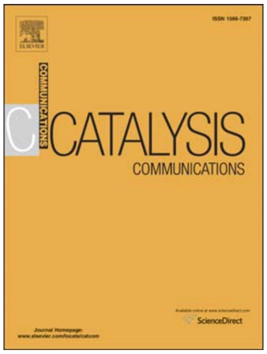

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Platinum- and gold-catalyzed hydroalkoxylation and tetramerization of propiolate esters

Qian Chen*, Changyuan Zhang, Chunxiao Wen, Jin Fang, Zhiyun Du*, Dongling Wu

School of Chemical Engineering and Light Industry, Guangdong University of Technology, Guangzhou 510006, China

*Corresponding authors. Tel.: +86 20 3932 2231; fax: +86 20 3932 2235.

E-mail addresses: qianchen@gdut.edu.cn (Q. Chen), zhiyundu@gdut.edu.cn (Z. Du).

ABSTRACT: $PtCl_2$ was found to efficiently catalyze intermolecular additions of propiolate esters with alcohols. The reaction of propiolate esters and alcohols in the presence of $PtCl_2$ gave (*E*)-vinyl ethers as the major products at 60 ^oC, whereas alkyl 3,3-dialkoxypropanoates were predominantly obtained when the reaction temperature was set to 80 ^oC. On the other hand, a novel regioselective tetramerization of propiolate esters catalyzed by $AuCl_3$ under mild conditions afforded 1,2,5,6-tetrasubstituted-cyclooctatetraene (1,2,5,6-COT) in moderate yields.

Keywords: Hydroalkoxylation; Tetramerization; Propiolate ester; Platinum catalyst; Gold catalyst

1. Introduction

It has been widely known that transition metal complexes catalyze intermolecular additions of nucleophiles to carbon-carbon multiple bonds [1−3]. Such addition reactions are perfectly suited to fulfill today's need for the atom economy [4] and atom efficiency [5]. The hydroalkoxylation and bis(hydroalkoxylation) of olefins or alkynes afford vinyl ethers [1,6−8] or acetals [1−3,6−15]. For examples, when alkyl acrylates or alkyl propiolates are treated with alcohols catalyzed by Ag^I, Cu^I or Pd^{II} [6−8,14,15], the reactions give alkyl 3,3-dialkoxypropanoates, which are very important precursors in organic synthesis and pharmaceutical chemistry [16]. For the alkyne unit of acetylenedicarboxylates, it is worth to mention that nucleophiles could directly add to the triple bonds in the absence of transition metal catalysts [17].

Platinum and gold catalysts are efficient reagents for intermolecular and intramolecular additions of nucleophiles to alkynes [1−3,18−22]. The hydration, hydroalkoxylation and hydroarylation of alkynes catalyzed by Pt and Au have been developed extensively during the last three decades [1−3,18−22]. The use of platinum and gold salts enables these reactions to proceed under mild conditions with high selectivity. Recently, Reetz [23], He [24] and Biffis [25] reported hydroarylations of electron-deficient alkynes with Au catalysts. He [26] also found the $AuCl_3$-catalyzed additions of *N*-methyl indole to ethyl propiolate. Yu [27] lately reported $PtCl_2$-catalyzed tandem cyclization/intermolecular addition reactions of *o*-alkynylanilines with electron-poor alkynes. On the other hand, alkyl propiolate is also an important material for the synthesis of cyclooctatetraene (COT), which is a highly valuable organic intermediate [28]. Since Reppe [29] first discovered the Ni-catalyzed tetramerization of ethyne affording COT in 1948, transition-metal mediated synthesis of COT has been of particular interest [30]. However, the regio- and chemo-selectivity of most tetramerization of alkynes are very low and different tetrasubstituted isomers are always obtained as a mixture, together with the trimerized and polymerized products [30]. For example, the reaction of ethyl propiolate catalyzed by $Ni(PCl_3)_4$ afforded two isomers of 1,2,4,6-tetrasubstituted-COT (28% yield) and 1,3,5,7-COT (1% yield) and two trisubstituted benzenes [31]. Gold catalysts also showed reactivities in the dimerization [32] and trimerization [33] of alkynes. However, to our knowledge, there are no reports describing gold-catalyzed tetramerization of alkynes to afford COTs. Herein, we report an efficient $PtCl_2$-catalyzed hydroalkoxylation and bis(hydroalkoxylation) of propiolate esters and a novel regioselective $AuCl_3$-catalyzed tetramerization of propiolate esters to afford 1,2,5,6-tetrasubstituted-COT.

2. Experimental

2.1. *General*

Nuclear magnetic resonance spectra were recorded on a Bruker AVANCE 400 spectrometer. All reactions were carried out in a sealed high pressure tube. Commercial reagents were used without purification unless otherwise noted. Flash chromatography was performed using the appropriate eluent on silica gel standard grade 60 (230-400 mesh).

2.2. *General procedure*

2.2.1. General procedure for monohydroalkoxylation of propiolate esters

To a solution of ethyl propiolate (98 mg, 1.0 mmol) in methanol (2 mL) was added catalytic $PtCl_2$ (5 mg, 0.02 mmol). The mixture was stirred at 60 ^{o}C for 12 h. The reaction solution was cooled to room temperature, and CH_2Cl_2 (20 mL) was added. The mixture was then filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel with hexanes-ethyl acetate (20:1) as the eluent to give a mixture of (*E*)-ethyl 3-methoxyacrylate(**4**) and ethyl 3,3-dimethoxypropanoate(**5**) (112 mg, 85% yield, **4**:**5** = 13:1, the ratio was determined by ^{1}H NMR) as a colorless oil.

2.2.2. General procedure for bis(hydroalkoxylation) of propiolate esters

To a solution of ethyl propiolate (98 mg, 1.0 mmol) and amyl alcohol (440 mg, 5.0 mmol) in toluene (2 mL) was added catalytic $PtCl_2$ (5 mg, 0.02 mmol). The mixture was stirred at 80 °C for 24 h. The reaction solution was cooled to room temperature. The mixture was then filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel with hexanes-ethyl acetate (20:1) as the eluent to give ethyl 3,3-bis(pentyloxy)propanoate (187 mg, 68% yield) as a colorless oil.

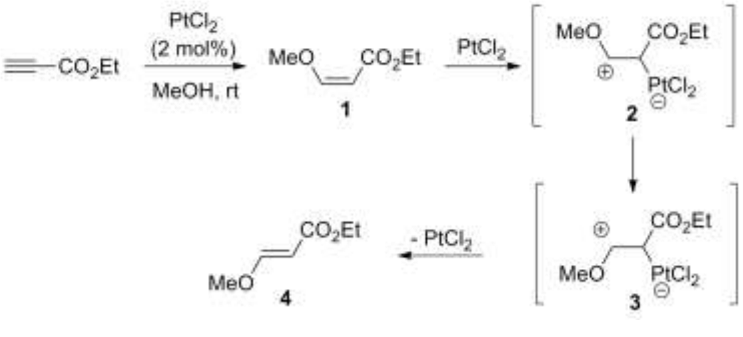
2.2.3. General procedure for tetramerization of propiolate esters

To a solution of ethyl propiolate (98 mg, 1.0 mmol) in 1,2-dichloroethane (2 mL) was added catalytic $AuCl_3$ (6 mg, 0.02 mmol). The mixture was stirred at room temperature for 4 h. The mixture was then filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel with hexanes-ethyl acetate (20:1) as the eluent to give (1*Z*,3*Z*,5*Z*,7*Z*)-tetraethyl cycloocta-1,3,5,7-tetraene-1,2,5,6-tetracarboxylate (41 mg, 42% yield) as a colorless oil.

3. Results and discussion

3.1. Hydroalkoxylation and bis(hydroalkoxylation)

The catalytic activity of $PtCl_2$ (2 mol%) was first tested for the reaction of ethyl propiolate in methanol at room temperature (Scheme 1). The reaction led to a poor conversion of ethyl propiolate to afford two isomers including (*Z*)-ethyl 3-methoxyacrylate **1** and (*E*)-ethyl 3-methoxyacrylate **4** in 16% and 26% isolated yields, respectively. Only **1** was detected at the start of the reaction, while **4** was generated after 3 h [34,35]. Moreover, treatment of (*Z*)-vinyl ether **1** with catalytic $PtCl_2$ in toluene at 60 °C for 3 h gave (*E*)-vinyl ether **4** in 90% yield, while no conversion was observed without the addition of $PtCl_2$. As our consideration, this isomerization can be probablely explained: (1) the complexation of $PtCl_2$ with **1** afforded Zwitterionic complex **2**; (2) the isomerization of cis form **2** gave its trans form **3** because the trans-arrangement is thermodynamically more stable than the initially formed cis form.



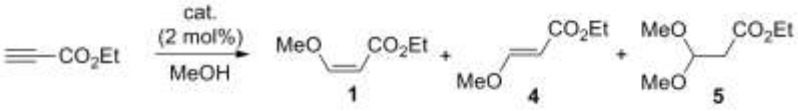
Scheme 1. $PtCl_2$-catalyzed hydromethoxylation of ethyl propiolate.

In order to achieve complete conversion of ethyl propiolate, the reaction temperature was raised to 60 °C. The starting material was consumed within 9 h and afforded a mixture of **1** and **4** (*Z*:*E* = 1:7), while ethyl 3,3-dimethoxypropanoate **5** was also observed. After additional 3 h, (*Z*)-vinyl ether was converted to the (*E*)-vinyl ether completely, and a mixture of **4** and **5** (**4**:**5** = 13:1) was isolated in 85% yield. On the other hand, terminal alkynes without electron-withdrawing groups such as 1-hexyne, phenylacetylene and propargyl alcohol did not give the corresponding products under the same conditions.

We then carried out a brief optimization of experimental conditions, and the results are summarized in Table 1. With the use of $PtCl_4$ as the catalyst, only trace of hydromethoxylation products was detected when the reaction was conducted at room temperature for 48 h (entry 3). Switching the catalyst from platinum to gold catalysts (AuCl, $AuCl_3$ and PPh_3AuSbF_6) decreased the yield of **4** and the ratio of **4** and **1**/**5** (entries 4−6). To avoid the formation of bis(hydroalkoxylation) product **5** at 60 °C, the reaction of stoichiometric amounts of methanol and ethyl propiolate catalyzed by $PtCl_2$ in an inert solvent (toluene) was carried out (entries 8−10). Unfortunately, only trace of **4** was observed when methanol (1 eq., 2 eq. or 5 eq.) was introduced. Thus, we concluded that the optimized combination for the monohydroalkoxylation of propiolate esters was to use 2 mol% of $PtCl_2$ as the catalyst and the reaction was set at 60 °C (entry 2).

Table 1

Platinum- and gold-catalyzed hydromethoxylation of ethyl propiolate.[a]



Entry	Cat.	T (°C)	Time (h)	Yield (%)[b]	**1**/**4**/**5**[c]
1	$PtCl_2$	rt	48	42	38/62/0
2	$PtCl_2$	60	12	85	0/93/7
3	$PtCl_4$	rt	48	trace	-
4	AuCl	rt	12	38	65/35/0
5	$AuCl_3$	rt	12	55	12/48/40
6	$PPh_3AuCl/AgSbF_6$	rt	12	35	45/55/0
7	PPh_3AuCl	rt	12	NR	-
8[d]	$PtCl_2$	60	24	trace	-
9[e]	$PtCl_2$	60	24	trace	-
10[f]	$PtCl_2$	60	24	trace	-

[a] The reaction of ethyl propiolate (1 mmol) and methanol (2 mL) was carried out in the presence of 2 mol% of catalysts.

[b] Isolated yields based on ethyl propiolate.

[c] Ratio was determined by ^{1}H NMR.

[d] The reaction of ethyl propiolate (1 mmol) and methanol (1 mmol) was carried out in toluene (2 mL).

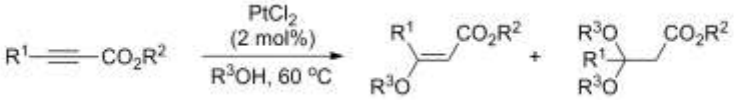
[e] The reaction of ethyl propiolate (1 mmol) and methanol (2 mmol) was carried out in toluene (2 mL).

[f] The reaction of ethyl propiolate (1 mmol) and methanol (5 mmol) was carried out in toluene (2 mL).

To investigate the scope of the monohydroalkoxylation protocol, we applied the optimum reaction conditions to the addition of variant alcohols to alkynes with electron-withdrawing groups and the results are illustrated in Table 2. The reactions of ethyl propiolate or benzyl propiolate with alcohols (MeOH, EtOH, *i*-PrOH or *t*-BuOH) afforded the desired products in 22-85% yields and the ratios of (*E*)-vinyl ethers and acetals were varied from 3/1 to 24/1 (entries 1−6). Additions of primary alcohols to propiolate esters gave the products in good yields, while *i*-PrOH and *t*-BuOH led to the formation of the desired products in low yields due to the steric hindrance of bulkier alcohols. The hydroalkoxylation of internal alkynes with electron-withdrawing group was also investigated (entries 7−9). Unfortunately, the reactions of diethyl acetylenedicarboxylate, ethyl 2-butynoate and ethyl phenylpropiolate under the same conditions gave the corresponding ketones (42%, 48% and 80% yield, respectively) due to the hydration of alkynes with trace amount of water in methanol. We then tried the hydroalkoxylation of these internal alkynes in anhydrous methanol, while no any hydromethoxylation product was detected. As a comparison with terminal alkynes (propiolate esters), internal alkynes with the substituent of electron-poor, electron-rich or phenyl group (entries 7−9) showed no reactivity for hydroalkoxylation, perhaps due to the steric hindrance.

Table 2

$PtCl_2$-catalyzed monohydroalkoxylation of alkynes.[a]



Entry	R^1	R^2	R^3OH	Yield (%)[b]	(*E*)-vinyl ether/acetal[c]
1	H	Et	MeOH	85	13/1
2	H	Et	EtOH	82	5/1
3	H	Bn	MeOH	82	24/1
4	H	Bn	EtOH	83	7/1
5	H	Bn	*i*-PrOH	38	4/1
6	H	Bn	*t*-BuOH	22	3/1

7	CO_2Et	Et	MeOH	-	-
8	Me	Et	MeOH	-	-
9	Ph	Et	MeOH	-	-

[a] The reaction of alkyne (1 mmol) and alcohol (2 mL) was carried out in the presence of 2 mol% of $PtCl_2$ at 60 °C.

[b] Isolated yields based on the corresponding alkynes.

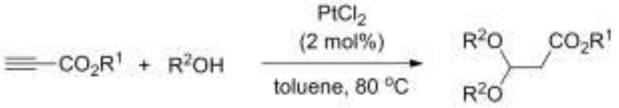
[c] Ratio was determined by ^1H NMR.

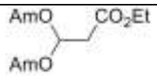
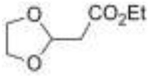
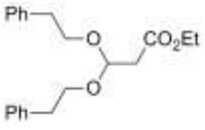
Having succeeded in monohydroalkoxylation of propiolate esters, we are encouraged to explore their bis(hydroalkoxylation) reactions to obtain acetals. We first examined the reaction of ethyl propiolate catalyzed by $PtCl_2$ in refluxing ethanol for 3 days. A mixture of the (*E*)-vinyl ether and the acetal ((*E*)-vinyl ether:acetal = 1:8) was obtained in 56% yield. In order to achieve complete conversion of vinyl ethers, several conventional solvents for platinum catalysts were then screened and toluene was proved to be the optimum solvent. Amyl alcohol was chosen as the nucleophile due to its higher boiling point. When ethyl propiolate and 5 equiv. of amyl alcohol were introduced with 2 mol% of $PtCl_2$ in toluene at 80 °C for 24 h, the reaction afforded the acetal in 68% yield, while vinyl ethers were consumed completely.

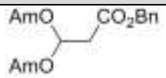
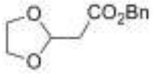
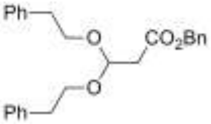
We then carried out bis(hydroalkoxylation) of propiolate esters with several alcohols and the results are illustrated in Table 3. Ethyl propiolate and benzyl propiolate underwent acetalization with primary alcohols to afford the corresponding acetals in 52-76% yields (entries 1−6). Ethylene glycol also gave the cyclic acetals in moderate yields using dioxane as the solvent due to its insolubility in toluene (entries 2 and 5).

Table 3

$PtCl_2$-catalyzed bis(hydroalkoxylation) of propiolate esters.[a]



Entry	R^1	R^2OH	Product	Yield (%)[b]
1	Et	AmOH		68
2	Et	$HOCH_2CH_2OH$		52[c]
3	Et	$PhCH_2CH_2OH$		58

4	Bn	AmOH		76
5	Bn	$HOCH_2CH_2OH$		54[c]
6	Bn	$PhCH_2CH_2OH$		65

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[a] The reaction of alkyne (1 mmol) and alcohol (5 mmol) was carried out in the presence of 2 mol% of $PtCl_2$ in toluene (2 mL) at 80 °C

[b] Isolated yields based on the corresponding alkynes.

[c] Dioxane was used as the solvent and 2.5 equiv. of ethylene glycol was introduced.

3.2. Tetramerization

During our research on the addition of alcohols to terminal alkynes, we happened to isolate a tetramerization product ($m/z = 393$ $[M + H]^+$) when ethyl propiolate was treated with the above catalysts in the absence of alcohols, while all reactions in table 1−3 did not give this type of by-product. The ^1H NMR and ^{13}C NMR spectra (Fig. 1) are in good agreement with the structure of 1,2,5,6-tetrasubstituted-cyclooctatetraene (1,2,5,6-COT). After a brief optimization of reaction conditions (screening Pt(II), Pt(IV), Au(I), Au(III) or Ag(I) catalysts), 1,2,5,6-COT (when E = CO_2Et, Scheme 2) was obtained in 42% yield as the major isomer when ethyl propiolate was catalyzed by $AuCl_3$ in 1,2-dichloroethane (DCE) at room temperature, while only trace of other isomers was detected. The other two substrates (E = CO_2Bn or $CO_2CH_2CH_2Ph$, Scheme 2) containing arene ring also gave the corresponding products in moderate yields, while the reaction temperature need to be raised to 80 °C. It is worth to mention that the tetramerization of alkyl propiolate catalyzed by Ni catalyst mainly provided 1,2,4,6- and 1,3,5,7-COT [30] and this novel tetramerization catalyzed by $AuCl_3$ regioselectively afforded a different type of tetrasubstituted-COT.

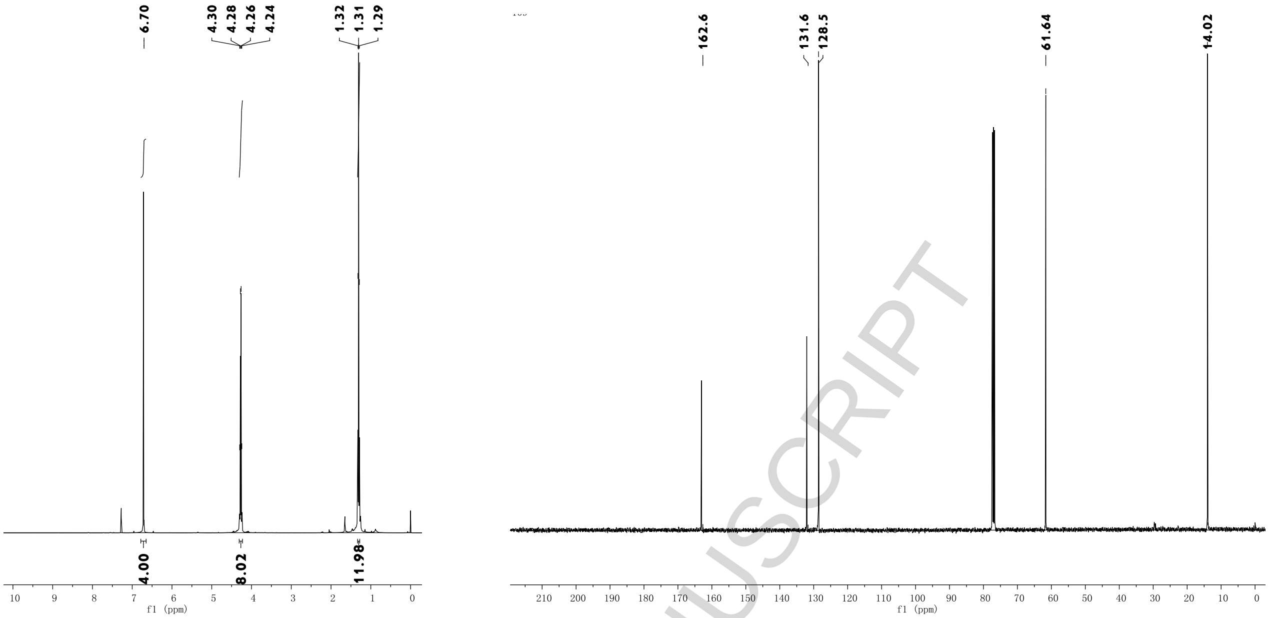
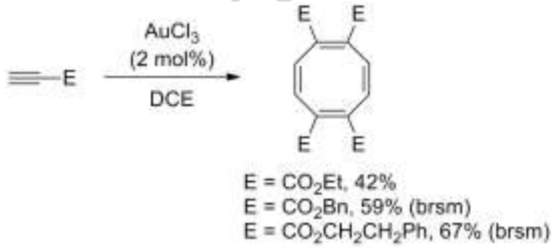


Fig. 1. ^{1}H NMR and ^{13}C NMR spectra of 1,2,5,6-tetrasubstituted-COT (with E = CO_2Et).



Scheme 2. Tetramerization of propiolate esters catalyzed by $AuCl_3$.

4. Conclusion

These results provide a facile entry to the synthesis of (*E*)-vinyl ether, alkyl 3,3-dialkoxypropanoates and 1,2,5,6-tetrasubstituted COT from propiolate esters, which demonstrate that $PtCl_2$ is an efficient catalyst for the hydroalkoxylation and bis(hydroalkoxylation) of electron-deficient alkynes to afford the exclusive anti-Markovnikov addition products and the regioselective tetramerization of alkyl propiolates is smoothly catalyzed by $AuCl_3$ under mild conditions. The previous work [6,8,14] has shown that Ag-, Pd-, and Cu salts are also active for hydroalkoxylations of electron-poor alkynes or alkenes and in some cases more effective. For examples, AgOTf catalyzes the stereoselective *trans* addition of alcohol to methyl propiolate to afford (*Z*)-vinyl ethers [6], and Cu(I)-catalyzed acetal formation from ethyl propiolate also gives ethyl 3,3-dialkoxypropanoates [14]. Our study shows that cationic platinum complexes are efficient for both mono- and bis(hydroalkoxylation) of propiolate esters when the reaction temperature is set to 60 ^{o}C and 80 ^{o}C, respectively. In the case of monohydroalkoxylation, our results are similar to the corresponding Ag-catalysis, whereas Pt-catalysis gives the product of (*E*)-vinyl ethers. In the case of oligomerization of alkyl propiolates, the previous work shows that Ni-catalysis gives 1,3,5,7-, 1,2,4,6- and 1,3,6,8-COT and trisubstituted benzenes with different regio-selectivities under different conditions [30]. In some cases the tetramerization can proceed selectively and one isomer then becomes the predominant product, which remain hard to explain and predict [30]. Our study shows $AuCl_3$ catalyzes a novel type of tetramerization to give 1,2,5,6-COT regioselectively, which is no published example to our knowledge. This interesting property of gold complexes should lead to new and useful applications in catalysis and organic synthesis. Further investigations on the oligomerization of alkynes are ongoing and will be reported in due course.

Acknowledgements

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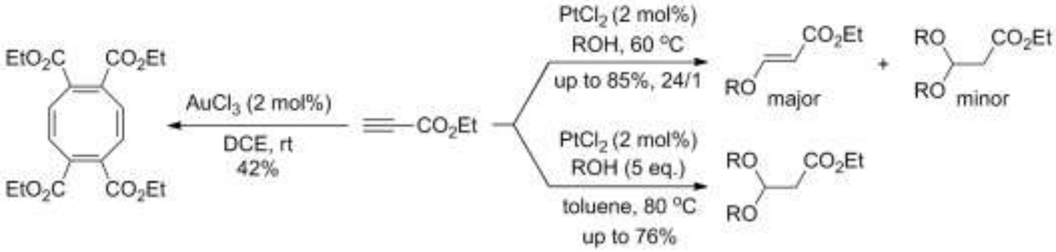

Graphical Abstract

Highlights

1. $PtCl_2$-catalyzed hydroalkoxylation of propiolate esters affords (*E*)-vinyl ethers.
2. $PtCl_2$-catalyzed bis(hydroalkoxylation) of propiolate esters affords acetals.
3. $AuCl_3$-catalyzed tetramerization of propiolate esters affords cyclooctatetraenes.