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Gold-Catalyzed Cyclization of Allene-Substituted Malonate Esters: Synthesis of *β*,*γ*-Unsaturated *δ*-Lactones

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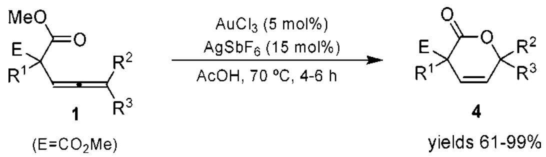
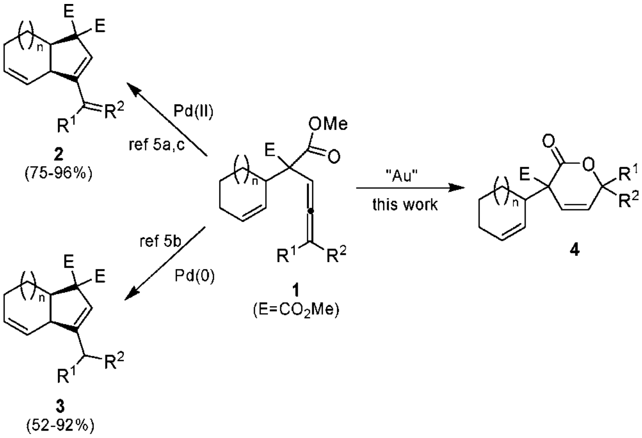
ABSTRACT



An efficient method for the preparation of *β*,*γ*-unsaturated *δ*-lactones has been developed. The starting materials for the synthesis of these compounds are allene-substituted malonates which undergo gold-catalyzed cyclization by means of nucleophilic attack of the ester moiety on the allene. It is worth mentioning that this is the first example where an ester group attacks as a nucleophile in a gold-catalyzed transformation of allenes.

Transition metal-catalyzed reactions of allenes have attracted a great deal of interest in recent years.[1] In particular, transition metal-catalyzed reactions of allenynes[2,3] and enallenes[4,5] leading to carbocyclization products have been extensively studied. We have recently reported on the palladium-catalyzed carbocyclization of enallenes **1** to give **2** and **3** (Scheme 1).[5a−c] In connection with our previous work we studied the corresponding reaction of **1** under gold

Scheme 1. Palladium- or Gold-Catalyzed Reaction of **1**



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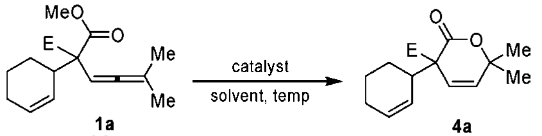
catalysis,[3b,6−10] but to our surprise the reaction took a completely different course. No carbocyclization was observed but instead attack by the ester group on the allene to give the δ-lactone took place. Nucleophilic attack by an ester on a C═C bond coordinated to a metal is rare[11] and is of synthetic utility since it allows the direct employment of an ester as a nucleophile.

Herein, we report the cyclization of allene-substituted malonates leading to β,γ-unsaturated δ-lactones. These lactones often occur in nature as structural units of natural products and have been used for the synthesis of biologically active compounds.[12]

The starting materials were readily prepared as described previously.[5a] Reaction conditions were optimized with use of allene-malonate **1a** (Table 1). Treatment of **1a** with $AuCl_3$ (5 mol %) in acetic acid at different temperatures furnished the desired δ-lactone **4a** although only in moderate yield, the best result being obtained at 70 °C (entries 1−3). Further increase of the reaction temperature to 90 °C did not improve the yield and led to decreased selectivity due to formation of thermal ene-reaction side product (entry 4).[5c,13] Other solvents such as MeOH, tetrahydrofuran (THF), and toluene were tried but with these solvents no reaction was observed (entries 5−7). The study of the reaction with $AuCl_3$ in the presence of various silver salt additives[14] to form cationic gold species led to an important increase of the yield (entries 8−10), the combination $AuCl_3$/$AgSbF_6$ giving the highest isolated yield of **4a** (79%). The use of other gold catalysts such as AuCl and $ClAu(PPh_3)_3$ also furnished lactone **4a** but in lower yields than with $AuCl_3$ (entries 11 and 12). A control experiment showed that the silver salt alone is not the catalyst (entry 13).

Table 1. Optimization of the Reaction Conditions of **1a**[a]



1a
($E=CO_2Me$)

4a

entry	catalyst[b]	temp (°C)	additive[c]	yield (%)[d]
1	$AuCl_3$	rt		15
2	$AuCl_3$	50		31
3	$AuCl_3$	70		46
4	$AuCl_3$	90		42[e]
5[f]	$AuCl_3$	reflux		
6[g]	$AuCl_3$	reflux		
7[h]	$AuCl_3$	70		
8	$AuCl_3$	70	AgOTf	75
9	$AuCl_3$	70	$AgBF_4$	52
10	$AuCl_3$	70	$AgSbF_6$	79
11	AuCl	70	AgOTf	70
12	$ClAu(PPh_3)_3$	70	AgOTf	53
13		70	$AgSbF_6$	

[a] The reactions were run in a 0.5 mmol scale with AcOH as a solvent. [b] 5% of catalyst was used. [c] 15% of additive was used for $AuCl_3$ and 5% when AuCl or $ClAu(PPh_3)_3$ were employed. [d] Isolated yields. [e] The yield is similar to that obtained at 70 °C but a substantial amount of a thermal-ene reaction side product was obtained (see ref 5c). [f] MeOH was used as a solvent. [g] THF was used as a solvent. [h] Toluene was used as a solvent.

Next we explored the scope of the reaction under the best conditions found for **1a**. Thus, a selection of diverse allene-malonates was prepared with various substituents (Table 2).

Substrates with cyclic alkenyl substituents directly linked to the malonate **1a**−**e** reacted to give products **4a**−**e** with yields ranging from moderate to good (entries 2−5). It was found that the corresponding acyclic olefinic compounds **1f** and **1g** gave **4f** and **4g**, respectively, in high yields (entries 6 and 7). The reason for the slightly lower yields in entries 3−5 is ascribed to the steric effect of the cycloalkene ring. Substrates with linear (**1h**−***l***) or branched (**1m**) alkyl chains gave in all cases excellent yields (entries 6−13). Finally, a substrate bearing an aromatic ring was found to give the expected δ-lactone **4n** in high yield (entry 14).

A change of the substituents of the pendant allene did not significantly affect the outcome of the reaction, and 4,4-dimethyl-, 4-ethyl-4-methyl-, and 4,4-pentamethylene-substituted allene-malonates gave comparable yields (compare **4b**,**c** with **4a** and **4j**,**k** with **4i**). Importantly, the method is also suitable for synthesis of spirolactones (**4c** and **4k**, entries 3 and 11), which are not readily obtained with other methods. This type of structure often exhibits biological activity.[7f,12,15] It is also interesting to note that the products are unsaturated in the β,γ-positions, which is difficult to

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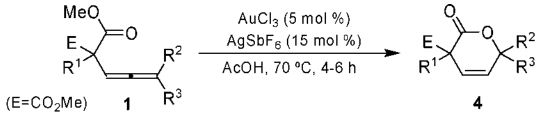
(11) Attack by an ester on a C═C bond is known to take place in iodolactonization[11a,b] and bromolactonization.[11c] In a recent example a *tert*-butyl ester was shown to lactonize under gold catalysis.[11d] In this case the authors showed that Au(III) catalyzes electrophilic cleavage of the *tert*-butyl ester during the reaction followed by gold-catalyzed cyclization of the in situ generated allenoic acid. (a) Fu, C.; Ma, S. *Eur. J. Org. Chem.* **2005**, 3942. (b) Marshall, J. A.; Wolf, M. A.; Wallace, E. M. *J. Org. Chem.* **1997**, *62*, 367. (c) Ma, S.; Wu, S. *Tetrahedron Lett.* **2001**, *42*, 4075. (d) Kang, J.-E.; Lee, E.-S.; Park S.-I.; Shin, S. *Tetrahedron Lett.* **2005**, *46*, 7431.

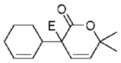
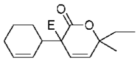
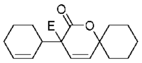
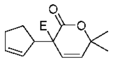
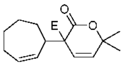
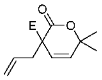
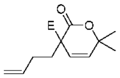
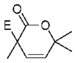
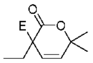
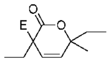
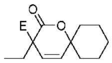
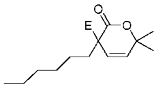
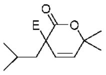
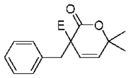
(12) See for example: (a) Ley, S. V.; Cox, L. R.; Meek, G. *Chem. Rev.* **1996**, *96*, 423. (b) Sanchez-Sancho, F.; Valverde, S.; Herradon, B. *Tetrahedron*: *Asymmetry* **1996**, *7*, 3209. (c) Collins, I. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1377.

(13) For more information of the thermal ene-reaction see: Närhi, K.; Franzén, J.; Bäckvall, J. E. *J. Org. Chem.* **2006**, *71*, 2914.

(14) For silver salt additives in gold catalysis see for example: refs 3b and 7a.

Table 2. Gold-Catalyzed Formation of β,γ-Unsaturated δ-lactones **4**



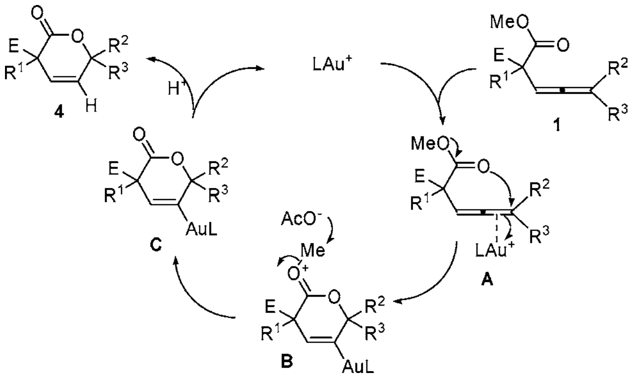
entry	cmpd	product		yield (%)[a]
1	**1a**		**4a**	79
2	**1b**[b]		**4b**	74
3	**1c**		**4c**	66
4	**1d**		**4d**	61
5	**1e**		**4e**	70
6	**1f**		**4f**	87
7	**1g**		**4g**	96
8	**1h**		**4h**	94
9	**1i**		**4i**	99
10	**1j**[b]		**4j**	89
11	**1k**		**4k**	88
12	**1l**		**4l**	99
13	**1m**		**4m**	98
14	**1n**		**4n**	89

[a] Isolated yield after column chromatography. [b] Two diastereoisomers are possible.

achieve since most methods toward unsaturated lactones provide products that are unsaturated in the α,β-positions.

The proposed mechanism for the formation of compounds **4** is shown in Scheme 2. The allene is activated by coordination to cationic gold and undergoes intramolecular nucleophilic attack by the carbonyl oxygen of the ester group to form the cyclic cationic species **B**,[16] which is demethylated by action of the solvent to produce the neutral vinyl-gold intermediate **C**.[17] Protonolysis of the gold−carbon bond in **C** affords lactone **4** and regenerates the cationic gold catalyst. The nucleophilic attack by the carboxy ester group on the coordinated allene seems to be unprecedented.[11]

Scheme 2. Proposed Mechanism for the Formation of δ-Lactones **4**



In summary, we have developed a new efficient route to β,γ-unsaturated δ-lactones by means of a gold-catalyzed intramolecular nucleophilic attack of a carboxy ester on an allene. The fact that the starting materials are easy and cheap to prepare makes the present method useful for the synthesis of these lactones, which are attractive intermediates in the synthesis of biologically active compounds.

Acknowledgment. We are grateful for financial support from the Swedish Research Council, the Swedish Foundation for Strategic Research, the Ministerio de Educación y Ciencia of Spain, and the Wenner-Gren Foundation.

Supporting Information Available: Experimental procedures and characterization data of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) Sannigrahi, M. *Tetrahedron* **1999**, *55*, 9007.

(16) Hydrolysis of the ester prior to lactonization was ruled out by a control experiment in which dimethyl 2-ethylmalonate was treated with the gold catalyst in acetic acid under the usual reaction conditions (cf. Table 1) for 6 h. No formation of the corresponding carboxylic acid was observed.

(17) When the reaction of **1a** was carried out in an NMR tube and followed by ^{1}H NMR formation of methyl acetate was observed.