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Gold(I)-catalyzed cyclization of *o*-(alkynyl)styrene ether mediated by MeOH for the construction of 2-aryl-1*H*-indene acetal

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ABSTRACT

A facile and highly efficient methodology was developed to synthesize the functional indene acetal through the cyclization of *o*-(alkynyl)styrene ether catalyzed by the Au(I) in the presence of MeOH. The 2-aryl-1*H*-indene acetals were obtained in excellent yields and could be easily transformed to indene aldehyde. Notably, the MeOH played a dual role, which includes acting as both a nucleophilic reagent and an auxiliary to mediate the cyclization of the 1,5-ene ether.

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Introduction

Currently, Au(I) or Pt(II)-catalyzed enyne cycloisomerization has attracted more and more chemists' interests because of the magic of this process, for the highly efficient transformation of simple acyclic subunits containing ene and yne fragments to the diversely functionalized cyclic structures.¹ Among them, the cycloisomerization of 1,5-ene substrates is one of the important reaction methodology research fields. A careful survey of all reports showed that 1,5-ene substrates are generally classified as three types: (1) the open-chain 1,5-eneynes **I**;² (2) 1,5-cycloenyne **II**;³ (3) *o*-(alkynyl) styrenes (1,3-dienynes) **III**⁴ (Fig. 1).

Through cyclization of these three types of substrates, the single cyclic structure, bicyclo- and indene or naphthalene structure could be constructed, respectively.^{1–4} The unique biological activity of indene derivatives⁵ motivated us to initiate the cyclization of *o*-(alkynyl)styrenes. To the best of our knowledge, most previous Letters mainly focused on the catalytic cyclization of *o*-(alkynyl)styrenes where the terminal carbon atom of the alkene was an alkyl or aryl substituent (single or double substituted).⁴ Herein, we subtly designed an alkoxy substituted *o*-(alkynyl)styrene **1a** to perform the cyclization in the presence of gold(I), and thus producing a new 2-aryl-1*H*-indene acetal compound **2a**, which can be easily transformed to functional indene aldehyde (Scheme 1).

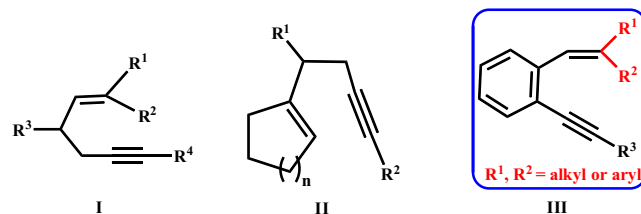
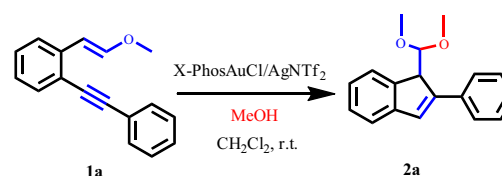


Figure 1. Three types of 1,5-eneynes.

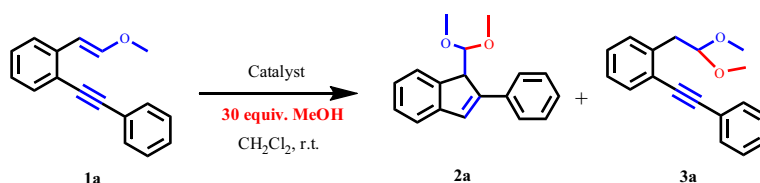
Scheme 1. The cyclization of *o*-(alkynyl)styrene ether.

Results and discussion

In our initial study, we selected 2-methoxy *o*-(phenylethynyl)-styrene **1a** as a model substrate. As a result, the reaction was extremely complicated in the absence of MeOH catalyzed by Au(I) or Pt(II or IV). From thin layer chromatography (TLC) tracing we could

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Table 1
Screening of catalysts used in this cyclization of 1,5-enyne ether **1a**^a

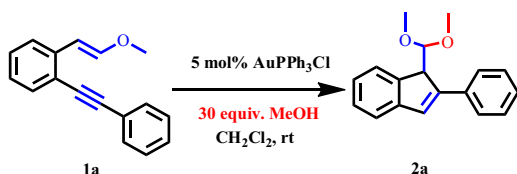
Entry	Catalyst (mol %)	Time (h)	Product	Total yield ^b (%)
1	PtCl ₂ (5)	21	2a/3a = 1/0.43	75
2	PtCl ₄ (5)	48	3a	88
3	Rh(PPh ₃) ₃ Cl (5)	48	N. R.	–
4	AuCl (5)	44	2a/3a = 1/2	75
5	AuCl ₃ (5)	39	2a/3a = 1/0.75	76
6	AuPPh₃Cl/AgNTf₂ (5/5)	2.5	2a	67

^a Standard procedure: 1-(2-methoxyvinyl)-2-(phenylethynyl)-benzenes **1a** (58.5 mg, 0.25 mmol) was added to a solution of catalyst (5 mol %) and MeOH (240 mg, 7.5 mmol, 30 equiv) in anhydrous DCM (0.5 mL). The reaction mixture was stirred at room temperature until complete disappearance of starting material **1a** observed by TLC. The solvent was removed under reduced pressure and the crude mixture was purified by flash chromatography on silica gel (petroleum ether/EtOAc 50:1).

^b Isolated yield.

see that there were more than 5 light spots on the TLC plate. Enlightened by the previous reports about the alkoxyacyclization of enynes,⁶ MeOH was introduced into our reaction system. To our delight, the reaction system became simple and gave two products **2a** and **3a** in good yields when using PtCl₂ as the catalyst (Table 1, entry 1). In the presence of PtCl₄, no cyclization product was obtained with only the MeOH adduct **3a** in 88% yield (entry 2). Changing to use Rh(PPh₃)₃Cl as the catalyst resulted in no reaction occurring with a great amount of starting material recovered. In two cases of the simple AuCl and AuCl₃, the reactions generated the mixture of **2a** and **3a** with different ratios. Nevertheless, after employing the AuPPh₃Cl/AgNTf₂ mixture catalytic system, only a single cyclization product **2a** was obtained in above moderate level yield of 67% (entry 6).

Inspired by the above results, we finely tuned the Ag salts (Table 2). Consequently, the reaction did not run in the absence of Ag salt (Table 2, entry 2). Using AgSbF₆, AgBF₄, AgPF₆, or

Table 2
The effect of counterions on this cyclization of 1,5-enyne ether **1a**^a

Entry	Ag salt (mol %)	Time (h)	Yield ^b (%)
1	AgNTf ₂ (5)	2.5	67
2	–	>24	–
3	AgSbF ₆ (5)	2.5	57
4	AgBF ₄ (5)	2.5	59
5	AgPF ₆ (5)	2.5	45
6	AgOTf (5)	2.5	61
7 ^c	AgNTf₂ (5)	10 min	96

^a Standard procedure: 1-(2-methoxyvinyl)-2-(phenylethynyl)-benzenes **1a** (58.5 mg, 0.25 mmol) was added to a solution of PPh₃AuCl (6.2 mg, 5 mol %), Ag salt (5 mol %) and MeOH (240 mg, 7.5 mmol, 30 equiv) in anhydrous DCM (0.5 mL). The reaction mixture was stirred at room temperature until complete disappearance of starting material **1a** observed by TLC. The solvent was removed under reduced pressure and the crude mixture was purified by flash chromatography on silica gel (petroleum ether/EtOAc 50:1).

^b Isolated yield.

^c Using 5 mol % X-PhosAuCl catalyst.

AgOTf, the reaction could smoothly proceed with moderate yields of cyclization product. In comparison, the AgNTf₂ showed advantageous over the other Ag salts (entries 1 and 3–6). And after changing the AuPPh₃Cl to X-PhosAuCl, a satisfying result was obtained with excellent yields of cyclization product (96% yield) in a very short time (10 min) (Table 2, entry 7).

The amounts of catalysts and MeOH were next examined. It was found that the reaction could still smoothly proceed and afford the target compound **2a** in excellent yield (95%) when only using MeOH as solvent (Table 3, entry 2). But in the absence of MeOH, the reaction became complicated (entry 3). Interestingly, when reducing the amount of catalyst (X-PhosAuCl/AgNTf₂) from 5 mol % to 2 mol %, or even to 1 mol %, the product yield remained nearly unchanged in a relatively short reaction time. Furthermore, decreasing the amount of MeOH, such as from 30 equiv to 20 equiv, 10 equiv, 5 equiv or even to 2 equiv, all these reactions gave the corresponding indene acetal in similar excellent yields (Table 3, entries 6–9). Based on the above all results, we concluded the optimal conditions: use 2 mol % X-PhosAuCl/2 mol % AgNTf₂ as the catalytic system, at room temperature in CH₂Cl₂ solvent with the aid of 2 equiv MeOH.

With the optimized conditions in hand, a variety of substituted enyne ethers were used to demonstrate the flexibility of our methodology (Table 4). Satisfyingly, we obtained good to excellent yields of indene acetal products for all enyne ethers tested, tolerating electron-withdrawing, as well as electron-donating groups (EWG and EDG, respectively) on different positions of the aromatic rings (styrene and aryl groups on the terminal of alkyne). Moreover, for the multisubstituted *o*-(alkynyl)styrene ether **1f**, the cyclization reaction could also smoothly proceed and give the 2-phenyl-1-methylindene acetal **2f** in 81% yield. In the case of the heteroaromatic alkynyl substituted styrene ether, the reaction could also efficiently produce the 2-thiophenyl-1*H*-indene-1-acetal (**2l**) in good yield (81%). Additionally, the aliphatic *o*-*tert*-butylalkynyl styrene ether could also perform the cyclization under the optimal conditions and produce the 2-*tert*-butyl indene acetal **2m** in good yield (63%).

Based on the correlating literature about the Au-catalyzed cyclization reaction of enynes,^{1–4} a rational mechanism for this Au(I)-catalyzed cyclization was proposed in Scheme 2. Gold(I) activation of the triple bond in *o*-(alkynyl)styrene ether **1a** to generate the intermediate **I** and followed by promoting the formation of the gold cationic intermediate **II** or oxonium ion intermediate **III**. Subsequently, the attack of methanol on these two

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