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Cyclobutenes as Isolable Intermediates in the Gold(I)-Catalysed Cycloisomerisation of 1,8-Enynes

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This work is dedicated with admiration to Professor William B. Motherwell

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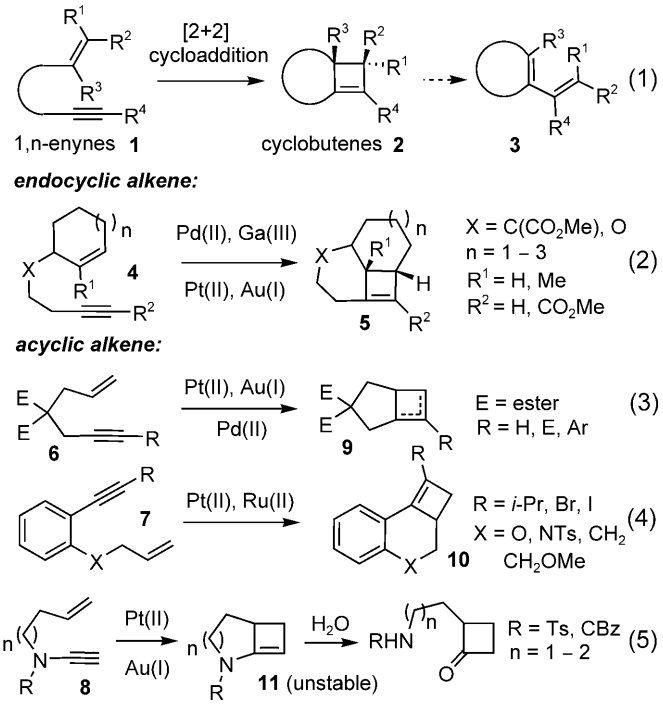
Abstract: The gold(I)-catalysed isomerisation of 1,8-enynes allows the efficient synthesis of functionalised bicyclo[5.2.0]nonenes. Notably, these cyclobutenes derivatives can be isolated as reactive intermediates that could undergo subsequent gold(I)-catalysed transformations such as isomerisation, fragmentation or ene reaction to furnish more structurally complex products. This study also provides useful information related to the mechanism leading to metathesis-type derivatives, examples of which were shown to be produced, in the present case, by a gold(I)-catalysed ring fragmentation of the cyclobutene moiety.

Keywords: [2+2] cycloaddition; cyclobutenes; gold; homogeneous catalysis



Scheme 1. Cyclobutenes as products in metal-catalysed cycloisomerisation of 1,n-enynes.

1,n-Enynes represent a privileged class of substrates in the area of transition metal-catalysed reactions.[1] They can indeed be cycloisomerised efficiently and generally selectively under mild conditions into a wide variety of products, depending on their substitution pattern and the nature of the metallic species used. Among these transformations, those related to the formation of a cyclobutene product **2** following a formal [2+2] cycloaddition of an 1,n-enyne **1** are much less common [Scheme 1, Eq. (1)].[2a]

This can be explained by the presence of a variety of other skeletal rearrangements that are generally more favoured than the [2+2] cycloaddition process, which leads to potentially more strained bicyclic products.[1,2a] A series of cyclobutenes derivatives have however been isolated as the products of the reaction when a specific substitution pattern of the alkene and/or alkyne disfavours the more commonly observed skeletal rearrangement. This is the case with 1,7-enyne substrates of type **4** bearing an endocyclic alkene moiety that reacts with an electrophilic Pd(II),[3a] Ga(III),[3b] Pt(II),[3c] or Au(I)[3d] catalyst to furnish tricyclic compounds of type **5** [Scheme 1, Eq. (2)]. Certain other 1,6- and 1,7-enynes **6**–**8**, possessing an acyclic alkene and an arylalkyne or ynamide moiety can also be transformed into the corresponding cyclobutenes **9**–**11** in the presence of a Pd(II),[4a,b] Pt(II),[4c–g] Au(I),[4h–j] or Ru(II)[4k] catalyst [Scheme 1, Eqs. (3)–(5)]. Cyclobutenes **2** have also been postulated as intermediates in a series of metal-catalysed

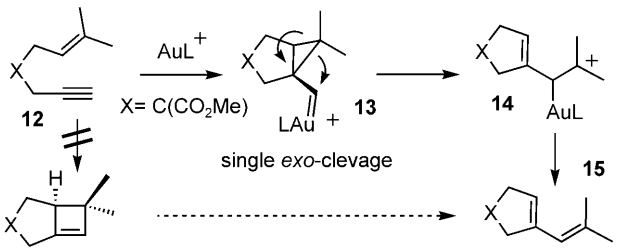
transformations of 1,n-enynes **1** that furnish metathesis type compounds **3** [Scheme 1, Eq (1)].[5]

In the specific case of the gold-catalysed single *exo*-cleavage skeletal rearrangement of 1,6-enynes such as **12**, DFT calculations have, however, lent support to mechanistic pathways that do not involve the intermediacy of such cyclobutenes (Scheme 2).[2a,6]

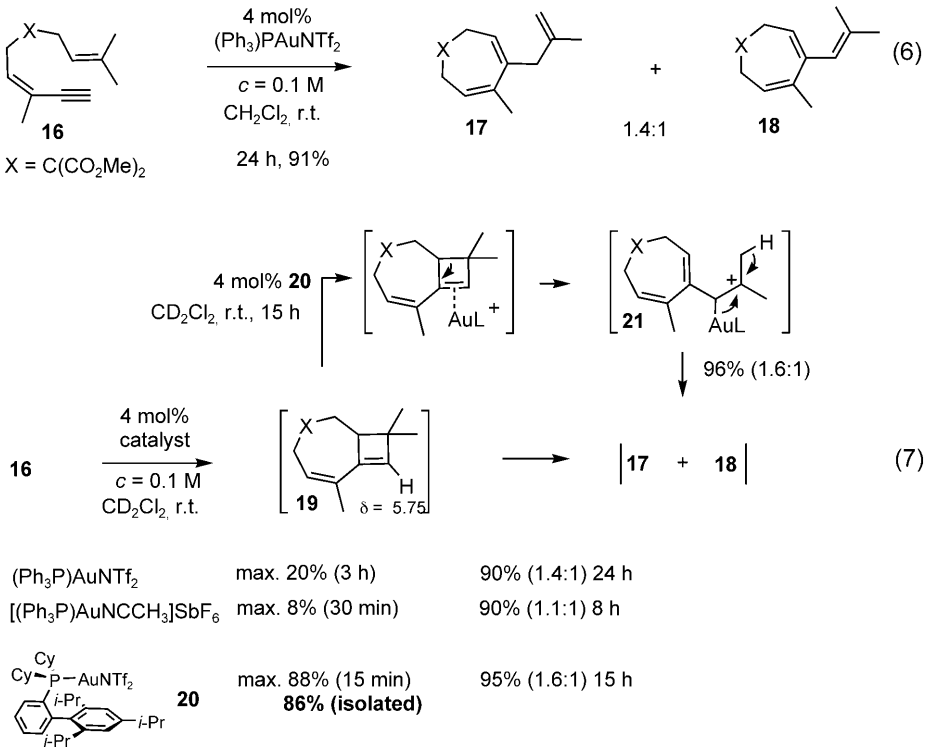
Following our previous investigations in the field of gold-catalysed cycloisomerisations of enynes,[7] we report herein that a series of 1,8-enynes can be transformed into functionalised cyclobutenes. These can be either isolated as the final products of the reaction or further transformed into various products including metathesis-type derivatives.

In an attempt to cycloisomerise 1,8-enynes into cycloheptene derivatives following a reaction pathway similar to that reported in the case of 1,6-enynes (see Scheme 2), substrate **16** was treated with 4 mol% of the stable $(Ph_3P)AuNTf_2$[8] in CH_2Cl_2 at room temperature [Scheme 3, Eq. (6)].[9] After 24 h, ^1H NMR analysis of the crude reaction mixture showed a complete and clean conversion of **16** into cycloheptadienes **17** and **18**, which were isolated as a 1.4:1 mixture in 91% yield. The formation of deconjugated cycloheptadiene **17** as the major product was however rather surprising and could not be directly explained following a mechanistic pathway analogous to that proposed for the cycloisomerisation of 1,6-enynes. Due to the difficulties encountered in monitoring the reaction by TLC, the conversion was performed in CD_2Cl_2 and monitored by ^1H NMR spectroscopy [Scheme 3, Eq. (7)].

We were pleased to see that another species, namely cyclobutene **19**, was involved in this transformation. This intermediate rapidly accumulated to a maximum of *ca.* 20% yield (after 3 h) and then gradually disappeared while the quantity of **17** and **18** continuously increased. In order to obtain more insight into the mechanism of this reaction and unambiguously establish the intermediacy of cyclobutene **19** in the formation of **17** and **18**, we envisaged its isolation and various gold(I) catalysts were therefore screened in order to optimise its yield.[10] While a faster transformation was observed when the more electrophilic gold(I) complex $[(Ph_3P)AuNCCH_3]SbF_6$ was used as the catalyst, a disappointing maximum *ca.* 8% yield of cyclobutene **19** (after 30 min) was observed. The use of the bulkier catalyst **20** had a remarkable impact on the course of the transformation. Gratifyingly, the se-



Scheme 2. Mechanistic pathway for the gold(I)-catalysed single *exo*-cleavage skeletal rearrangement of 1,6-enynes.

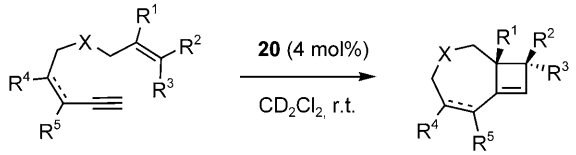


Scheme 3. Cycloisomerisation of enyne **16**/optimisation of the formation of cyclobutene intermediate **19**.

lectivity was improved in this case and cyclobutene **19** could be isolated in 86% yield when the reaction was quenched after 15 min. Resubmitting **19** to the same reaction conditions, furnished a mixture of cycloheptadienes **17** and **18** in the same yield and ratio as those obtained starting from 1,8-enyne **16**.[11] Additionally, the **17**:**18** ratio remains unchanged when the mixture is re-treated with catalyst **20**, indicating that deconjugated diene **17** is not converted into conjugated diene **18**.[12] Cyclobutene **19** also proved to be stable in solution in the absence of gold catalyst **20**, thus excluding its conversion into conjugated diene **18** by conrotatory ring opening. We have hence established the intermediacy of cyclobutene **19** in the formation of cycloheptadienes **17** and **18**, which could arise through carbocation **21** following a gold-catalysed fragmentation of the cyclobutene moiety.[12] Notably, even if the gold-catalysed cycloisomerisations of 1,6-enyne **12** and 1,8-enyne **16** furnish structurally similar metathesis type compounds **15** and **18**, these are produced by two different mechanistic pathways. The formation of deconjugated cycloheptadiene **17** as the major product of the reaction is however difficult to rationalise, more especially when contrasted with the reaction of 1,6-enyne **12**, which exclusively furnishes conjugated diene **15** *via* a postulated carbocationic intermediate **14** that is similar to **21**.[13]

Given the novelty of this transformation and the presence of the bicyclo[5.2.0]nonane framework in the skeleton of a number of natural products, we decided to study the scope of the [2+2]cycloaddition. As seen from the results compiled in Table 1, the re-

Table 1. Scope of the Au(I)-catalysed [2+2]cycloaddition.



22a – p **23a – p**

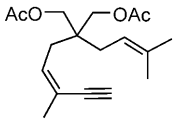
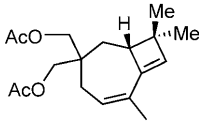
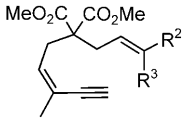
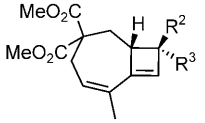
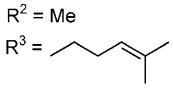
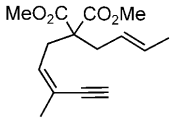
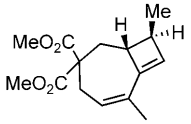
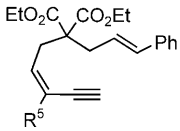
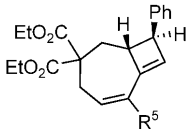
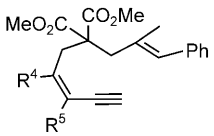
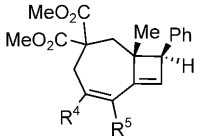
Entry	Substrate		Product		*t*	Yield [%][a]
1	**22a**		**23a**		0.25 h	90
2	**22b**		**23b**		3 h	83
3	**22c**		**23c**		24 h	0[b]
4	**22d**		**23d**		10 h	80
5	**22e**		**23e**		8.5 h	57 (82)[c]
6	**22f**		**23f**		7.5 h	66

Table 1. (Continued)

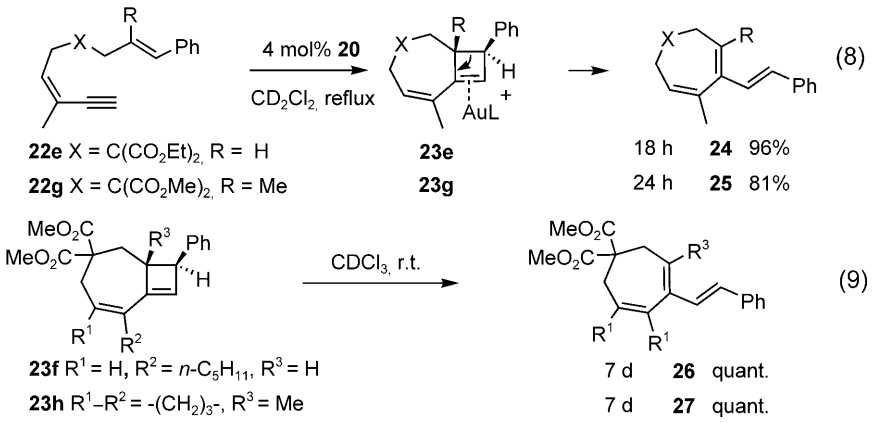
Entry	Substrate		Product		*t*	Yield [%][a]
7	**22g**	R^4=H, R^5=Me	**23g**		13.5 h	72
8	**22h**	R^4–R^5=-$(CH_2)_3$-	**23h**		2 h	62
9	**22i**	R^4=H, R^5=Me	**23i**		0.25 h	85
10	**22j**	R^4=H,R^5=*n*-C_5H_{11}	**23j**		1.5 h	78
11	**22k**	R^4–R^5=-$(CH_2)_3$-	**23k**		3 h	77
12	**22l**	R^4–R^5=-$(CH_2)_4$-	**23l**		5 min	85
13	**22m**		**23m**		10 min	86
14	**22n**		**23n**		22 h	62[b]
15	**22o**		**23o**		16 h	65
16	**22p**		**23p**		1 h 6 h	49[d] (1:1)[f] 41[e] (1:1)[f]

[a] Isolated yields.
[b] Under reflux.
[c] NMR spectroscopic yield.
[d] In refluxing 1,2-dichloroethane.
[e] With [(2,4-di-*t*-BuPhO)$_3$PAu]SbF$_6$ as the catalyst (4 mol%).
[f] Diastereoisomeric ratio.

action proved to be quite general and various 1,8-enynes **22a–p** reacted using 4 mol% of gold complex **20** to give cyclobutenes **23a–p** in generally good yields (41–90%).[14]

The transformation could be performed with substrates possessing diversely substituted alkenes, with the exception of 1,8-enyne **22c**, bearing a neryl chain which, surprisingly, did not react (entry 3).[15] The esters at C(4) could be replaced by diacetoxymethyl groups whithout loss of efficiency (entry 1) and other acyclic (entries 6, 10), carbocyclic (entries 8, 11, 12) or aromatic (entries 13, 15) susbtituents were tolerated at postions C(6) and/or C(7) of the 1,8-enyne. Notably, the time necessary to reach a maximum yield of the cylobutene was generally dependant on the nucleophilicity of the alkene, while the yield was function of the presence of possible competitive reactions affecting the cyclobutene ring. Cyclobutenes **23i–m** derived from enynes possessing a methallyl group (entries 9–13) were for instance rapidly formed and did not suffer subsequent transformation.[16] In contrast, the reaction was very slow for substrates **22n–o** bearing a simple allyl moiety. A highly competitive isomerisation process took place in this case, that ultimately led to the formation of cyclobutene **23n–o** in which the C=C bond of the cyclobutene had migrated at the ring junction. Finally, even if it makes the transformation easier, the presence of an unsaturation conjugated with the alkyne is not essential. Substrate **22p** could for instance be transformed into cyclobutene **23p** using 4 mol% of catalyst **20** in refluxing 1,2-DCE (49%) or 4 mol% of the more electrophilic [(2,4-di-*t*-BuPhO)$_3$PAu]SbF$_6$ catalyst[6] at room temperature (41%) (entry 16).

Certain 1,8-enynes could be ultimately transformed into metathesis-type derivatives by gold-catalysed fragmentation of the intermediate cyclobutene, as previously observed for enyne **16**. For example,

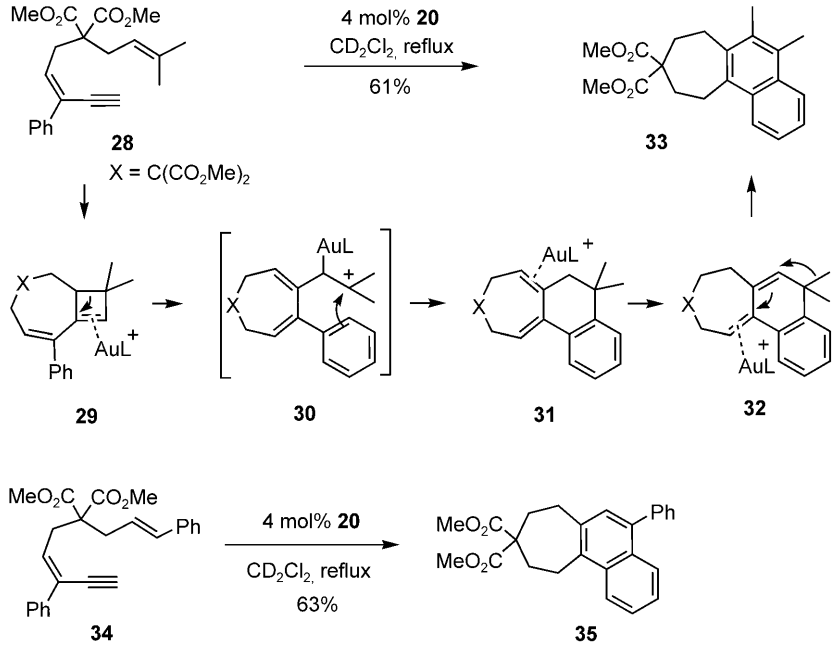


Scheme 4. Examples of cyclobutene ring fragmentation.

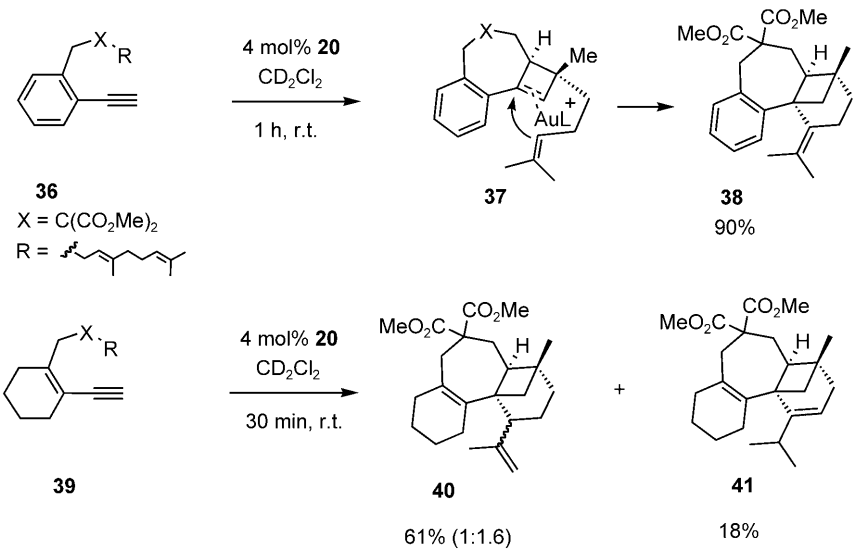
enynes **22e** and **22g** furnished cycloheptadienes **24** and **25** as single isomers in, respectively, 96% and 81% yield [Scheme 4, Eq. (8)].[17] Thus, cyclobutenes **23f** and **23h**, possessing the same substitution pattern as **23e** and **23g**, were stable in CD_2Cl_2 but were slowly rearranged into **26** and **27** by traces of HCl contained in $CDCl_3$ [Scheme 4, Eq. (9)]. A remarkable sequence of [2+2]cycloaddition/ring fragmentation/Friedel–Crafts reaction/diene isomerisation/Wagner–Meerwein rearrangement was observed in the case of enyne **28** (Scheme 5).[18] The fragmentation of cyclobutene **29** produced the carbocationic species **30**, which was trapped by the pendant phenyl group. The resulting tricyclic compound **31** was subsequently isomerised into naphthalene derivative **33**.[19] A similar result was observed in the case of substrate **34**.

For substrates bearing a geranyl chain, the [2+2] cycloaddition could be followed by an impressive gold-catalysed ene reaction that stereoselectively furnished tetracylic compound **38** in an excellent 90% yield in the case of enyne **36** and a mixture of compounds **40** and **41** in the case of enyne **39** (Scheme 6).[2c,18]

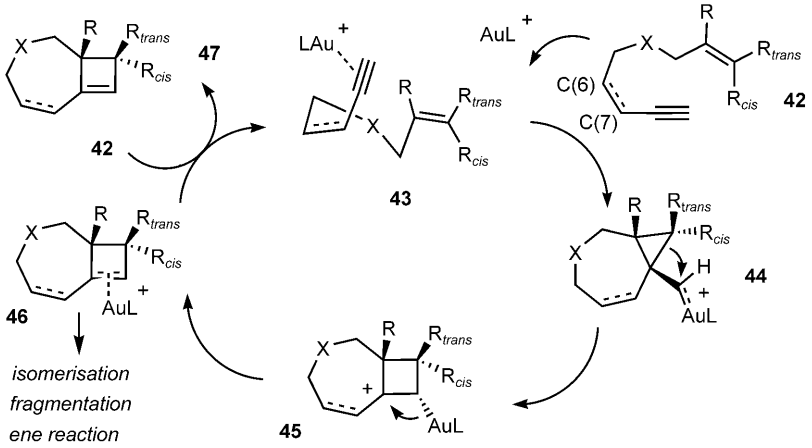
A mechanistic proposal for the [2+2] cycloaddition of 1,8-enynes is presented in Scheme 7. The electrophilic gold(I) activation of the alkyne in substrate **42** might lead to the formation of a cyclopropyl gold carbene (or gold-stabilised cyclopropylmethyl carbocation)[20] **44**. A subsequent ring expansion could then furnish the cyclobutyl carbocation **45** which would evolve into cyclobutene gold complex **46**. A final substitution of the coordinated cyclobutene **47** by the



Scheme 5. Multiple-steps Au(I)-catalysed isomerisation of **28** and **34**.



Scheme 6. Multiple-steps Au(I)-catalysed isomerisation of **36** and **39**.

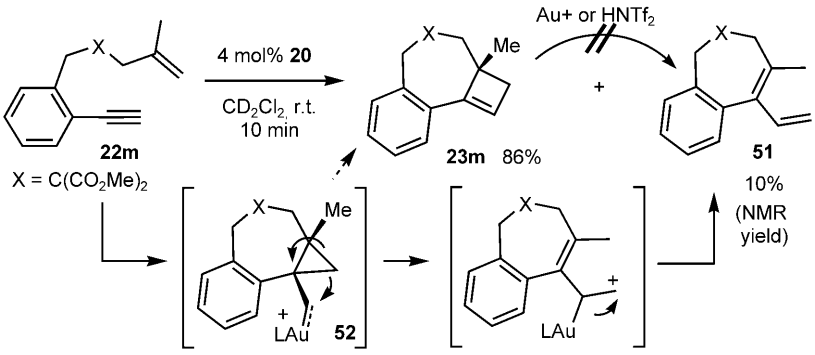


Scheme 7. Mechanistic proposal.

substrate would complete the cycle.[21]. The ring expansion leading to **45** might be more favoured in the present case than in the cycloisomerisation of 1,6-enynes (Scheme 2) due to a reduction of geometric constraints (7- *versus* 5-membered cycle) and a possible greater stabilisation of the resulting cationic charge by the unsaturation between C(6) and C(7).

Even if the intermediacy of **44** could not be experimentally proved,[22] it is nevertheless supported by the formation of conjugated diene **51** as a minor product in the cycloisomerization of enyne **22m** (Scheme 8). Cyclobutene **23m** proved to be stable in CH_2Cl_2 in the presence of catalyst **20** or $HNTf_2$, thus excluding the formation of **51** by ring fragmentation. This latter might, however, be competitively formed from a common cyclopropyl intermediate **52** by a rearrangement similar to that proposed for the isomerisation of 1,6-enynes (Scheme 2).

In summary, it was found that a variety of functionalized bicyclo[5.2.0]nonenes could be accessed by a gold(I)-catalysed [2+2]cycloaddition of 1,8-enynes. These cyclobutenes could be isolated as intermediates that could suffer subsequent gold(I)-catalysed transformations such as isomerisation, fragmentation or ene reaction to furnish more structurally complex products. This study provides useful information related to the mechanism leading to metathesis-type derivatives, which were shown to be produced, in the present case, by a gold(I)-catalysed ring fragmentation of the cyclobutene moiety. It also highlights the diversity of products which can be formed from a single mechanistic class depending on the relative stability of the intermediates involved.



Scheme 8. Experimental result supporting the formation of a gold-stabilised cyclopropyl methyl carbocation intermediate.

Experimental Section

Typical Procedure

To a solution of **16** (13.9 mg, 0.05 mmol) in 0.5 mL of CD_2Cl_2 in an NMR tube was added 4 mol% of gold catalyst **20** (2 mg, 0.002 mmol). The reaction was monitored by ^{1}H NMR spectroscopy. After 0.25 h, the reaction was quenched by the addition of Et_3N (0.1 mL), the mixture concentrated under vacuum and the residue purified by flash chromatography (SiO_2, petroleum ether/Et_2O = 95/5) to afford product **19**: yield: 12 mg (86%).

Acknowledgements

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References

[1] For recent reviews on the cycloisomerisation of 1,n-enynes, see: a) V. Michelet, P. Y. Toullec, J. P. Genêt, *Angew. Chem.* **2008**, *120*, 4338–4386; *Angew. Chem. Int. Ed.* **2008**, *47*, 4268–4315; b) E. Jiménez-Núñez, A. M. Echavarren, *Chem. Rev.* **2008**, *108*, 3326–3350; c) L. Zhang, J. Sun, S. A. Kozmin, *Adv. Synth. Catal.* **2006**, *348*, 2271–2296; d) C. Bruneau, *Angew. Chem.* **2005**, *117*, 2380–2386; *Angew. Chem. Int. Ed.* **2005**, *44*, 2328–2334.

[2] For a review on the [2+2] cycloaddition of enynes, see: a) C. Nieto-Oberhuber, S. López, E. Jiménez-Núñez, A. M. Echavarren, *Chem. Eur. J.* **2006**, *12*, 5916–5923. For a selection of recent metal-mediated syntheses of cyclobutenes, see: b) H. Xu, W. Zhang, D. Shu, J. B. Werness, W. Tang, *Angew. Chem.* **2008**, *120*, 9065–9068; *Angew. Chem. Int. Ed.* **2008**, *47*, 8933–8936; c) O. Debleds, J.-M. Campagne, *J. Am. Chem. Soc.* **2008**, *130*, 1562–1563; d) A. Fürstner, C. Aïssa, *J. Am. Chem. Soc.* **2006**, *128*, 6306–6307; e) Y. Liu, M. Liu, Z. Song, *J. Am. Chem. Soc.* **2005**, *127*, 6662–6663.

[3] a) B. M. Trost, M. Yanai, K. Hoogsteed, *J. Am. Chem. Soc.* **1993**, *115*, 5294–5295; b) N. Chatani, H. Inoue, T. Kotsuma, S. Murai, *J. Am. Chem. Soc.* **2002**, *124*, 10294–10295; c) A. Fürstner, F. Stelzer, H. Szillat, *J. Am. Chem. Soc.* **2001**, *123*, 11863–11869; d) C. Nieto-Oberhuber, S. López, M. Paz Muñoz, D. J. Cárdenas, E. Buñuel, C. Nevado, A. M. Echavarren, *Angew. Chem.* **2005**, *117*, 6302–6304; *Angew. Chem. Int. Ed.* **2005**, *44*, 6146–6148.

[4] a) B. M. Trost, G. J. Tanoury, *J. Am. Chem. Soc.* **1988**, *110*, 1636–1638; b) B. M. Trost, M. K. Trost, *Tetrahedron Lett.* **1991**, *32*, 3647–3650; c) A. Fürstner, P. W. Davies, T. Gress, *J. Am. Chem. Soc.* **2005**, *127*, 8244–8245; d) G. B. Bajracharya, I. Nakamura, Y. Yamamoto, *J. Org. Chem.* **2005**, *70*, 892–897; e) F. Marion, J. Coulomb, C. Courillon, L. Fensterbank, M. Malacria, *Org. Lett.* **2004**, *6*, 1509–1511; f) F. Marion, J. Coulomb, A. Servais, C. Courillon, L. Fensterbank, M. Malacria, *Tetrahedron* **2006**, *62*, 3856–3871; g) T. Matsuda, S. Kadowaki, T. Goya, M. Murakami, *Synlett* **2006**, 575–578; h) C. Nieto-Oberhuber, S. López, A. M. Echavarren, *J. Am. Chem. Soc.* **2005**, *127*, 6178–61795; i) S. Couty, C. Meyer, J. Cossy, *Angew. Chem.* **2006**, *118*, 6878–6882; *Angew. Chem. Int. Ed.* **2006**, *45*, 6726–6730; j) C. H. Oh, A. Kim *Synlett* **2008**, 777–781; k) A. Fürstner, A. Schlecker, C. W. Lehmann, *Chem. Commun.* **2007**, 4277–4279.

[5] a) A. Fürstner, H. Szillat, F. Stelzer, *J. Am. Chem. Soc.* **2000**, *122*, 6785–6786; b) E. M. Simmons, R. Sarpong, *Org. Lett.* **2006**, *8*, 2883–2886; c) J. Blum, H. Beer-Kraft, Y. Bradieh, *J. Org. Chem.* **1995**, *60*, 5567–5569; see also Refs.[3b,c,4a]

[6] For DFT calculations on the skeletal rearrangement and the [2+2] cycloaddition of 1,6-enynes, see Refs.[2a,3d] See also: C. Nieto-Oberhuber, P. Pérez-Galán, E. Herrero-Gómez, T. Lauterbach, C. Rodriguez, S. López, C. Bour, A. Rosellón, D. J. Cárdenas, A. M. Echavarren, *J. Am. Chem. Soc.* **2008**, *130*, 269–279.

[7] a) F. Gagosz, *Org. Lett.* **2005**, *7*, 4129–4132; b) A. Buzas, F. Gagosz, *J. Am. Chem. Soc.* **2006**, *128*, 12614–12615; c) A. K. Buzas, F. M. Istrate, F. Gagosz, *Angew. Chem.* **2007**, *119*, 1159–1162; *Angew. Chem. Int. Ed.* **2007**, *46*, 1141–1144; d) S. Böhringer, F. Gagosz, *Adv. Synth. Catal.* **2008**, *350*, 2617–2630.

[8] N. Mezailles, L. Ricard, F. Gagosz, *Org. Lett.* **2005**, *7*, 4133–4136.

[9] For recent reviews on gold catalysis, see: a) Z. Li, C. Brower, C. He, *Chem. Rev.* **2008**, *108*, 3239–3245; b) A. Arcadi, *Chem. Rev.* **2008**, *108*, 3266–3325; c) D. J. Gorin, F. D. Toste, *Chem. Rev.* **2008**, *108*, 3351–3378; d) A. S. K. Hashmi, M. Rudolph, *Chem. Soc. Rev.* **2008**, *37*, 1766–1775; e) A. S. K. Hashmi, *Chem. Rev.* **2007**, *107*, 3180–3211; f) A. Fürstner, P. W. Davies, *Angew. Chem.* **2007**, *119*, 3478–3519; *Angew. Chem. Int. Ed.* **2007**, *46*, 3410–3449; g) E. Jiménez-Nùnez, A. M. Echavarren, *Chem. Commun.* **2007**, 333–346.

[10] $HNTf_2$ and $AgNTf_2$ did not catalyse the formation of **19**.

[11] $HNTf_2$ also catalysed the formation of **17** and **18** (1:1) from **19**.

[12] ^{1}H NMR spectroscopy monitoring showed a gradual disappearance of **19** to give **17** and **18** with a **17**:**18** ratio remaining the same during the whole process. See Supporting Information for deuterium-labelling experiments supporting this mechanism.

[13] The involvement of a carbocationic species of type **21** is in agreement with the transformation of enynes **28** and **34** in which similar cationic species could participate in a Friedel–Crafts reaction (see Scheme 5).

[14] Reactions were performed in CD_2Cl_2 in order to monitor the transformation by ^{1}H NMR spectroscopy.

[15] The lack of reactivity of **22c** might be explained by a steric interaction between R_{cis} and AuL in an intermediate of type **45** (see Scheme 7).

[16] Compounds **23i–m** were stable in the presence of gold catalyst **20**.

[17] Compounds **22e** and **22g** were stable in CD_2Cl_2 whitout gold catalyst **20**.

[18] See Supporting Information for a complete mechanistic proposal based on ^{1}H NMR monitoring.

[19] The formation of **29** and **31** was observed by ^{1}H NMR monitoring.

[20] The exact nature of such an intermediate is not known. For a discussion, see: A. Fürstner, L. Morency, *Angew. Chem.* **2008**, *120*, 5108–5111; *Angew. Chem. Int. Ed.* **2008**, *47*, 5030–5033; see also: A. S. K. Hashmi, *Angew. Chem.* **2008**, *120*, 6856–6858; *Angew. Chem. Int. Ed.* **2008**, *47*, 6754–6756.

[21] An alternative *syn*-cyclopropyl gold carbene undergoing ring expansion could also be envisaged, see Refs.[2a,3d]

[22] All attempts to trap a gold carbene intermediate of type **44** were unsuccessful (oxidation, cyclopropanation).

