOAc didn't promote the reaction at all (entry 2), AgClO<sub>4</sub>, AgBF<sub>4</sub> and AgOTf were not very effective (entry 3), in the case of CF<sub>3</sub>CO<sub>2</sub>Ag, the reaction proceeded well, leading to the formation of **5a** in 47% yield (entry 4). Increasing the reaction temperature from room temperature to 60 °C or addition of 2 equiv CF<sub>3</sub>CO<sub>2</sub>Na afforded a slightly lower yield (entries 5-6). Finally applying 1 equiv of CF<sub>3</sub>CO<sub>2</sub>Ag to the reaction mixture offered a significant increase to 91% yield of desired product (entry 8), which may result from less decomposition of propargyl ketones. The combine use of equivalent AgBF<sub>4</sub> and CH<sub>3</sub>CO<sub>2</sub>Na afforded **5a** in 83% yield, which proved that trifluoroacetate anion plays an important role in the reaction (entry 9).

Table 1. Optimization of Cycloisomerization



entry <sup>d</sup>	catalyst	equiv	solvent	time (h)	yield <sup>b</sup> (%)
1	AuCl <sub>3</sub>	0.3	CH <sub>3</sub> CN	5min	-
2	AgX <sup>c</sup>	0.3	acetone	24	nr
3	AgY <sup>d</sup>	0.3	acetone	24	<5
4	CF <sub>3</sub> CO <sub>2</sub> Ag	0.3	acetone	36	47
5 <sup>e</sup>	CF <sub>3</sub> CO <sub>2</sub> Ag	0.3	acetone	8	34
6 <sup>f</sup>	CF <sub>3</sub> CO <sub>2</sub> Ag	0.3	acetone	36	39
7	CF <sub>3</sub> CO <sub>2</sub> Ag	0.7	acetone	24	72
8	CF <sub>3</sub> CO <sub>2</sub> Ag	1.0	acetone	10	91
9 <sup>g</sup>	AgBF <sub>4</sub>	1.0	acetone	10	83
10 <sup>h</sup>	CF <sub>3</sub> CO <sub>2</sub> Ag	1.0	acetone	10	55
11 <sup>i</sup>	CF <sub>3</sub> CO <sub>2</sub> Ag	1.0	acetone/water	10	trace
12	CF <sub>3</sub> CO <sub>2</sub> Ag	1.0	THF	10	83
13	CF <sub>3</sub> CO <sub>2</sub> Ag	1.0	DMF	10	65
14	CF <sub>3</sub> CO <sub>2</sub> Ag	1.0	chlorobenzene	24	-
15	CF <sub>3</sub> CO <sub>2</sub> Ag	1.0	CH <sub>2</sub> Cl <sub>2</sub>	10	-
16	Rh(PPh <sub>3</sub> ) <sub>3</sub> Cl	0.3	CH <sub>3</sub> CN	0.5	-
17	PdX <sup>j</sup>	0.3	CH <sub>3</sub> CN	0.5	-
18	CuI	0.3	DMA <sup>k</sup>	24	-
19	ZnCl <sub>2</sub>	0.3	CH <sub>2</sub> Cl <sub>2</sub>	24	nr
20	In(OTf) <sub>3</sub>	0.3	toluene	24	nr

<sup>a</sup>conditions: **3a** (~0.05mmol), anhydrous solvents were used. <sup>b</sup>isolated yield, nr denotes no reaction, - denotes decomposition.

<sup>c</sup>AgX=AgOAc, AgNO<sub>3</sub>. <sup>d</sup>AgY=AgBF<sub>4</sub>, AgOTf, AgClO<sub>4</sub>. <sup>e</sup>reaction temperature was 60°C. <sup>f</sup>addition of 2 equiv CF<sub>3</sub>CO<sub>2</sub>Na. <sup>g</sup>addition of 1 equiv CF<sub>3</sub>CO<sub>2</sub>Ag. <sup>h</sup>undistilled acetone was used. <sup>i</sup>acetone:water = 10:1. <sup>j</sup>PdX = Pd(MeCN)<sub>2</sub>Cl<sub>2</sub>, Pd(PPh<sub>3</sub>)<sub>4</sub>. <sup>k</sup>DMA= dimethylacetamide.

The effect of water was also examined (entries 10 and 11). Use of undistilled acetone gave only modest yield of the product, treatment of **3a** with 1 equiv of silver trifluoroacetate in 10:1 acetone-water,<sup>9c</sup> no furan product **5a** was detected and the precipitation of silver in the form of a silver mirror on magnetic stir bar was observed. The reaction seems to be inhibited due to the key intermediate Ag(I)-complex was reduced to Ag(0) in the presence of water.

Screening of solvents revealed that aprotic polar solvent acetone was the best. Comparable conversion was observed when tetrahydrofuran and dimethylformamide were used as the solvents. With dichloromethane or chlorobenzene as the solvent, only undefined side products were detected.

Several Lewis acids and transition-metal complexes<sup>5-6,8,9b,14-16</sup> were tested as well. However, Rh(PPh<sub>3</sub>)<sub>3</sub>Cl, Pd(MeCN)<sub>2</sub>Cl<sub>2</sub>, Pd(PPh<sub>3</sub>)<sub>4</sub> and CuI lead to completely decomposition to undefined side products. ZnCl<sub>2</sub> and In(OTf)<sub>3</sub> had no catalytic activity.

With optimized conditions in hand, we proceeded to explore the substrate scope of the reaction, and the results are summarized in Figure 1. Generally, a range of substrates with electron-

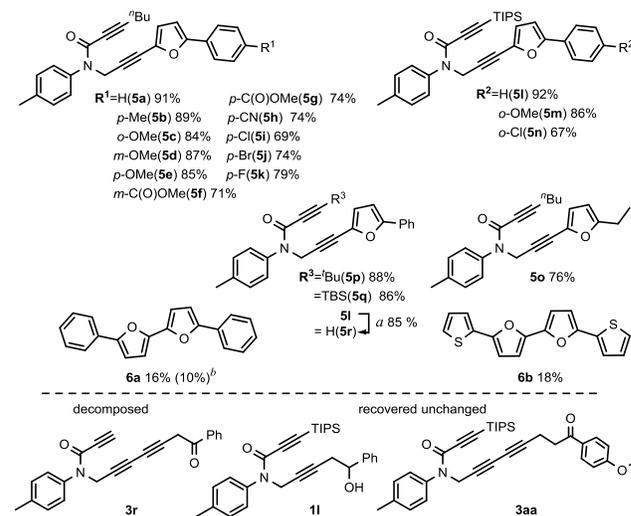


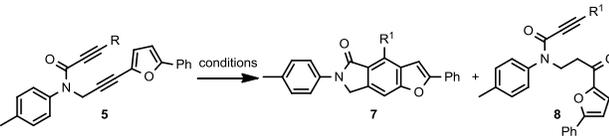
Figure 1. Substrate scope of the cycloisomerization. The reactions were performed on approximately 0.1 mmol scale, CF<sub>3</sub>CO<sub>2</sub>Ag (1 equiv, 2 equiv for **4a**, **4b**), freshly distilled anhydrous acetone was used, rt, 10h, isolated yield was given. <sup>a</sup>KHF<sub>2</sub>, MeOH, 35°C, 24h <sup>b</sup>AgNO<sub>3</sub> instead of CF<sub>3</sub>CO<sub>2</sub>Ag.

donating or electron-withdrawing group at the phenyl ring were synthesized and tested. These include methoxy- (**5c-e**, **5m**), methyl- (**5b**), chloro- (**5i**, **5n**), bromo- (**5j**), fluoro- (**5k**), nitrile- (**5h**), ester- (**5f-g**) groups where yield ranging from 67% to 91% were obtained. Alkylated furan derivative (**5o**) was also obtained in 76% yield. And tertbutyldimethylsilyl (TBS)-, triisopropylsilyl (TIPS)-, *t*-butyl ('Bu)- terminated substrates afforded the corresponding products in moderate to good yield as well (**5l-n**, **5p-q**). Substrate without protecting group (**3r**) was completely decomposed to dark-colored unidentified substances. Propargyl ketones **4** resulted in only small amount of products **6a** and **6b** along with lots of dark-colored presumably oligomeric materials, using AgNO<sub>3</sub> as catalyst also afforded **6a** in low yield. Unoxidized substrate **1l** and similar substrate **3aa** containing longer alkyl chain and were completely unreactive.

We began with the **5a** as the model substrate for intramolecular dehydro Diels-Alder reaction (Table 2). When heated to 150 °C in dimethylformamide without any catalyst under nitrogen atmosphere, **5a** afforded the corresponding furan-based tricyclic compound **7a** only in 17% yield. Then we examined various Lewis acids<sup>17</sup>, particularly those oxyphilic ones, in hope of activating the carbonyl group. Unfortunately, most of them still remained ineffective (entries 2 and 4) or lead to completely decomposition (entry 3). However, further screening of catalysts such as Fe(OTf)<sub>3</sub>, Al(OTf)<sub>3</sub> and TfOH exhibited unique catalytic activity, these catalysts promoted the hydration of alkyne

to afford **8** under air atmosphere (entries 5-7).

Table 2. Optimization of Dehydro Diels-Alder Reaction and Hydration Reaction



entry <sup>a</sup>	R	Catalyst	Conditions <sup>g</sup>	7 <sup>b</sup> (%)	8 <sup>b</sup> (%)
1 <sup>c</sup>	<sup>n</sup> Bu	/	DMF/150°C/1h	17	/
2	<sup>n</sup> Bu	M <sup>d</sup> (OTf) <sub>n</sub>	DCE/80°C/8h	nr	
3	<sup>n</sup> Bu	Sc(OTf) <sub>3</sub>	DCE/80°C/8h	-	
4	<sup>n</sup> Bu	BF <sub>3</sub> -Et <sub>2</sub> O	DCE/30°C/8h	nr	
5	<sup>n</sup> Bu	Fe(OTf) <sub>3</sub>	DCE/80°C/1h	/	55
6	<sup>n</sup> Bu	Al(OTf) <sub>3</sub>	DCE/80°C/14h	/	75(79 <sup>e</sup> )
7	<sup>n</sup> Bu	TfOH	DCE/80°C/8h	/	68
8	<sup>n</sup> Bu	AlX <sub>n</sub> <sup>f</sup>	DCE/80°C/8h	nr	
9 <sup>c</sup>	<sup>n</sup> Bu	Al(OTf) <sub>3</sub>	DCE/80°C/8h	/	trace
10	TIPS	/	DMF/150°C/1h	81(84 <sup>e</sup> )	/

<sup>a</sup>The reactions were performed on approximately 0.05 mmol scale, 1 equiv of the catalyst, under air atmosphere. nr denotes no reaction, - denotes decomposition. <sup>b</sup>isolated yield. <sup>c</sup>under nitrogen atmosphere, anhydrous solvents were used. <sup>d</sup>M=Li, Zn, Ca, Cu, Mg. <sup>e</sup>addition of 4 equiv water, reaction time was 4h. <sup>f</sup>AlX<sub>n</sub> = AlCl<sub>3</sub>, Al<sub>2</sub>(SO<sub>4</sub>)<sub>2</sub>. <sup>g</sup>DCE= dichloroethane.

To our surprise, using sterically hindered **5l** instead of **5a**, without any catalyst, offering a significant increase to 81% yield of desired product **7d**, neither air nor water needed to be excluded. Although there was a steric repulsion between bulky terminal group and β-H of furan (for **7b**, distance = 2.082Å, see Supporting Information Figure S6. X-ray structure of **7b**), no rearrangement of cyclic allene was observed (**Scheme 1, c**).<sup>12</sup>

Under optimized conditions, the substrate scope of hydration of alkyne and dehydro Diels-Alder reaction was investigated, and the results are summarized in **Figure 2**.

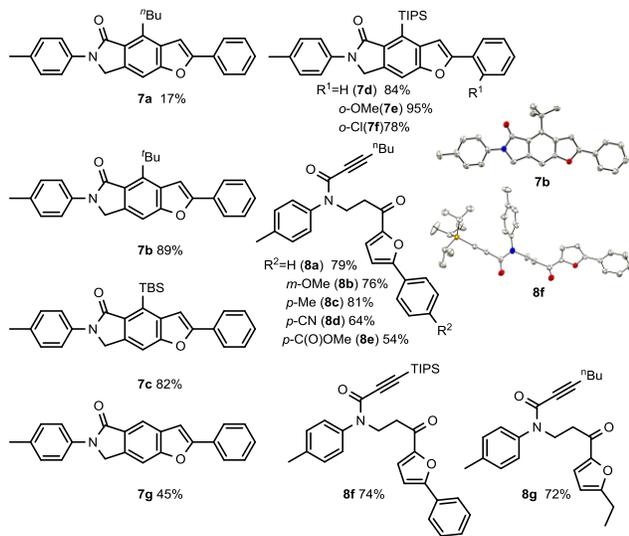


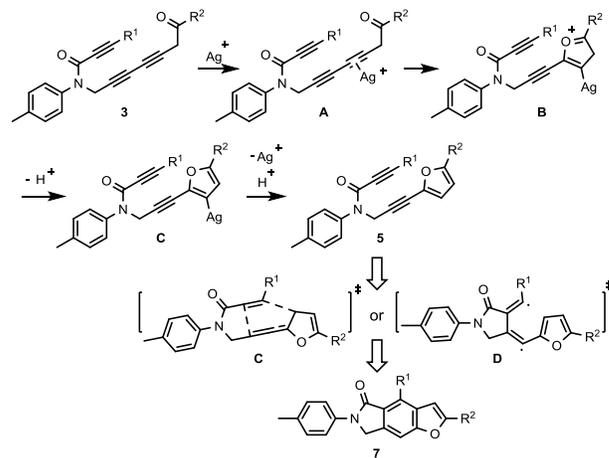
Figure 2. Substrate scope of the reactions. Dehydro Diels-Alder reaction conditions: furans (0.1-0.2 mmol), anhydrous DMF, 150°C, N<sub>2</sub>, 1h. Hydration reaction conditions: furans (~0.1 mmol),

Al(OTf)<sub>3</sub> (1 equiv), H<sub>2</sub>O (4 equiv), DCE, 80°C, Air, 4h. Isolated yield was given.

Substrates with butyl group (<sup>n</sup>Bu) afforded **7a** in 17% yield along with undefined compound<sup>18</sup>, and the substrates with bulkier protecting group(**7b-d**) gave higher yield (78-95%) of furan-based tricyclic products than the deprotected substrate **7g** (45%). In most of the examples the hydration reaction gave products with over 70% yield (**8a-c, f-d**), nitrile and ester substituted substrates (**8d-e**) gave only moderate yield.

A suggested mechanism was depicted in **Scheme 3**, the process was initiated by coordination of Ag(I) with the triple bond of propargyl ketone **3**, which make it more electrophilic and thus undergoes subsequent intramolecular attack by an oxygen

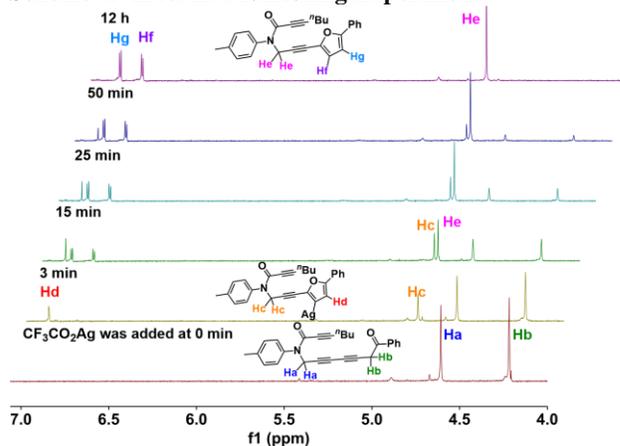
### Scheme 3. Proposed Mechanism



lone pair to afford oxo-cation **B**, rapid hydrogen transfers in intermediate **B** subsequently led to the Ag-furan intermediate **C**, which was observed in <sup>1</sup>H-NMR spectroscopy. The Ag-furan intermediate **C** could undergo direct S<sub>E</sub> protonolysis with loss of Ag(I) to afford the furan product **5**,<sup>9c</sup> which undergo intramolecular dehydro Diels-Alder reaction to afford furan-based tricyclic compound **7**, the cycloaddition might involve a biradical intermediate **D**,<sup>12</sup> which was stabilized by bulkier terminal protecting group and reduce the activation energy, thus promoted the reaction.

Considering the difference of catalytic activity of different aluminum salts (**Table 2**, entry **6** and **8**), the hydration reaction might involve a Brønsted/Lewis co-catalysis, however a neat Brønsted catalysis after hydrolysis of the metal triflate cannot be excluded.<sup>19</sup>

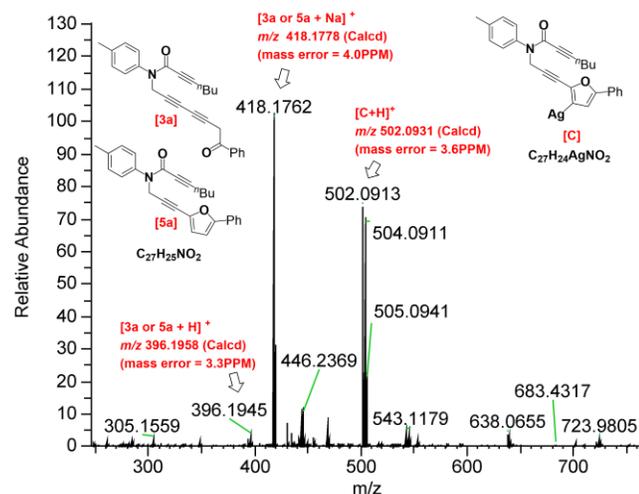
### Scheme 4. <sup>1</sup>H NMR Monitoring Experiment



<sup>1</sup>H-NMR spectroscopy was used to monitor the reaction progress of **3a** (Scheme 4). After CF<sub>3</sub>CO<sub>2</sub>Ag was added, the quite clean formation of Ag-furan intermediate **C** was found within a short time (characteristic peak for furan proton Hd at δ = 6.93, for methylene proton Hc at δ = 4.83; relative peak areas Hd:Hc = 1:2, see Supporting Information Figure S2 for details), as the reaction proceeded, the signal of product **5a** started to appear and increase, eventually all the intermediate and starting material consumed and only the product **5a** was obtained. This <sup>1</sup>H-NMR study clearly suggested that Ag(I)-furan intermediate **C** indeed is a metastable intermediate.

By using electrospray ionization mass spectrometry (ESI-MS), besides quasi-molecular ion of starting material (**3a**) or product (**5a**), a new prominent signal at *m/z* 502.0913 was detected (Scheme 5), which was attributed to Ag(I)-furan intermediate **C** (see Supporting Information Figure S4 for isotopic distribution of the species).

#### Scheme 5. ESI-MS Study of the Reaction Intermediate



No new peaks appeared to occur during the reaction progress in <sup>19</sup>F-NMR spectroscopy. After addition of AgNO<sub>3</sub> or CF<sub>3</sub>CO<sub>2</sub>Na to propargyl ketone **3a** in d<sub>6</sub>-acetone respectively, isomerization to the corresponding allenyl ketone was not observed in <sup>1</sup>H-NMR spectroscopy, these indicated trifluoroacetate anion might act as a ligand or counter anion rather than a base. However, the role of trifluoroacetate anion still remained to be investigated.

In conclusion, a simple and mild method for the synthesis of 2-alkynyl furans derivatives from propargyl ketone by selective activation of alkyne by CF<sub>3</sub>CO<sub>2</sub>Ag is established, and a follow-up method for the conversion of 2-alkynyl furan derivatives to corresponding furo[2,3-*f*]isoindol-5-one tricyclic compounds or alkyne hydration products has also been developed. By using <sup>1</sup>H-NMR spectroscopy and mass spectrometry, the reaction mechanism of the Ag-promoted cycloisomerization has been well investigated. These methods would find many useful applications in the field of drug discovery and pharmaceutical synthesis.

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental details and spectroscopic characterization of all new compounds.

## Accession Codes

CCDC 2125597, 2125444, 2125598 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via [www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif), or by emailing [data\\_request@ccdc.cam.ac.uk](mailto:data_request@ccdc.cam.ac.uk), or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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## Notes

The authors declare no competing financial interest.

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(18) Using nitrobenzene instead of DMF as solvent, the undefined compound was the only product. The single crystals were prepared by slow volatilization of its solution in MBTE or petroleum ether respectively, but structure analysis of the single crystals was failed. Initial characterization by <sup>1</sup>H-NMR, <sup>13</sup>C-NMR, <sup>1</sup>H-<sup>1</sup>H COSY, DEPT, HSQC, HMBC, IR and mass spectrometry did not elucidate the exact structure of the side product, though we were able to conclude that the molecule contain the chiral or pro-chiral center (two pair of chemical inequivalence CH<sub>2</sub> was observed) and <sup>n</sup>Bu was involved in the reaction.

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