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Synthesis of Highly Substituted γ-Butyrolactones by a Gold-Catalyzed Cascade Reaction of Benzyl Esters

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Abstract: Easily accessible benzylic esters of 3-butynoic acids in a gold-catalyzed cyclization/rearrangement cascade reaction provided 3-propargyl γ-butyrolactones with the alkene and the carbonyl group not being conjugated. Crossover experiments showed that the formation of the new C–C bond is an intermolecular process. Initially propargylic–benzylic esters were used, but alkyl-substituted benzylic esters worked equally well. In the case of the propargylic–benzylic products, a simple treatment of the products with aluminum oxide initiated a twofold tautomerization to the allenyl-substituted γ-butyrolactones with conjugation of the carbonyl group, the olefin, and the allene. The synthetic sequence can be conducted stepwise or as a one-pot cascade reaction with similar yields. Even in the presence of the gold catalyst the new allene remains intact.

Introduction

Gold has emerged as a powerful tool in the field of organic chemistry, becoming one of the main areas of catalysis research.[1] The last 14 years have witnessed an increasing number of publications illustrating the great potential of gold catalysts in the synthesis of complex organic molecules. Most of the reactions are highly selective, atom economic, and can be performed under mild conditions.[1]

γ-Butyrolactones are very common structural units in many biologically active compounds and natural products.[2] Figure 1 depicts some representative molecules containing a γ-butyrolactone substructure, which possess cytotoxic, antibiotic, and antimicrobial activities.[2]

Different strategies have been reported for the synthesis of γ-butyrolactones.[3] including metathesis[4] and organocatalysis,[5] as well as, palladium,[6] molybdenum,[7] ruthenium,[8] rhodium,[9] and gold catalysis.[10] Among the examples of gold-catalyzed syntheses of γ-butyrolactone scaffolds, the reports of Hammond and co-workers,[10a] Gouverneur and co-workers,[10b] and Blum and co-workers[10c] are of particular interest for this investigation.

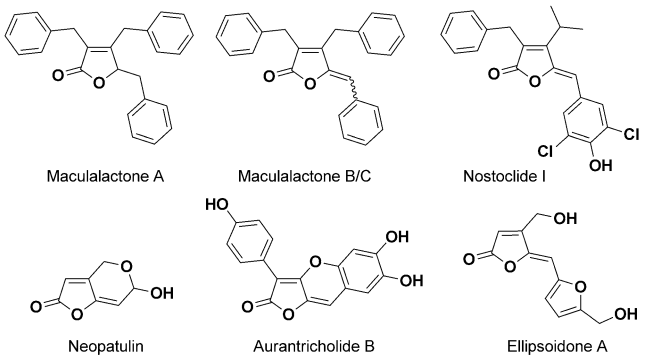

Figure 1. Bioactive molecules containing a butyrolactone core.

Hammond and coworkers reported on the stoichiometric reaction of allenoate **1** with cationic gold complexes. Stable vinyl gold(I) complexes **2** could be successfully isolated, revealing their role as intermediates in further cascade reactions. In particular, the trapping of these species with electrophiles such as iodine, which furnished iodo-substituted butenolides **3** (Scheme 1a) was demonstrated.[10a] Gouverneur and coworkers used a similar approach for the formation of vinyl gold complexes starting from allenoate **1**. These authors were the first to describe gold-catalyzed cyclization followed by an oxidative cross-coupling process with alkynes promoted by Selectfluor as external oxidant[10b] (Scheme 1b). Blum and coworkers also used organogold(I) complexes **2** as key intermediates for their investigations on the formation of butenolides **5**. These authors used allenoates **1** bearing an allylic moiety as cationic leaving group. To induce deallylation, palladium complexes were used for the formation of π-allyl Pd complex **6**. Subsequent transmetalation between gold complex **2** and Pd com-

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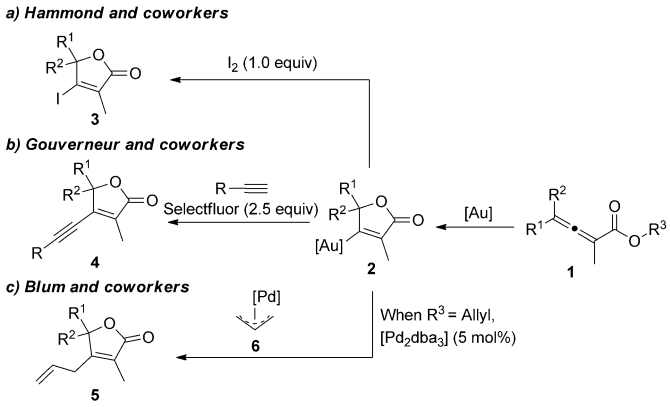


Scheme 1. Transformations of aurated butyrolactone intermediate **2**. dba = dibenzylideneacetone.

plex **6**, followed by C–C bond formation by reductive elimination afforded butenolides **5** (Scheme 1c).[10c]

Herein, we present an alternative pathway towards γ-butyrolactones by using alkynes as precursors and showing a subsequent twofold tautomerization to allenyl-substituted γ-butyrolactones.

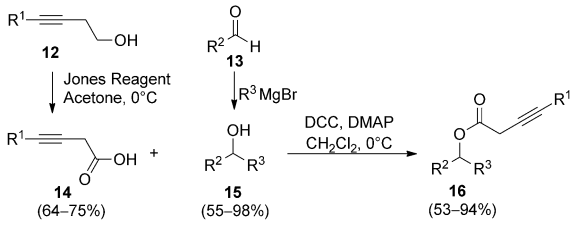
Results and Discussion

Initially, butyrolactone **10** was unexpectedly obtained as the product of a cascade reaction starting from substituted propargylic ester **7**. The expectation had been that this propargylic ester, bearing a tethered alkyne, would undergo a carbene-transfer cascade reaction related to the recent reports on gold carbene transfers over pendant alkynes (Scheme 2).[11] Curiously, with propargylic ester **7** no such migration was observed. Butyrolactone **10** was obtained as the only product. Instead of the expected 5-*exo-dig* cyclization at the terminal alkyne (to initiate the carbenoid pathway), a 5-*endo-dig* cyclization at the non-terminal alkyne had taken place, followed by intermolecular C–C coupling between vinyl gold species **8** and carbocation **9**. This process is proposed to take place in a similar fashion to that reported by Blum and coworkers;[10c] but in the case reported herein, no palladium is necessary (Scheme 2).[12] Furthermore, when the reaction product was treated with aluminum oxide (Al_2O_3), a different product was observed. This product corresponded to allene **11**, the product of an isomerization reaction promoted by the basic sites of Al_2O_3.[13]

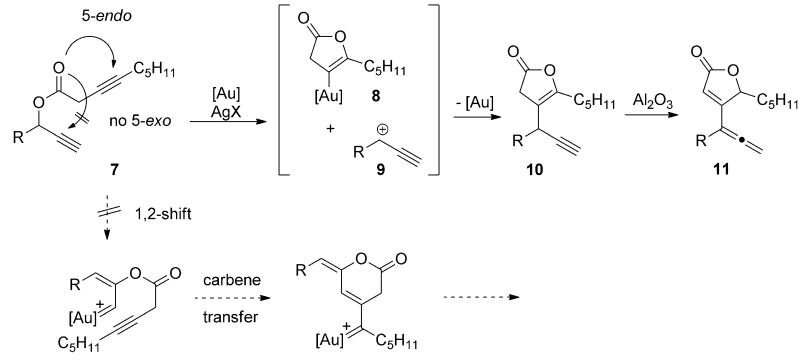
The internal double bond of **10** was proven by the absence of vinylic protons in the ^{1}H NMR spectrum, and the absence of internal alkyne was proven by signals at $\delta = 80$ and 77 ppm in the ^{13}C NMR spectrum. The propargylic–allylic proton had a typical signal at $\delta = 4.55$ ppm in the ^{1}H NMR spectrum. This signal changed significantly after the rearrangement to **11**; a vinylic proton at approximately $\delta = 5.65$ ppm indicated the presence of a trisubstituted double bond and the typical allene signal at $\delta = 208$ ppm was visible in the ^{13}C NMR spectrum.

This preliminary result indicated the potential of this methodology for the synthesis of diverse highly substituted lactones **10** and **11**, bearing an alkyne or allene moiety, which could be further functionalized. It also motivated us to study the reaction mechanism and to investigate the scope and limitations of this transformation in detail.

The first stage of this investigation corresponds to the synthesis of substituted propargylic esters **16**. These compounds were obtained in moderate-to-high yields (53–94%) by means of a three-step synthetic procedure starting from readily available primary alcohols **12** and aldehydes **13**. Primary alcohols **12** were submitted to Jones oxidation conditions, leading to carboxylic acids **14** in moderate yields (64–75%), whereas aldehydes **13** gave rise to secondary alcohols **15** in moderate-to-high yields (55–98%) after nucleophilic addition of suitable Grignard compounds. Finally, a Steglich esterification[14] between the previously obtained carboxylic acids **14** and secondary alcohols **15** led to propargylic esters **16** in moderate-to-high yield (Scheme 3).



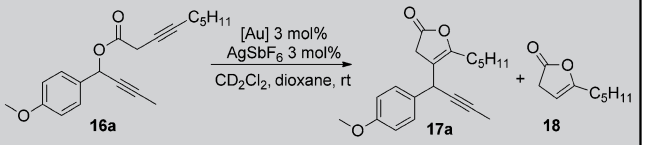
Scheme 3. Synthesis of propargylic esters **16**. DCC = *N*,*N*-dicyclohexylcarbodiimide; DMAP = 4-dimethylaminopyridine.

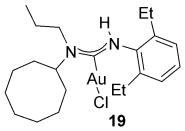


Scheme 2. Gold-catalyzed cascade reaction of propargylic ester **7**.

An initial screening of reaction conditions was performed with substrate **16a**. The precatalysts, silver salts, and solvents were screened to find the best conditions to promote the formation of lactones **17** in high yields. Firstly, different ligands at the gold catalysts were screened, $AgSbF_6$ was used as the counter ion and dichloromethane as solvent (Table 1).

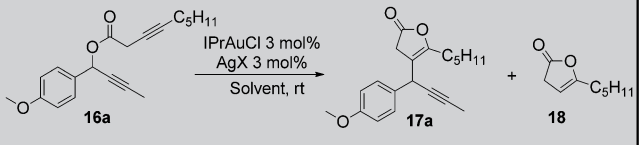
Table 1. Screening of gold precatalysts for substrate **16a**.[a]



	[Au][b]	*t* [h]	Conversion [%][e]	Yield [%][e] **17a**:**18**
1	Ph_3PAuCl	4	57	40:4
2	SPHOSAuCl	4	80	58:8
3	XPHOSAuCl	4	100	76:3
4	IPrAuCl	3	100	91:4
5	IPrAuCl[c]	12	77	70:5
6	 **19**	4	100	68:11
7	phosphiteAuCl	4	100	81:2
8	–[d]	5	50	0:42
9	*p*-TsOH	5	66	0:56

[a] The reactions were carried out in a NMR tube by using 0.1 mol of the substrate and 500 μL of the corresponding deuterated solvent. [b] SPHOS = 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl; XPHOS = 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl; IPr = 1,3-bis(diisopropylphenyl)imidazol-2-ylidene; Phosphite = tris(2,4-di-*tert*-butylphenyl)-phosphite; Ts = Tosyl. [c] 2 mol% of gold and silver were used. [d] Only $AgSbF_6$ was used. [e] Determined by ^1H NMR spectroscopy using dioxane as an internal standard.

Table 2. Screening of silver salts and solvents.[b]



	[Ag]	Solvent	*t* [h]	Conversion [%][b]	Yield [%][b] **17a**:**18**
1	$AgSbF_6$	CH_2Cl_2	3	100	91:4
2	$AgNTf_2$	CH_2Cl_2	4	74	62:4
3	AgOTf	CH_2Cl_2	4	86	65:7
4	$AgSbF_6$	$CHCl_3$	4	64	45:7
5	$AgSbF_6$	acetone	4	76	45:26
6	$AgSbF_6$	toluene	4	99	68:18
7	$AgSbF_6$	benzene	4	97	29:64

[a] The reactions were carried out in an NMR tube using 0.1 mol of the substrate and 500 μL of the corresponding deuterated solvent. [b] Determined by ^1H NMR spectroscopy using dioxane as an internal standard.

Triphenylphosphine gold chloride showed only moderate conversion and yield for the formation of lactone **17a** (Table 1, entry 1). A change in the electronic properties of the ligand showed improvements in the conversion and yield of the reaction. That is, Buchwald-type ligands SPHOS and XPHOS achieved high conversions and yields up to 76% (entries 2 and 3). Pleasingly, carbene-type ligand IPrAuCl achieved full conversion and 91% yield in only three hours at room temperature (entry 4). Based on this result, it was decided to decrease the catalyst loading to 2 mol%. Unfortunately, only 77% conversion and 70% yield could be reached after 12 h at room temperature (entry 5). NAC–gold chloride (NAC = nitrogen acyclic carbene) **19** also showed full conversion after 4 h, achieving 68% yield (entry 6). Similar results were observed with phosphite–gold chloride, reaching full conversion and 81% yield (entry 7). Nevertheless, among the catalysts screened, IPrAuCl provided the best yield in the shortest reaction time. Finally, control experiments without gold catalysts were carried out. In the presence of only silver salt, no formation of the expected lactone **17a** was observed; instead, 42% yield of compound **18** was formed (entry 8). This product is a result of the protodeauration of the vinyl gold(I) intermediate that participates in the reaction. A similar result was obtained with *p*-toluenesulfonic acid (entry 9). These results indicate that the cascade cyclization/C–C coupling is only promoted by gold catalysts.

With the best ligand in hand, different counter ions and solvents were screened (Table 2). Of the silver salts employed, full conversion was only observed with $AgSbF_6$ (entry 1). Although $AgNTf_2$ (entry 2) and AgOTf (entry 3) achieved good yields (up to 65%), $AgSbF_6$ was the best counterion for this transformation, providing 91% yield. For the screening of solvents the combination IPrAuCl/$AgSbF_6$ was used.

In chloroform, only 64% conversion and 45% yield was reached after 4 h (entry 4). By the same manner, although toluene and benzene achieved almost full conversion, yields of only 68 and 29%, respectively, were detected (entries 6 and 7).

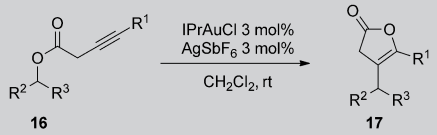
Therefore, the optimized conditions for the transformation of propargylic esters **16** into highly substituted lactones **17** by 5-*endo-dig* cyclization/C–C coupling are 3 mol% IPrAuCl/$AgSbF_6$ in dichloromethane at room temperature.

Under the optimized conditions the scope of the gold-catalyzed reaction was next investigated. Table 3 summarizes the results obtained with various propargylic esters **16**. In most cases, lactones **17** could be obtained in moderate-to-high yields. To understand the factors that control the gold-catalyzed reaction, different functionalities at the three variable positions were investigated.

Initial variations at the acetylenic position (R^1) of ester **16** showed no remarkable differences in terms of reaction yields. Lactones **17a**, **17b**, and **17c** were successfully obtained in high yields (Table 3, entries 1–3). However, the reaction exhibits significant changes in the reaction time. Thus, when a phenyl moiety was used, the reaction time was increased up to 12 h (entry 3), four times longer than the 3 h needed with long- and short-chained alkyl groups (entries 1 and 2). This outcome is not surprising when the rigidity and larger steric hindrance of the phenyl substituent is taken into account.

Next, the migrating fragment (R^2–C–R^3) was investigated. To understand the mechanism of the reaction in terms of the C–C coupling between the vinyl gold species and the migrating carbocation, we performed a series of experiments varying the stability of this fragment. To accomplish this, initially only R^2 was varied and R^3 was allowed to remain constant as an internal alkyne. As expected, the results showed a strong depend-

Table 3. Reaction scope.



16 17

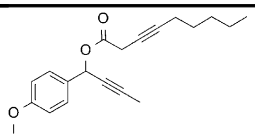
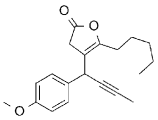
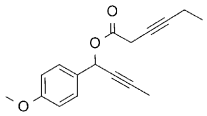
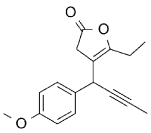
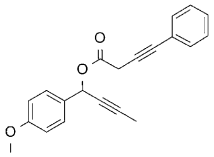
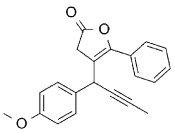
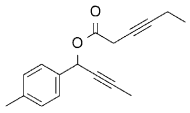
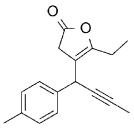
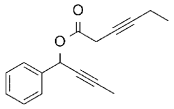
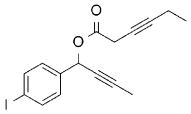
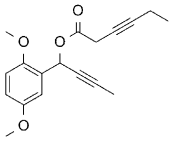
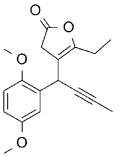
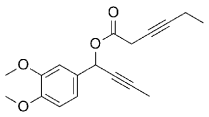
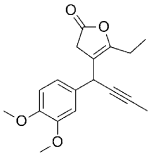
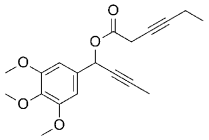
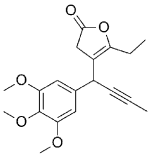
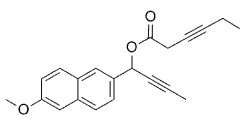
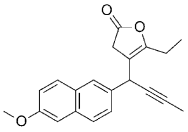
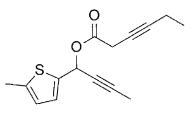
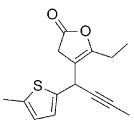
	Starting material	*t* [h]	Product	Yield of **17** [%]
1		3		**17a** (75)
2		3		**17b** (70)
3		12		**17c** (75)
4[a]		3		**17d** (50)
5		24	–	–[c]
6		3	–	–[d,e]
7		3		**17e** (55)
8		3		**17f** (61)
9		0.5		**17g** (65)
10		3		**17h** (51)
11		3		**17i** (62)

Table 3. (Continued)

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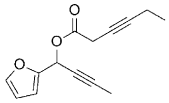
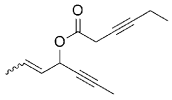
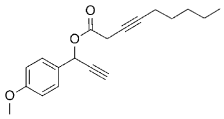
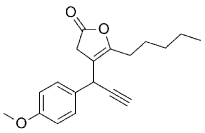
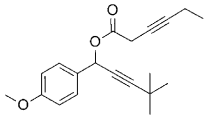
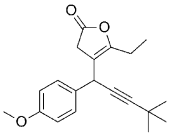
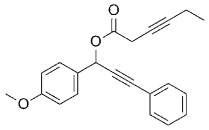
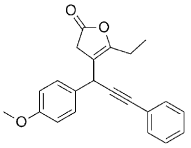
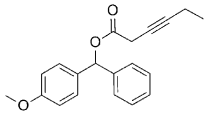
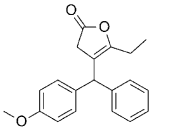
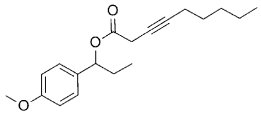
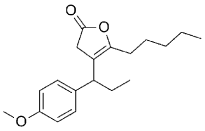
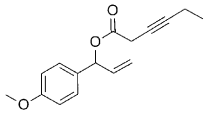
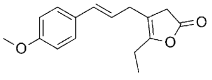
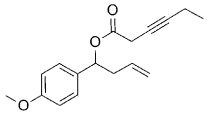
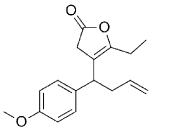
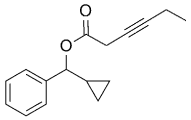
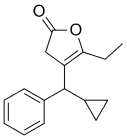
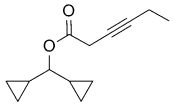
12		3	–	–[d]
13[b]		24	–	–[e]
14		0.25		**17j** (45)
15		3		**17k** (76)
16[f]		3		**17l** (24)
17		3		**17m** (89)
18		3		**17n** (88)
19		3		**17o** (46)
20		24		**17p** (65)
21[a]		24		**17q** (47)
22[a]		24	–	–[d,e]
23[a,b]		24	–	–[e]

[a] 5 mol% of catalyst was used. [b] The reaction was carried out at 40 °C. [c] Protodeauration product was formed. [d] Decomposition was detected. [e] No reaction was observed. [f] A 3:7 mixture of propargylester/allenyl ester was employed as starting material.

ency on the electron density of the substituent group (R^2). Thus, when aryl groups bearing electron-donating groups (EDG) were used as substituents in R^2, the corresponding lactones were obtained in moderate-to-high yields in short reaction times (entries 4, and 7–10). Although 5 mol% of gold was used for the transformation of propargylic ester **16d** (entry 4), its conversion achieved the lowest yield among these examples. Lactone **17d** bears only a methyl group at the aryl ring, thus lacking of the mesomeric effect present in the other examples owing to the methoxy groups. By the same manner, lactone **17g**, bearing three methoxy groups at the aryl group, was obtained in 65% yield after only 30 min of reaction (entry 9). On the other hand, when aryl groups bearing electron-withdrawing groups (EWG), or without substituents, were used, the formation of lactones **17** was not accomplished (entries 5 and 6). In those cases, only decomposition and/or unsubstituted lactones (i.e. **18**) were observed. These results indicate that for these systems the carbocation formed is not stable enough to enable the C–C coupling with the vinyl gold species, which instead undergoes simple protodeauration. The formation of **17o** and **17p** (entries 19 and 20) was slower (24 h). Different to the allylic ester in entry 19, the homoallylic ester is not activated by the olefin, in the case of the cyclopropyl group there is also no kinetic benefit for the conversion.

Entry 23 shows a tertiary alcohol, in this case no reaction of the substrate was detected and the starting material could be reisolated. Because the preparation of such tertiary esters is quite difficult, this lack of reactivity is no serious synthetic restriction.

Heteroaryl groups at the R^2 position were also examined. For this purpose, only π-excessive heterocycles, such as thiophene, were used. Thus, derivate **17i**, bearing a methylthiophene substituent, could be obtained after 3 h in 62% yield (entry 11). On the other hand furan did not convert (entry 12). A vinyl group was also investigated as a substituent R^2—no conversion was observed even after 24 h at 40 °C (entry 13). The fact that formation of the unsubstituted lactone (product of the protodeauration of vinyl gold intermediate) was not observed could be explained by considering an extremely high activation energy related to a remarkably lower stability of the migrating carbocation. Therefore, it is possible to conclude that the formation of any product, in this case, is inhibited by a significant increase in the activation energy needed to form both intermediates; the vinyl gold species and the migrating carbocation. This indicates that the formation of these two species is strictly linked to the stability of the carbocation. With these results in mind, in the next experiments the R^2 fragment was kept constant, as an aryl group bearing a methoxy substituent, and R^3 was varied by using different alkynyl, alkenyl, and alkyl groups (entries 14–20). Derivates **17j** and **17k**, possessing a terminal and an internal alkyne at the R^3 position, respectively, were obtained in moderate-to-high yield (entries 14 and 15). The best yield was achieved with derivate **17m** bearing a phenyl group (89%, entry 17), which offers extra stabilization to the carbocation. Lactone **17n**, possessing an alkyl chain, could also be obtained in high yield after 3 h of reaction (88%, entry 18). When a vinyl group was employed as substituent, the initially formed carbocation has the possibility to migrate into the allylic system. In this case, the product corresponding to the C–C coupling between the vinyl gold species and the less hindered carbocation was observed in 46% yield (entry 19). No formation of the branched product was detected. An allylic moiety at the R^3 position avoids this problem and still offers the stabilization needed to perform the reaction. Thus, derivate **17p** was obtained in 65% after 24 h of reaction (entry 20). Finally, taking into account the high stability of cyclopropyl carbonium ions,[15] stabilization coming from cyclopropyl rings was investigated. Derivate **17q**, bearing a phenyl group and a cyclopropyl ring, was satisfactorily obtained in 47% yield after 24 h (entry 21). This result corroborates the higher stabilization coming from the cyclopropyl ring, as propargylic ester **16e**, bearing also a phenyl ring, but instead of the cyclopropyl ring an alkyne moiety, could not be transformed into the desired lactone (entry 5). When two cyclopropyl rings were used as substituents only decomposition was observed (entry 22).

These results indicate that the high stabilizing effect from an aromatic substituent is needed to diminish the activation energy, allowing the formation of the migrating carbocation and the vinyl-gold-species intermediate. It is possible to conclude, that when an aromatic ring bearing EDGs is present at the R^2 position, the synthesis of highly substituted lactones bearing terminal and internal alkynyl, alkenyl, alkyl, cycloalkyl groups, and aromatic moieties takes place in moderate-to-high yields.

As mentioned before, an isomerization of lactones **17** bearing an alkyne moiety was observed when the gold-catalyzed reaction was purified by chromatography using Al_2O_3 instead of silica gel. This type of isomerization has been reported by Larock and co-workers and Hashmi and co-workers in the synthesis of allenyl ketones.[13] Figure 2 depicts the allenyl-substi-

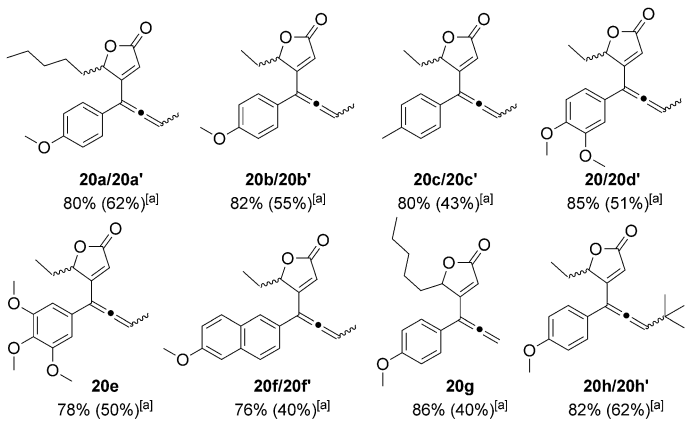


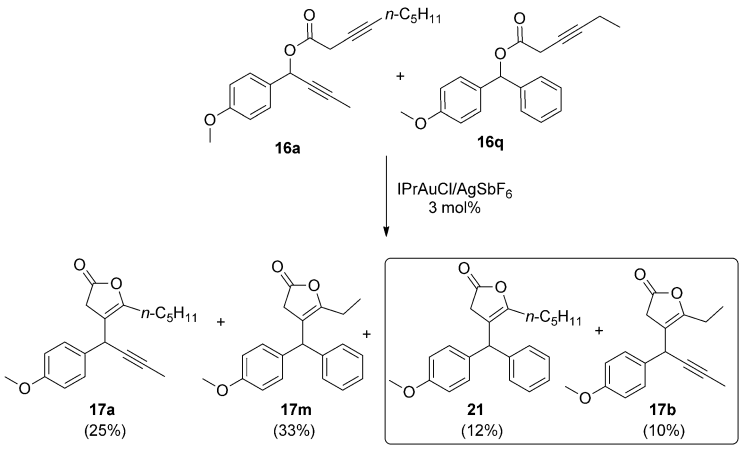
Figure 2. Isomerization of lactones **17** to allenyl-substituted lactones **20**. [a] Yield in parentheses refers to the one-pot gold-catalyzed reaction and isomerization starting from propargylic esters **16** (conditions: column chromatography on aluminum oxide using hexane/ethyl acetate).

tuted lactones **20** obtained from the Al_2O_3-promoted twofold tautomerization of the corresponding lactones **17**.

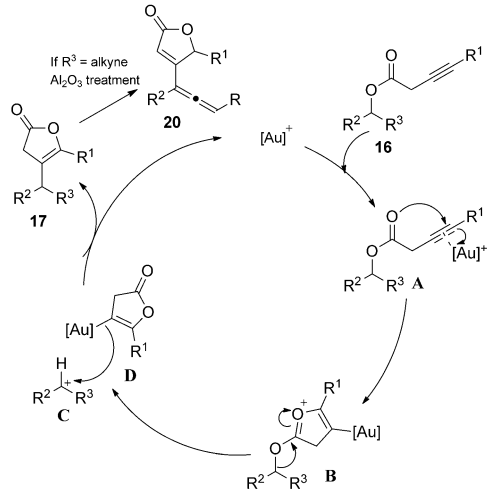
For each case, the yields corresponding to the cascade gold-catalyzed reaction/isomerization from propargylic esters **16**, as well as the yields of the isomerization from isolated lactones **17**, are given.

Allenyl-substituted lactones **20** were satisfactorily obtained in high yields (76–86%) after the Al_2O_3-promoted isomerization of previously isolated lactones **17**. No significant variations in the performance of this transformation were observed, demonstrating the broad scope and wide applicability of this method. On the other hand, moderate yields (40–62%) were obtained starting from propargylic esters **16**. As expected, there is a dependency on the electron density of the substituents, and the overall yields are, therefore, strongly related to those obtained for the gold-catalyzed synthesis of lactones **17**. In most cases, allenyl-substituted lactones **20** were obtained as a mixture of two diastereomers as a result of the axial chirality of the trisubstituted allene moiety.

In conclusion, lactones **17** and allenyl-substituted lactones **20** are easily accessible from properly functionalized propargylic esters **16**. The reaction only takes place when carbocation-stabilizing substituents are present in the structure, allowing the formation of the vinyl-gold species and the carbocation intermediates. To corroborate those observations and to propose a more precise reaction mechanism, a crossover experiment with derivates **16a** and **16q** was carried out. The aim of the crossover experiment was to unequivocally verify whether the C–C coupling of the vinyl gold species with the carbocation indeed takes place in an intermolecular fashion, or if the carbocation is not properly formed and the coupling takes place in an intramolecular fashion. Scheme 4 depicts the results, which were monitored by ^{1}H NMR spectroscopy, GC-MS and HRMS.



Scheme 4. Crossover experiment of propargylic esters **16a** and **16q**.



Scheme 5. Proposed reaction mechanism.

The experiment gave the expected lactones **17a** and **17m**, but also the cross-coupled products **17b** and **21** (Scheme 4). The fact that the yields obtained for the expected lactones (25–33%) are higher than those for the cross-coupling products (10–12%) indicates that although the reaction follows an intermolecular pathway, the C–C coupling of the two species formed from the same molecule must be rapid and close-ion pairs might dominate. Furthermore, the higher yields obtained for derivates containing two phenyl rings, **17m** and **21**, are in accordance with the greater stabilization of the carbocation that should be formed. This outcome demonstrates that the gold-catalyzed formation of substituted lactones **17** indeed takes place by formation of stabilized carbocations that react in an intermolecular fashion with the vinyl gold intermediates.

According to the results obtained, Scheme 5 shows the catalytic cycle for the gold-catalyzed cascade cyclization/C–C coupling of propargylic esters **16**. The first stage implies π activation of propargylic esters **16** by the gold species, forming complex **A**. This activation allows nucleophilic attack of the oxygen atom through 5-*endo-dig* cyclization, leading to the oxonium intermediate **B**, which in turn generates the stabilized carbocation **C** and the vinyl gold(I) intermediate **D**. C–C coupling between the electrophile and the vinyl gold species gives rise to the highly substituted lactones **17** under liberation of the catalyst, which closes the catalytic cycle. Final isomerization, promoted by basic Al_2O_3, of properly functionalized lactones **17** generates the allenyl-substituted lactones **20**.

Conclusion

This methodology is based on the gold(I)-catalyzed 5-*endo-dig* cyclization of propargylesters **16**, followed by trapping of vinyl gold(I) intermediates with stable carbocations, leading to highly substituted lactones. The reaction performs satisfactorily when propargylic esters bearing terminal and internal alkynyl, alkenyl, alkyl, cycloalkyl groups, and aromatic moieties are used. The presence of an aromatic ring with EDGs is needed to stabilize the carbocation. Novel highly substituted lactones were synthesized in high-to-moderate yields and with high atom economy. In some cases, these new lactones possess an

exocyclic alkyne or allene moiety, which could enable further functionalizations towards more complex targets.

Acknowledgements

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Keywords: alkynes · allenes · furans · gold · lactones

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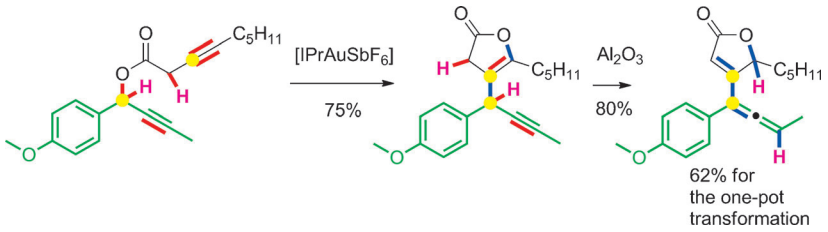
FULL PAPER

Synthetic Methods

*M. C. Blanco Jaimes, A. Ahrens, D. Pflästerer, M. Rudolph, A. S. K. Hashmi**

■■ – ■■

Synthesis of Highly Substituted γ-Butyrolactones by a Gold-Catalyzed Cascade Reaction of Benzyl Esters



Six is the magic number: In the gold-catalyzed rearrangements of simple diyne substrates with an ester bridge six bonds are cleaved and six new bonds are formed in a one-pot conversion (see scheme).