Au_2O_3 as a Stable and Efficient Catalyst for the Selective Cycloisomerization of γ-Acetylenic Carboxylic Acids to γ-Alkylidene-γ-Butyrolactones

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Abstract: The high potential of commercially available Au_2O_3 as a catalyst in the cyclization of alkynes bearing carboxylic acids to the corresponding γ-alkylidene-γ-butyrolactones through a general, efficient and easy procedure is presented. The reaction shows a high degree of chemo-, regio-, and stereoselectivity. The 5-*exo* mode of cyclization and *anti* auration are a general trend for the Au_2O_3 catalyst.

Keywords: gold catalyst, cycloisomerization, γ-acetylenic carboxylic acids, atom economy, γ-alkylidene-γ-butyrolactones

After a long period of underestimation, homogeneous gold catalysis has recently emerged as an exciting area of modern synthetic organic chemistry.[1] The ability of gold metal centers to coordinate and activate carbon–carbon multiple bonds towards the intramolecular addition of a variety of nucleophiles has been thoroughly investigated.[1] Carbon, nitrogen, oxygen, and sulfur-based nucleophiles have been studied and a flurry of methodologies dealing with the syntheses of carbo- and heterocycles has appeared.[2] γ-Alkylidene lactones represent an important family of enol esters due to the presence of this moiety in a number of natural products of biological relevance[3,4] and in synthetic intermediates with applications in pharmaceuticals.[5] The transition-metal-catalyzed cyclization of 4-alkynoic acids constitutes a major route[6] for the construction of five-membered exocyclic enol lactones and has been the subject of a large number of investigations. Earlier on, silver,[4a,b,7] mercury,[4c,8] palladium,[9] ruthenium,[10] and rhodium[11] complexes have demonstrated interesting catalytic activities in this regard. Recently, palladium- and nickel-containing clusters[12] have been reported to exhibit even higher catalytic activities. Despite those efforts, many catalysts suffer from limited scope, toxicity concerns, exacting reaction conditions (high temperatures, exclusion of moisture and air, and the use of base additives) and poor selectivities. As part of our ongoing research program[13] dealing with the activation of alkynes towards a variety of nucleophiles, we introduced gold(I) chloride[14] as an active catalyst for the cyclization of functionalized 4-alkynoic acids. In an effort to extend the scope of our initial system, to reach higher activity and to increase selectivity, we decided to engage in a survey of the catalytic properties of commercially available, easy to handle, late-transition-metal Lewis acids. In this paper, we describe the development of a robust, highly selective procedure for the synthesis of γ-alkylidene lactones using the less toxic[1k] Au_2O_3 as a catalyst.

Despite the fact that the AuCl methodology is remarkably mild and simple, some limitations have been identified. The use of highly hydroscopic gold chloride complexes can result in undesired side reactions, as hydration of the alkynes becomes competitive.[15] This side reaction was extremely substrate-dependent, and the need for a catalyst offering improved chemoselectivity was evident. A perfect regioselectivity for the cyclization step in favor of the 5-*exo* isomer was observed for terminal alkynes, whereas a mixture of 5-*exo* and 6-*endo* products resulted from the cyclization of internal alkynes. The group of Pale has also proposed a system based on a combination of 10 mol% of AuCl, and 10 mol% of K_2CO_3 to promote the reaction.[16] In line with potential applications in the total synthesis of γ-alkylidenes, emphasis was put on the search for alternative catalysts affording a high level of both regio- and stereoselectivity. On the basis of our study on the *exo*-selective cycloisomerization of γ-acetylenic acids,[14] we tested the reactivity of the phenyl-substituted substrate **1a** in the presence of 5 mol% of a variety of transition-metal salts in acetonitrile for a test period of 2 hours (Table 1). Whereas the cyclization of **1a** in the presence of AuCl led to a mixture of **2a** and **3a**, Au_2O_3 furnished the butyrolactone **2a** in almost quantitative yield (entry 2 vs. entry 3). It is noteworthy that Au_2O_3 has only previously been used in oxidation of methane to methanol.[17,1j] $AuCl_3$ led to a complex mixture of side products (entry 4). Interestingly, the use of $KAuCl_4$ favored the hydration process due to the competitive intermolecular Markovnikov addition of water[15] furnishing ketone **3a** (entry 5). Platinum chloride and $[Ir(COD)Cl]_2$ both promote the cyclization process with a high level of chemoselectivity as the γ-keto acid **3a** was not observed (entries 6 and 7). The oxidation state of the metal and therefore the electrophilic behavior of the catalyst was crucial as the presence of Ir(III) chloride did not give any product (entry 8). Other late-transition-metal halides (entries 9–11) and $Sc(OTf)_3$ exhibited considerably lower activities in the conditions tested. As a comparison, we also tested a Brønsted acid (HCl, entry 13), no trace of compound **2a** could be detected after 3 hours. In a second set of experiments, we decided to explore the catalytic potential of other group 10–12 metal oxides.

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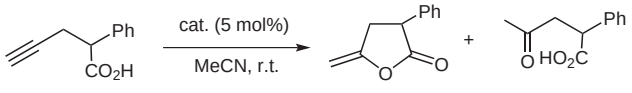
PtO_2, AgO, and HgO all catalyzed the cyclization with a high level of chemo- and regioselectivity, HgO and Au_2O_3 presenting the highest activities (entries 14–16 and entry 3). To highlight the chemoselectivity of Au_2O_3 in favor of the intramolecular addition of the acid versus the intermolecular addition of H_2O,[15] the standard reaction was conducted in a mixture MeCN–H_2O (6:1) and proceeded to give the butyrolactone **2a** in 92% isolated yield (entry 17). No traces of product resulting from the addition of the external nucleophile could be detected in the reaction mixture.

Table 1 Catalyst Screening for the Cyclization of **1a**[a]



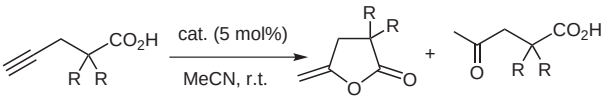
1a **2a** **3a**

Entry	Catalyst	Conversion (%)	Ratio **2a**/**3a**[b] (%)	Yield (%)[c]
1	None	0	–	–
2	AuCl	100	60:40	n.i.
3[d]	Au_2O_3	100	100:0	95
4	$AuCl_3$	100[e]	n.d.	–
5	$KAuCl_4$	100	0:100	98
6	$PtCl_2$	100	100:0	81
7[d]	$[Ir(COD)Cl]_2$	100	100:0	92
8	$IrCl_3$	0	–	–
9	$RuCl_3$	3	100:0	n.i.
10	$RhCl_3$	3	100:0	n.i.
11	$InCl_3$	7	100:0	n.i.
12	$Sc(OTf)_3$	4	100:0	n.i.
13	HCl	0	–	–
14	PtO_2	15	100:0	n.i.
15	Ag_2O	80	100:0	n.i.
16	HgO	100	100:0	89
17[d,f]	Au_2O_3	100	100:0	92

[a] Reaction conditions: substrate **1a** stirred at r.t. for 3 h in the presence of 5 mol% catalyst in MeCN (1 mol/L).
[b] Product ratio **2a**/**3a** determined on the basis of ^1H NMR spectra.
[c] Isolated yields correspond to analytically pure samples upon filtration on a pad of silica gel and evaporation of the solvents.
[d] 2.5 mol%.
[e] Decomposition.
[f] MeCN–H_2O (6:1) as solvent. n.d.: not determined. n.i.: not isolated.

Considering these encouraging preliminary results, we extended the comparison to the cyclization of pent-4-ynoic acid (**1b**) and 2,2-dimethylpent-4-ynoic acid (**1c**). Results are summarized in Table 2.

Table 2 Cyclization of Acetylenic Acids **1b** and **1c**



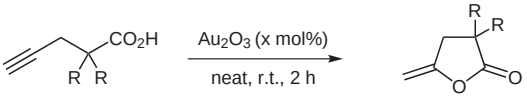
R = H, **1b** R = Me, **1c** R = H, **2b** R = Me, **2c** R = H, **3b** R = Me, **3c**

Entry	Substrate	Catalyst	Conversion (%)	Yield **2** (%)[a]	Yield **3** (%)[a]
1	**1b**	AuCl	100	0	77
2[b]	**1b**	Au_2O_3	100	90	0
3	**1b**	$PtCl_2$	100	73	0
4[b]	**1b**	$[Ir(COD)Cl]_2$	100	30	0
5	**1c**	AuCl	0	–	–
6[b]	**1c**	Au_2O_3	100	99	0
7	**1c**	$PtCl_2$	100	44	0
8[b]	**1c**	$[Ir(COD)Cl]_2$	100	70	0

[a] Isolated yield.
[b] 2.5 mol%.

Using 5 mol% of AuCl in acetonitrile, acetylenic acid **1b** was chemospecifically converted into the corresponding γ-keto acid **3b** (entry 1) whereas acid **1c** was recovered unreacted in almost quantitative yield (entry 5). Experimentally, in the latter case, we observed the formation of presumably Au(0) nanoparticules, which are therefore inert for such reaction. This observation suggests that the deactivating process associated with gold halides proceeds from a redox reaction between the catalytic species and the substrate. In contrast, Au_2O_3, $PtCl_2$, and $[Ir(COD)Cl]_2$ showed full conversions of the starting acids into lactones **2b** and **2c** (entries 2–4 and 6–8). Chemical yields upon purification by filtration are moderate to excellent and highly dependent on the volatility of the products formed. Taking into account the high stability of Au_2O_3 towards the reaction media and its high efficiency, catalytic tests in the absence of additional solvent have been undertaken with liquid substrates **1b** and **1c** (Scheme 1). Quantitative yields have been obtained for both acids. Using this protocol, the substrate-to-metal ratio was enhanced, respectively, to 200 and 1000 for acids **1b** and **1c**.

In order to assess the versatility of the gold(III) oxide catalyst, various acetylenic acids were submitted to cyclization under the above-mentioned conditions using Au_2O_3 (Table 3).[18] Terminal 4-pentynoic acid derivatives ob-



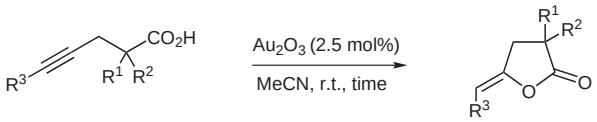
R = H, **1b** R = Me, **1c** R = H, **2b** x = 0.25, 99% R = Me, **2c** x = 0.05, 99%

Scheme 1 Catalyst loading for the cyclization of acetylenic acids **1b** and **1c**

tained after monosaponification of the corresponding malonates[14] are cyclized in excellent yields in the presence of a variety of functional groups such as alkenes, alkynes, and esters (Table 3, entries 1–7). No side products resulting from the attack of internal nucleophiles (such as carbon–carbon double bonds, through 1,6-enyne cycloisomerization) could be observed. In these cases, Au_2O_3 is as efficient and selective as AuCl but is much easier to handle. Remarkably, lowered activities are observed compared to the AuCl catalyst in the presence of bulky substituents (Table 3, entries 2 and 3). Thus, longer reaction times are required to reach complete conversion. However, chemical yields were not altered and the corresponding lactone **2e** was isolated in 98% yield. The cyclization of halogenated alkyne (Table 3, entry 8) led to lowered yields due to decomposition of the starting material. Remarkably, total regiospecificity in favor of the γ-butyrolactone was obtained for the substrate featuring both a propargyl and a homopropargyl side chain (Table 3, entries 6 and 7).[19] The cyclization of internal acetylenic acid was interesting considering that a mixture of 5-*exo* and 6-*endo* adduct was obtained in the presence of AuCl (R^3 = Et). The aryl-substituted internal acetylenic acid **1k** reacted smoothly in 2 hours reaction time and allowed complete conversion and excellent yield of lactone **2k** (Table 3, entry 9). The case of the alkyl-substituted alkynes was extremely challenging and rewarding (Table 3, entries 10–12): in contrast with the AuCl system and other metal-based systems,[6] a perfect regiospecificity for the 5-*exo* product with a *Z*-stereochemistry resulting from *anti* auration was observed. The lactones **2l** and **2m** were isolated in 99% and 92% yields, respectively (Table 3, entries 10, 12). It is noteworthy that a substrate-to-catalyst ratio of 100 could be used with maintained efficiency in the case of carboxylic acid **1l**. Despite the fact that the activity of Au_2O_3 was moderate compared to AuCl, complete regio- and stereoselectivities were observed without any side reaction, as in the case of internal alkynes, where AuCl was not offering sufficient selectivity.

In conclusion, we have demonstrated that simple, commercially available, and highly stable Au_2O_3 catalyzes the cyclization of g-acetylenic acids with high yields to form γ-alkylidene-γ-butyrolactones through a general, efficient, and easy manipulative procedure. The reaction shows a high degree of chemoselectivity as the competitive addition of other protic oxygen nucleophiles is completely inhibited. Simple carboxylic acids as well as functionalized ones may cyclize smoothly and selectively. The 5-*exo* cyclization and *anti* auration are general for the Au_2O_3 catalyst. Catalyst ratios as low as 0.1 mol% have been obtained for pentynoic acids. Further studies will be directed towards the immobilization of such a system to evaluate the activity and the possibility of recycling of supported gold catalysts.

Table 3 Cyclization of Various γ-Acetylenic Carboxylic Acids[20]



1d R^1 = CO_2Et, R^2 = *n*-Bu, R^3 = H
1e R^1 = CO_2Et, R^2 = Bn, R^3 = H
1f R^1 = CO_2Me, R^2 = allyl, R^3 = H
1g R^1 = CO_2Me, R^2 = cinnamyl, R^3 = H
1h R^1 = Ph, R^2 = propargyl, R^3 = H
1i R^1 = CO_2Me, R^2 = homopropargyl, R^3 = H
1j R^1 = CO_2Me, R^2 = Cl, R^3 = H
1k R^1 = CO_2Et, R^2 = *n*-Bu, R^3 = 4-CNC_6H_4
1l R^1 = R^2 = Me, R^3 = Et
1m R^1 = CO_2Me, R^2 = allyl, R^3 = Et

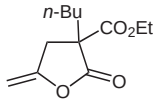
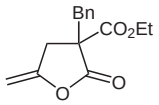
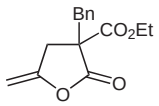
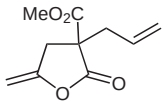
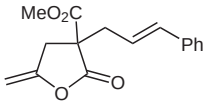
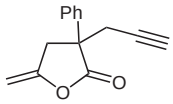
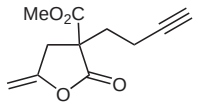
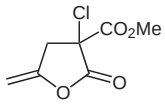
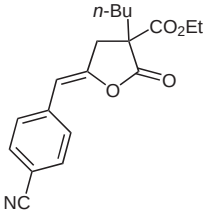
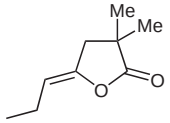
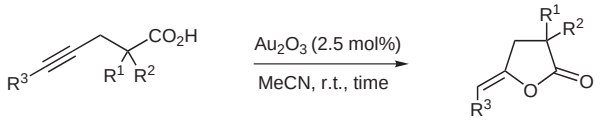
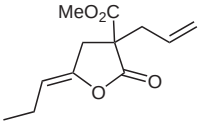
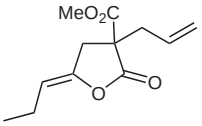
Entry	**1**	Product	**2**	Time (h)	Yield (%, conversion)[a]
1	**1d**		**2d**	2	99 (100)
2	**1e**		**2e**	2	n.i. (25)
3	**1e**		**2e**	6	98 (100)
4	**1f**		**2f**	2	89 (100)
5	**1g**		**2g**	2	79 (100)
6	**1h**		**2h**	2	99 (100)
7	**1i**		**2i**	2	80 (100)
8	**1j**		**2j**	2	54 (100)
9	**1k**		**2k**	2	96 (100)
10[b]	**1l**		**2l**	6	99 (100)

Table 3 Cyclization of Various γ-Acetylenic Carboxylic Acids[20]



1d $R^1 = CO_2Et$, $R^2 = n$-Bu, $R^3 = H$
1e $R^1 = CO_2Et$, $R^2 = Bn$, $R^3 = H$
1f $R^1 = CO_2Me$, $R^2 =$ allyl, $R^3 = H$
1g $R^1 = CO_2Me$, $R^2 =$ cinnamyl, $R^3 = H$
1h $R^1 = Ph$, $R^2 =$ propargyl, $R^3 = H$
1i $R^1 = CO_2Me$, $R^2 =$ homopropargyl, $R^3 = H$
1j $R^1 = CO_2Me$, $R^2 = Cl$, $R^3 = H$
1k $R^1 = CO_2Et$, $R^2 = n$-Bu, $R^3 = 4\text{-}CNC_6H_4$
1l $R^1 = R^2 = Me$, $R^3 = Et$
1m $R^1 = CO_2Me$, $R^2 =$ allyl, $R^3 = Et$

Entry	1	Product	2	Time (h)	Yield (%, conversion)[a]
11	**1m**		**2m**	2	n.i. (33)
12	**1m**		**2m**	16	92 (100)

[a] Isolated yields.
[b] Substrate-to-catalyst ratio: 100.

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References and Notes

(1) For representative examples and seminal references, see: (a) Fürstner, A.; Davies, P. W. *Angew Chem. Int. Ed.* **2007**, *46*, 3410. (b) Gorin, D. J.; Toste, D. *Nature (London)* **2007**, *446*, 395. (c) Hashmi, A. S. K.; Hutchings, G. J. *Angew Chem. Int. Ed.* **2006**, *45*, 7896. (d) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Commun.* **2007**, 333. (e) Ma, S.; Yu, S.; Gu, Z. *Angew. Chem. Int. Ed.* **2006**, *45*, 200. (f) Hashmi, A. S. K. *Angew. Chem. Int. Ed.* **2005**, *44*, 6090. (g) Hoffmann-Röder, A.; Krause, N. *Org. Biomol. Chem.* **2005**, *3*, 387. (h) Hashmi, A. S. K. *Gold Bull.* **2004**, *37*, 51. (i) Pyykkö, P. *Angew. Chem. Int. Ed.* **2004**, *43*, 4412. (j) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180. (k) Shaw, C. F. III. *Chem. Rev.* **1999**, *99*, 2589. (l) Michelet, V.; Toullec, P. Y.; Genet, J.-P. *Angew. Chem. Int. Ed.* **2008**, *47*, in press.

(2) (a) Zhang, L.; Sun, J.; Kozmin, S. A. *Adv. Synth. Catal.* **2006**, *348*, 2271. (b) Nieto-Oberhuber, C.; López, S.; Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Eur. J.* **2006**, *12*, 5916. (c) Nevado, C.; Echavarren, A. M. *Synthesis* **2005**, 167. (d) Arcadi, A.; Di Giuseppe, S. *Curr. Org. Chem.* **2004**, *8*, 795. (e) Bianchi, G.; Arcadi, A. In *Targets in Heterocyclic Systems*, Vol. 8; Attanasi, O. A.; Spinelli, D., Eds.; Springer: Berlin, **2004**, 82. (f) Aubert, C.; Fensterbank, L.; Gandon, V.; Malacria, M. *Topics Organomet. Chem.* **2006**, *19*, 259.

(3) For a review discussing natural products exhibiting the γ-butyrolactone substructure, see: (a) Koch, S. S. C.; Chamberlin, A. R. *In Studies in Natural Products Chemistry*, Vol. 16; Atta-ur-Rahman, Ed.; Elsevier Science: Amsterdam, **1995**, 687. For reviews discussing the synthetic routes to γ-alkylydene-γ-butyrolactones, see: (b) Seitz, M.; Reiser, O. *Curr. Opin. Chem. Biol.* **2005**, *9*, 285. (c) Negishi, E.-I.; Kotora, M. *Tetrahedron* **1997**, *53*, 6707. For representative examples from Pd chemistry, see: (d) Balme, G.; Monteiro, N.; Bouyssi, D. *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-I., Ed.; John Wiley and Sons: New York, **2002**, 2245–2265. (e) Hosokawa, T.; Murahashi, S.-I. *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-I., Ed.; John Wiley and Sons: New York, **2002**, 2169–2192. (f) Xu, C.; Negishi, E.-I. *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-I., Ed.; John Wiley and Sons: New York, **2002**, 2289.

(4) For specific cases of natural product synthesis where cyclizations of alkynoic acids constitute a key step, see: (a) Algueró, M.; Bosch, J.; Castañer, J.; Castellá, J.; Castells, J.; Mestres, R.; Pascual, J.; Serratosa, F. *Tetrahedron* **1962**, *18*, 1381. (b) Jong, T. T.; Williard, P. G.; Porwoll, J. P. *J. Org. Chem.* **1984**, *49*, 735. (c) Imagawa, H.; Fujikawa, Y.; Tsuchihiro, A.; Kinoshita, A.; Yoshinaga, T.; Takao, H.; Nishizawa, N. *Synlett* **2006**, 639.

(5) (a) Wright, A. D.; de Nys, R.; Angerhofer, C. K.; Pezzuto, J. M.; Gurrath, M. *J. Nat. Prod.* **2006**, *69*, 1180. (b) Chen, C.-H.; Lo, W.-L.; Liu, Y.-C.; Chen, C.-Y. *J. Nat. Prod.* **2006**, *69*, 927.

(6) For comprehensive reviews dealing with transition-metal-catalyzed heteroatom–hydrogen additions to alkynes, see: (a) Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev.* **2004**, *104*, 3079. (b) Beller, M.; Seayad, J.; Tillack, A.; Jiao, H. *Angew. Chem. Int. Ed.* **2004**, *43*, 3368. (c) Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127. (d) For Ru-catalyzed intermolecular reactions, see: Bruneau, C.; Dixneuf, P. H. *Acc. Chem. Res.* **1999**, *32*, 311.

(7) Silver catalysis: (a) Castaner, J.; Pascual, J. *J. Chem. Soc.* **1958**, 3962. (b) Pale, P.; Chuche, J. *Tetrahedron Lett.* **1987**, *27*, 6447. (c) Dalla, V.; Pale, P. *New. J. Chem.* **1999**, *23*, 803. (d) Dalla, V.; Pale, P. *Tetrahedron Lett.* **1994**, *35*, 3525. (e) Oh, C. H.; Yi, H. J.; Lee, J. H. *New. J. Chem.* **2007**, *31*, 835.

(8) Mercury catalysis: (a) Yamamoto, M. *J. Chem. Soc., Chem. Commun.* **1978**, 649. (b) Yamamoto, M. *J. Chem. Soc., Perkin Trans. 1* **1981**, 582. (c) Amos, R. A.; Katzenellenbogen, J. A. *J. Org. Chem.* **1978**, *43*, 560. (d) Amos, R. A.; Katzenellenbogen, J. A. *J. Am. Chem. Soc.* **1981**, *103*, 5459. (e) Rollinson, S. W.; Amos, R. A.; Katzenellenbogen, J. A. *J. Am. Chem. Soc.* **1981**, *103*, 4114. (f) Sofia, M. J.; Katzenellenbogen, J. A. *J. Org. Chem.* **1984**, *50*, 2331. (g) Spencer, R. W.; Tam, T. F.; Thomas, E.; Robinson, V. J.; Krantz, A. *J. Am. Chem. Soc.* **1986**, *108*, 5589.

(9) Palladium catalysis: (a) Lambert, C.; Utimoto, K.; Nozaki, H. *Tetrahedron Lett.* **1984**, *25*, 5323. (b) Yanagihara, N.; Lambert, C.; Iritari, K.; Utimoto, K.; Nozaki, H. *J. Am. Chem. Soc.* **1986**, *108*, 2753. (c) Arcadi, A.; Burini, A.; Cacchi, S.; Delmastro, M.; Marinelli, F.; Pietroni, B. R. *J. Org. Chem.* **1992**, *57*, 976. (d) Cavicchioli, M.; Bouyssi, D.; Goré, J.; Balme, G. *Tetrahedron Lett.* **1996**, *37*, 1429. (e) Wang, X.; Lu, X. *J. Org. Chem.* **1996**, *61*, 2254. (f) Huo, Z.; Patil, N. T.; Jin, T.; Pahadi, N. K.; Yamamoto, Y. *Adv. Synth. Catal.* **2007**, *349*, 680. (g) Bellina, F.; Ciucci, D.; Vergamini, P.; Rossi, R. *Tetrahedron* **2000**, *56*, 2533. (h) Ahmed, Z.; Albrecht, U.; Langer, P. *Eur. J. Org. Chem.* **2005**, 3469. (i) Subramanian, V.; Batchu, V. R.;

Barange, D.; Pal, M. *J. Org. Chem.* **2005**, *70*, 4778.
(j) Duchêne, A.; Thibonnet, J.; Parrain, J.-L.; Anselmi, E.; Abarbri, M. *Synthesis* **2007**, 597.

(10) Ruthenium catalysis: Jimenez-Tenotio, M.; Puerta, M. C.; Valerga, P.; Moreno-Dorado, F. J.; Guerra, F. M.; Massanet, G. M. *Chem. Commun.* **2001**, 2324.

(11) Rhodium catalysis: (a) Marder, T. B.; Chan, D. M. T.; Fultz, W. C.; Calabrese, J. C.; Milstein, D. *J. Chem. Soc., Chem Commun.* **1987**, 1885. (b) Chan, D. M. T.; Marder, T. B.; Milstein, D.; Taylor, N. J. *J. Am. Chem. Soc.* **1987**, *109*, 6385. (c) Elgafi, S.; Field, L. D.; Messerle, B. A. *J. Organomet. Chem.* **2000**, *607*, 97.

(12) Cluster catalysis: (a) Wakabayashi, T.; Ishii, Y.; Ishikawa, K.; Hidai, M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 3123; and references cited therein. (b) Takei, I.; Wakebe, Y.; Suzuki, K.; Enta, Y.; Suzuki, T.; Mizobe, Y.; Hidai, M. *Organometallics* **2003**, *22*, 4639.

(13) (a) Charruault, L.; Michelet, V.; Taras, R.; Gladiali, S.; Genêt, J.-P. *Chem. Commun.* **2004**, 850. (b) Nevado, C.; Charruault, L.; Michelet, V.; Nieto-Oberhuber, C.; Muñoz, M. P.; Méndez, M.; Rager, M.-N.; Genêt, J.-P.; Echavarren, A. M. *Eur. J. Org. Chem.* **2003**, 706. (c) Antoniotti, S.; Genin, E.; Michelet, V.; Genêt, J.-P. *J. Am. Chem. Soc.* **2005**, *127*, 9976. (d) Genin, E.; Antoniotti, S.; Michelet, V.; Genêt, J.-P. *Angew. Chem. Int. Ed.* **2005**, *44*, 4949. (e) Toullec, P. Y.; Genin, E.; Leseurre, L.; Genêt, J.-P.; Michelet, V. *Angew. Chem. Int. Ed.* **2006**, *45*, 7427. (f) Genin, E.; Leseurre, L.; Toullec, P. Y.; Genêt, J.-P.; Michelet, V. *Synlett* **2007**, 1780. (g) Leseurre, L.; Toullec, P. Y.; Genêt, J.-P.; Michelet, V. *Org. Lett.* **2007**, *9*, 4049.

(14) (a) Genin, E.; Toullec, P. Y.; Antoniotti, S.; Brancour, C.; Genêt, J.-P.; Michelet, V. *J. Am. Chem. Soc.* **2006**, *128*, 3112. (b) Genin, E.; Toullec, P. Y.; Antoniotti, S.; Brancour, C.; G enêt, J.-P.; Michelet, V. *ARKIVOC* **2007**, *(v)*, 67.

(15) For references dealing with the gold-catalyzed hydration of alkynes, see: (a) Fukuda, Y.; Utimoto, K. *J. Org. Chem.* **1991**, *56*, 3729. (b) Teles, J. H.; Brode, S.; Chabanas, M. *Angew. Chem. Int. Ed.* **1998**, *37*, 1415. (c) Mizushima, E.; Sato, K.; Hayashi, T. M. *Angew. Chem. Int. Ed.* **2002**, *41*, 4563. (d) Schneider, S. K.; Herrmann, W. A.; Herdtweck, E. *Z. Anorg. Allg. Chem.* **2003**, *629*, 2363.

(16) (a) Harkat, H.; Weibel, J.-M.; Pale, P. *Tetrahedron Lett.* **2006**, *47*, 6273. (b) For a recent Au-catalyzed cyclization of γ- and δ-acetylenic acids, see: Marchal, E.; Uriac, P.; Legoin, B.; Toupet, L.; van de Weghe, P. *Tetrahedron* **2007**, *63*, 9979.

(17) (a) Jones, C. J.; Taube, D.; Ziatdinov, V. R.; Periana, R. A.; Nielsen, R. J.; Oxgaard, J.; Goddard, W. A. III. *Angew. Chem. Int. Ed.* **2004**, *43*, 4626. (b) De Vos, D. E.; Sels, B. F. *Angew. Chem. Int. Ed.* **2005**, *44*, 30.

(18) **General Procedure for the Cycloisomerization of γ-Acetylenic Acid 1**
Substrate **1b** (98 mg, 1 mmol) was placed in 5 mL Schlenk tube under argon and 1 mL of degassed MeCN was added. Gold(III) oxide (11.1 mg, 0,025 mmol) was added and the reaction mixture stirred at r.t. for 2 h. Filtration of the reaction mixture on a pad of 2 cm of silica using 15 mL of EtOAc and evaporation of the solvents allowed the isolation of product **2b** as colorless oil in an analytically pure form (89 mg, 90% yield).

(19) **2-(Methoxycarbonyl)-2-(prop-2-ynyl)hex-5-ynoic Acid (1i)**
Substrate **1i** was prepared in a two-step procedure using malonic synthesis. Sodium hydride (1.1 equiv, 60 wt.% in mineral oil) was added portionwise at 0 °C to a solution of dimethyl propargylmalonate (1 equiv) in anhydrous DMF. The reaction was allowed to warm up to r.t. and but-3-ynyl trifluoromethylsulfonate ester (1.1 equiv) slowly added. The mixture was stirred at r.t. overnight, quenched upon addition of 10 mL of H_2O and extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with brine (30 mL), dried over $MgSO_4$, and solvents evaporated under reduced pressure. Dimethyl 2-(but-3-ynyl)-2-(prop-2-ynyl)malonate was obtained as a colorless oil (18%) after purification by silica gel chromatography (cyclohexane–EtOAc, 90:10). Monosaponification was conducted following a reported procedure.[14] A solution of KOH (1.2 equiv) in anhydrous MeOH (0.4 mol/L) was added to a cooled (0 °C) solution of substrate (1 equiv) in anhydrous MeOH (0.4 mol/L). The mixture was stirred at r.t. for 6 h. Solvent was removed under reduced pressure and the crude product redissolved in Et_2O. The organic layer was treated three times with sat. $NaHCO_3$, the aqueous phases collected, acidified to pH 1 with concd HCl, and then extracted with Et_2O. This organic layer was then dried over $MgSO_4$ and the solvents removed under reduced pressure to give **1i** as a colorless oil (48% yield).
2-Methoxycarbonyl-2-[but-3′-ynyl]-4-methylene-butyrolactone (2i)
^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.80–4.83 (m, 1 H), 4.39–4.41 (m, 1 H), 3.79 (s, 3 H), 3.39 (dt, *J* = 18.9, 2.0 Hz, 1 H), 2.98 (dt, *J* = 18.9, 2.0 Hz, 1 H), 2.05–2.40 (m, 4 H), 1.99 (t, *J* = 2.6 Hz, 1 H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 171.9, 168.9, 152.3, 89.9, 82.1, 69.8, 54.6, 53.4, 35.3, 32.6, 14.3. MS (CI, NH_3): *m/z* (%) = 209 (8) $[M + H]^+$, 226 (100) $[M + NH_4]^+$, 244 (8) $[M + NH_3 + NH_4]^+$. HRMS (CI-NH_3): *m/z* calcd for $C_{11}H_{13}O_4$: 209.0814; found: 209.0819.

(20) **2,2-Dimethylhept-4-ynoic Acid (1l)**
Methyl isobutyrate (1.07g, 10.5 mmol) was added dropwise at –78 °C to a solution of LDA solution in THF (15 mL, 0.7 mol/L, 10.5 mmol). The solution was stirred at –78 °C for 20 min then 1-bromobut-2-yne (1.47g, 10 mmol) slowly added dropwise. The reaction was stirred at –78 °C for 2 h then allowed to warm up to r.t. The reaction mixture was quenched with sat. aq $NaHCO_3$ solution and extracted with Et_2O. The combined organic layers were collected, washed with brine, dried over $MgSO_4$, and the solvents removed under reduced pressure. The crude oil was purified by flash chromatography [PE (30–60)–EtOAc, 95:5] to give methyl 2,2-dimethylhept-4-ynoate as a colorless oil (1.48 g, 88% yield). Saponification was conducted following a published procedure.[2] Methyl 2,2-dimethylhept-4-ynoate (1.01g, 6 mmol) was added to a solution of KOH (403 mg, 7.2 mmol) in MeOH and the reaction mixture was stirred at r.t. for 16 h. Solvent was removed under reduced pressure and the crude product dissolved in Et_2O. The organic layer was treated three times with sat. Na_2CO_3, the aqueous phases collected, acidified to pH 1 with concd HCl, and then extracted with Et_2O. This organic layer was then dried over $MgSO_4$ and the solvents removed under reduced pressure to give **1l** as a colorless oil (590 mg, 64% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.41 (t, *J* = 2.4 Hz, 2 H), 2.16 (qt, *J* = 7.5, 2.4 Hz, 2 H), 1.28 (s, 3 H), 1.11 (t, *J* = 7.5 Hz, 1 H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 183.2, 84.3, 75.5, 42.2, 29.7, 24.3, 14.2, 12.4. MS (CI, NH_3): *m/z* (%) = 155 (15) $[M + H]^+$) 172 (100) $[M + NH_4]^+$. HRMS (CI-NH_3): *m/z* calcd for $C_9H_{15}O_2$: 155.1072; found: 155.1075.
2,2-Dimethyl-4-propylydenebutyrolactone (2l)
^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.60 (tt, *J* = 7.4, 1.7 Hz, 1 H), 2.61 (dt, *J* = 1.5, 1.5 Hz, 2 H), 2.16 (dtq, *J* = 7.5, 7.4, 1.4 Hz, 2 H), 1.29 (s, 6 H), 0.98 (t, *J* = 7.5 Hz, 3 H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 180.4, 144.8, 107.2, 40.8, 40.0, 24.6, 18.5, 14.2. MS (CI, NH_3): *m/z* (%) 172 (20) $[M + NH_4]^+$, 188 (100) $[M + NH_4 + H_2O]^+$. HRMS (CI-NH_3): *m/z* calcd for $C_9H_{15}O_2$: 155.1072; found: 155.1071.