Chapter 2
New Advances in the Gold-Catalyzed Cycloisomerization Reactions of Enynes: 1,5-hydride Shifts and Access to Ketomacrolactones

In this chapter will be presented some new results obtained in the field of gold catalyzed cycloisomerizations of 1,6-enynes. A new reaction based on a 1,5-hydride shift process has been disclosed, allowing the formation of functionalized allenes. The end of this chapter gathers some results we got toward the synthesis of macrocyles using a gold catalyzed cycloisomerization reaction of oxygen-tethered 1,6-enynes. Before the results being described and discussed, we will briefly introduce other gold catalyzed reactions that feature 1,5-hydride shifts.

2.1 Introduction

2.1.1 Bibliography

2.1.1.1 C(sp^3)-H Functionalization Through 1,5-hydride Shifts

Methodologies allowing the direct functionalization of relatively unreactive C–H bonds have raised a growing interest from the organic chemists community, as it facilitates the formation of C–C and C-heteroatom bonds without requiring a prefunctionalized C–X bond (X = halogens, triflates…).[1] The majority of these methodologies deals with C(sp^2)–H bonds, even if recently some promising catalytic systems have emerged toward the activation of the strong C(sp^3)-H bond. In general, they rely on the direct insertion of a metal into the desired C–H bond. However, a turn in this chemistry appeared in 2005 with the work of Sames and co-workers [6–8]. They proposed an alternative approach based on an initial activation of an unsaturation by an electrophilic metal catalyst that triggers the cleavage of a C–H bond in 1,5-relationship to the activated π-system.[2]

[1] For a selection of recent reviews on C-H bond functionalization, see: [1–4]. See also [5].
[2] For a review gathering some examples of this type of reaction see: [9].

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The resulting ate-complex **1** then reacts intramolecularly on the electrophilic position generated by the departure of the H atom to form a C–C bond (Scheme 2.1).

Although the reaction is limited due to its intramolecular character and requires the presence of a stabilizing group (mainly heteroatoms such as O or N), this strategy allows the activation of sterically hindered C(sp^3)–H bonds, a strong limitation in the direct metal insertion based processes. Some examples are presented in Scheme 2.2, and it is worth adding that aryl can also play the role of the stabilizing group, rather than nitrogen or oxygen.

2.1.1.2 Related Reactions Catalyzed by Gold and Platinum

Given the fact that gold and platinum are excellent and selective activators of C–C unsaturations, the transposition of the Sames' strategy into the realm of gold and platinum catalyzed reactions came naturally. Indeed, these metals efficiently promoted the 1,5-migration of an hydride onto an activated triple bond when starting from precursors **6** and **8**,[3] resulting in products **7**, **9**, **10** of formal alkyne hydroalkylation (Scheme 2.3).

The gold version of this rearrangement can be plagued by side reactions,[4] and a selectivity issue between 5-*exo* (such as **9**) or 6-*endo* products (such as **10**) is also met, mainly due to steric interactions. The proposed mechanism starts complexation by the electrophilic metal center onto the alkyne that triggers the 1,5-hydride shift.[5] The C-C bond formation occurs at the resulting vinylmetal species **11** in a 5-*exo* manner, to give carbene **12**. Then, depending on steric factors that allow the requisite conformation of carbene **12**, a 1,2-H or a 1,2-alkyl shift takes place, leading to products **7**/**9** or **10**, respectively (Scheme 2.4).

The team of Gagosz further extended this rearrangement to propargyl ethers **13** and thus disclosed a practical method for the synthesis of substituted allenes **14** [12]. In this case the vinylgold species **15** rather undergoes a gold elimination concomitant with the adjacent C–O bond cleavage, leading to the obtention of substituted allene **14** and benzaldehyde as products (Scheme 2.5).

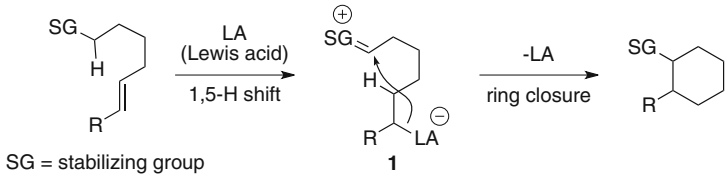
It is worth noting that substrates similar to **13** with R^1 = ester gave *endo* hydroalkylation products upon the conditions reported in Scheme 2.3. This mechanistic divergence still lacks rationalization. The team of Gagosz also developed the allenic version of the hydroalkylation reaction depicted in Scheme 2.3 [13]. This study also features a comparison with strong Brønsted acids. The latter were shown to give a different outcome than gold, though able to perform the 1,5-migration process (Scheme 2.6).

The postulated mechanism starts with activation of the allene inducing the migration of the hydride α to the oxygen atom. From intermediate **19** two different pathways are then likely to occur: with gold, carbometalation of the oxonium

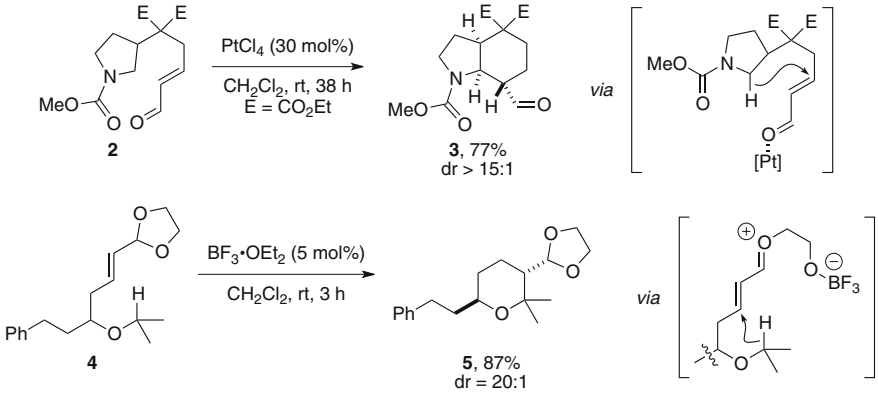
[3] With Pt(IV): [10].

[4] With cationic Au(I): [11].

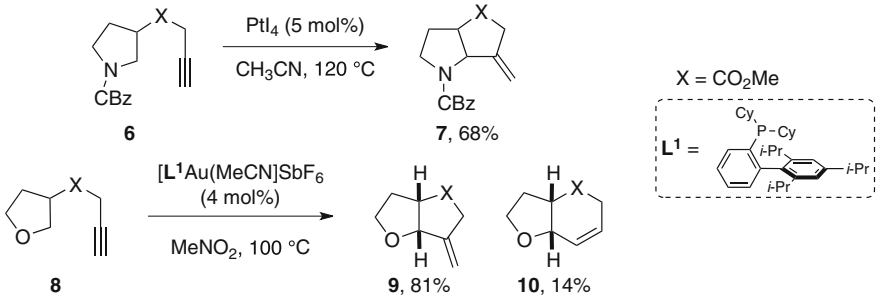
[5] Sames also invoked the possibility of a platinum vinylidene, see Ref. [10].



Scheme 2.1 Sames' strategy for the activation of C(sp^3)–H bonds

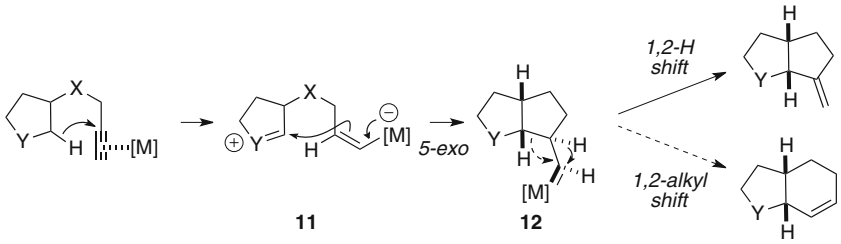


Scheme 2.2 Examples of the indirect C(sp^3)–H functionalization strategy developed by Sames

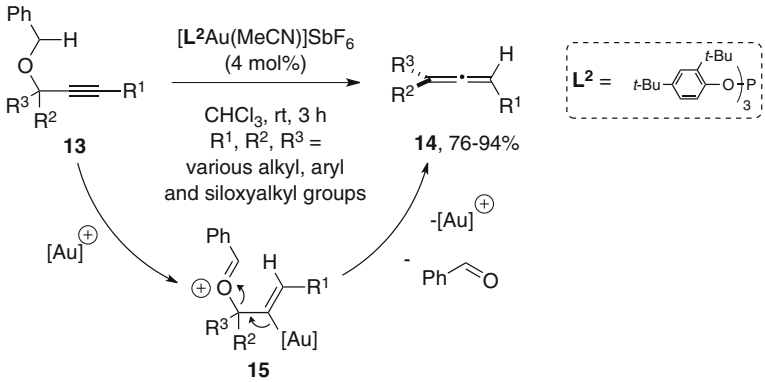


Scheme 2.3 1,5-hydride shifts onto a Pt- or Au-activated C–C triple bond

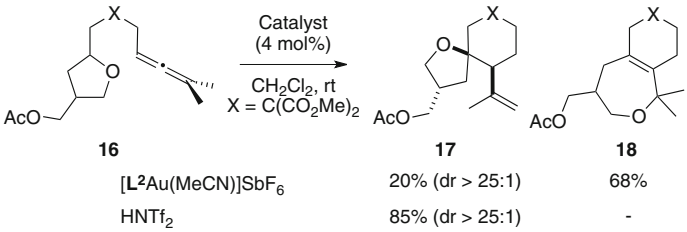
moiety can take place giving complex **20**, on which a gold-triggered furan opening allows rearrangement into **18** through allylic carbocation **21**. On the other hand, the pathway leading to product **17** involves the nucleophilic attack of the double bond in **19** onto the oxonium to produce carbocation **22** (which may evolve to **20** through gold elimination). The latter, depending on the catalyst, furnishes the spiro compound **17** in a one or two steps sequence. Neither **17** nor **18** rearranged into the other upon gold or acid catalysis, which is consistent with such mechanistic divergence (Scheme 2.7).



Scheme 2.4 Mechanism of the Pt- or Au-catalyzed hydroalkylation



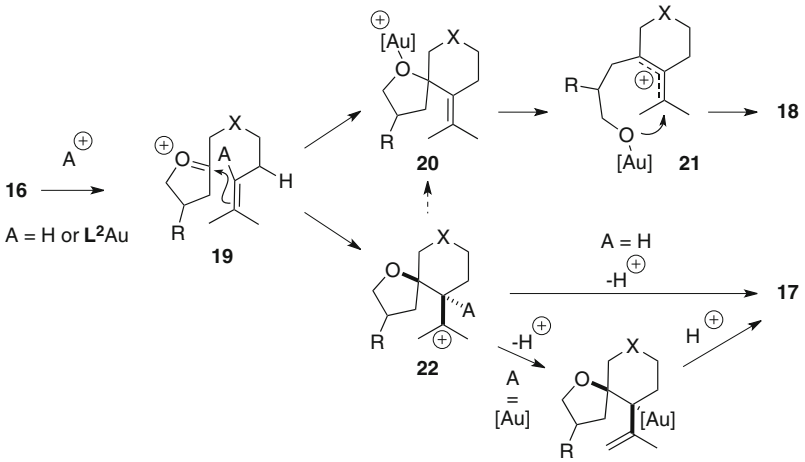
Scheme 2.5 Synthesis of allenes through 1,5-hydride shift/aldehyde elimination sequence



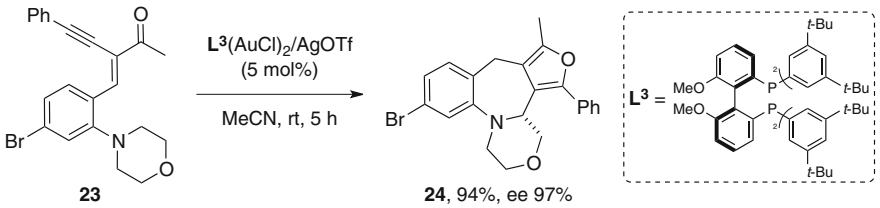
Scheme 2.6 Gold and acid catalyzed hydroalkylation of allenes

Cationic intermediates generated in gold catalysis can also react with a hydride through 1,5-intramolecular migration providing the design of the substrate allows it. This concept was successfully realized in an enantioselective version by the team of Zhang, starting from compound **23** (Scheme 2.8) [14, 15].

The mechanism of this reaction begins with the activation of the triple bond by cationic gold that induces a 5-*endo* nucleophilic attack of the neighboring carbonyl



Scheme 2.7 Mechanism for the Au- or acid-catalyzed hydroalkylation of allenes

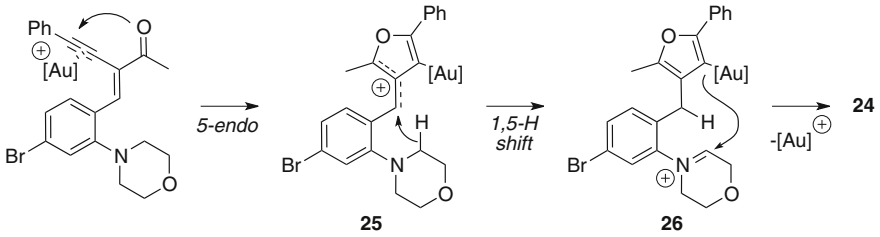


Scheme 2.8 Zhang's enantioselective Au-catalyzed functionalization of C(sp3)–H bonds

oxygen. The resulting stabilized carbocation **25** and the hydride α to nitrogen are in 1,5 relationship, therefore a migration process is likely to occur, leading to iminium **26**. The latter then reacts with the nucleophilic C-Au bond to form the seven-membered ring in an enantioselective manner and regenerates the catalyst (Scheme 2.9).

It is worth mentioning that a 1,6-hydride shift was proposed to occur in a particular case of enynes cycloisomerization upon platinum catalysis [16]. 1,5-sigmatropic shifts were also catalyzed by this metal [17]. 1,3-Hydride shifts onto platinum or gold carbenes have been more frequent [18, 19], and a sporadic example of a 1,5-hydride shift onto a platinum carbene has been reported to this date by the team of Oh [20].[6]

[6] See also Ref. [21].



Scheme 2.9 Mechanism of Zhang's Au-catalyzed functionalization of C(sp3)–H bonds

2.1.2 Presentation and Objectives of the Project

As we were interested in the formation of allenes through gold-catalyzed processes for the development of tandem reactions, the direct transformation of enynes into allenes appeared to us as a promising tool. In view of our own results in the 1,6-allenyne series [22, 23], those of Liang and co-workers [24] and those presented above, we sought it was possible to obtain allenes upon gold catalysis, based on a 1,5-shift of an external propargylic substituent that could occur on an intermediate cyclopropylcarbene.

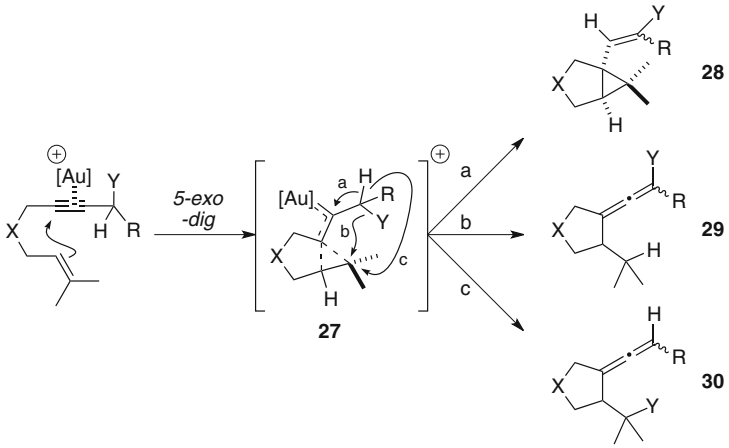
Considering cyclopropylcarbene **27**, several competitive processes could be at stake: a donor Y substituent could promote either a 1,2-H shift (path a, Scheme 2.10) to give a bicyclo[3.1.0]hexane derivative **28** [26] or a 1,5-H shift onto the cyclopropane head carbon to lead to exocyclic allene **29** (path b). If Y is also a good leaving group, its own migration could also be envisioned (path c). To enhance the carbocationic character of the cyclopropane head carbon and thus, to increase the chance to perform selectively the 1,5-migration process, geminal substitution at the external olefinic carbon should be decisive.

Below are presented the results we obtained in the development of such reaction.

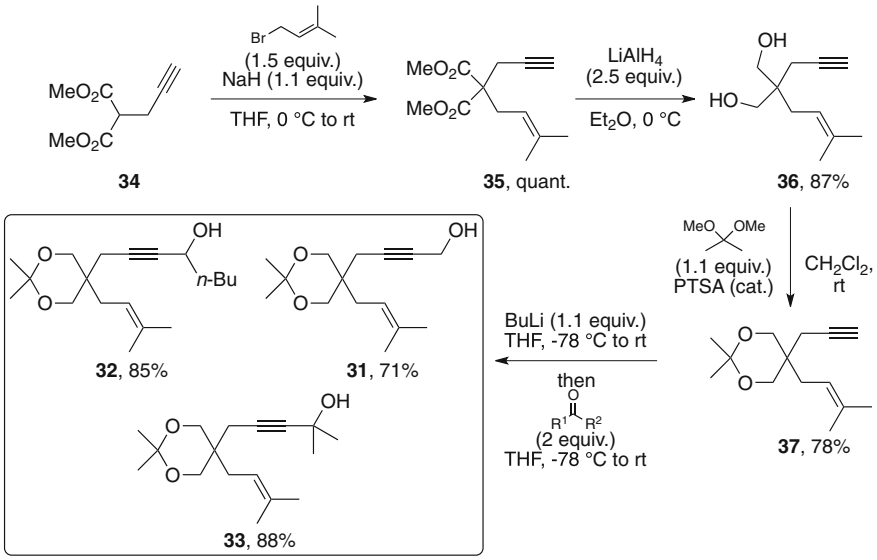
2.2 Validation of Our Hypothesis: Synthesis of Allenes Through a Gold-Catalyzed Cyclization and/or 1,5-migration Processes

2.2.1 Synthesis of Test Substrates and Reactivity

We first assessed 1,6-enyne substituted at the external propargylic position by a primary, a secondary or a tertiary alcohol **31**–**33**, and displaying a prenyl group to give better chances to perform the migration process. The synthesis of such precursors was straightforward starting from commercially available dimethylpropargyl malonate **34** (Scheme 2.11). Deprotonation of the latter using sodium hydride in the presence of dimethallyl bromide furnishes 1,6-enyne **35**. Reduction



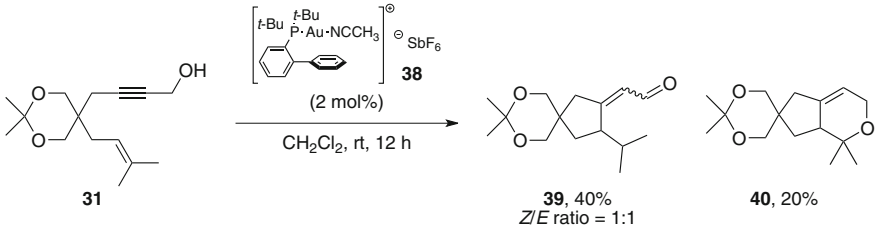
Scheme 2.10 Anticipated mechanistic scenarii



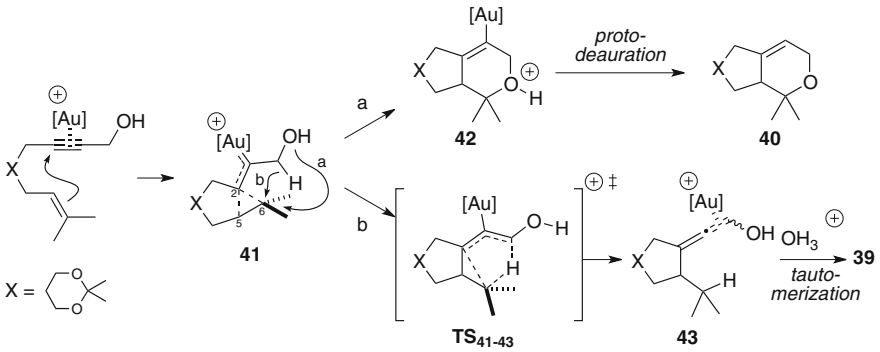
Scheme 2.11 Synthesis of test substrates **31–33**

of the *gem*-diester moiety with lithium aluminium hydride followed by transacetalization with 2,2-dimethoxypropane led to dioxane tethered enyne **37**. Then, formation of the lithium acetylide by treatment with *n*-butyllithium followed by addition onto either formaldehyde, valeraldehyde or acetone gives 1,6-enyne precursors **31**, **32** or **33**, respectively.

With these substrates in hand, we could assess their reactivity toward gold catalysis. We chose cationic gold(I) catalyst **38** [25] to carry out the experiment,



Scheme 2.12 Au-catalyzed cycloisomerization of 1,6-enyne **31**

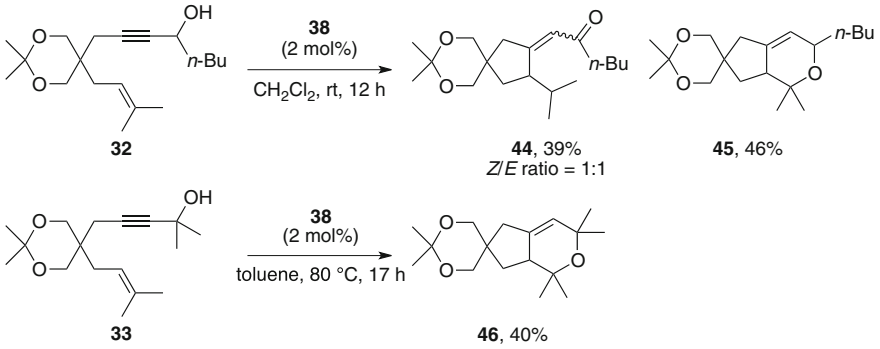


Scheme 2.13 Mechanistic rationale accounting for the formation of **39** and **40**

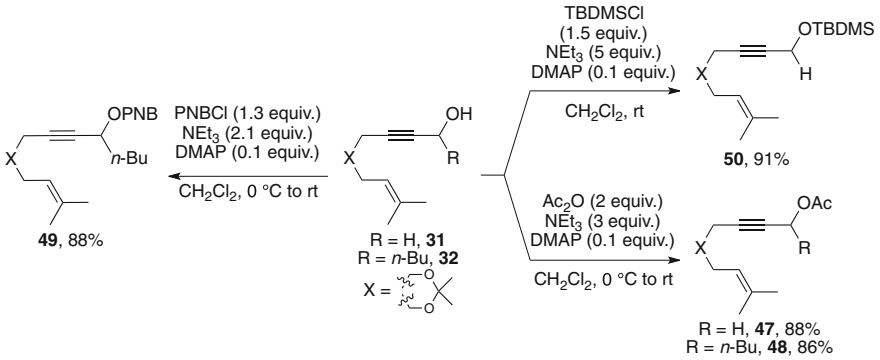
on one hand for practical reason because it is air-stable and easy to handle and on the other hand, it has been shown to be very efficient in promoting various enyne rearrangement. Its cationic nature also avoids recourse to silver salts which have been shown to promote cyclization reactions on related substrates [24]. Submission of **31** to catalytic amounts of **38** gave after 12 h at room temperature a mixture of products **39** and **40** (Scheme 2.12).

The mechanism accounting for the formation of **39** and **40** is depicted below. Complexation of gold onto the triple bond triggers the formation of cyclopropylgold carbene **41**. The latter can then evolve along two different pathways: nucleophilic attack of the free hydroxy group onto C6 delivers vinylgold oxonium **42** which after protodeauration gives dihydropyranyl derivative **40** (path a, Scheme 2.13).

The mechanism leading to **39** is somewhat original. Formation of this product can only be explained by a 1,5-hydride shift from the propargylic position to C6. This process was most probably made possible by assistance of the hydroxy group whose non bonding electron pairs can delocalize into the σ-antibonding orbital of the adjacent C–H bond. Gold-complexed allenol **43** is thus formed which upon decoordination/ tautomerization delivers aldehyde **39** (path b). The discovery of this new rearrangement of enynes prompted us to explore the scope and optimize this process.



Scheme 2.14 Reaction of substrates **32** and **33** with catalyst **38**



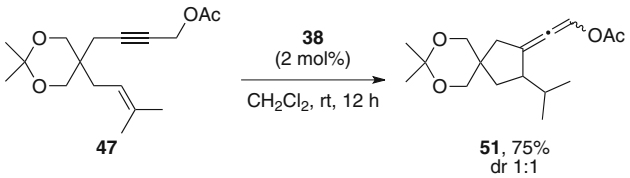
Scheme 2.15 Synthesis of esters and silylether derivatives

Precursor **32** gave a comparable yield of 1,5-hydride shift product upon catalysis with **38**, nonetheless the amount of dihydropyranyl derivative **45** was more than doubled. Unsurprisingly, substrate **33** that does not have any hydrogen at the external propargylic position reacted only along path a, nonetheless with harscher conditions than for **31** and **32** (Scheme 2.14).

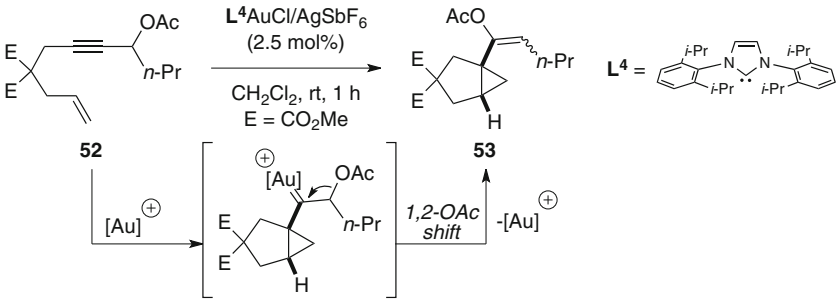
To prevent nucleophilic attack from the oxygen, we then synthesized a series of O-protected substrates, assuming they would exclusively react along path b.

2.2.2 Oxygen-Protected Precursors

Starting from alcohols **31** and **32**, we synthetized a range of ester and silyl protected precursors. Acylation or benzoylation were realized with the acetic anhydride or *p*-nitrobenzoyl chloride (PNBCl) in the presence of triethylamine and 4-dimethylaminopyridine, and allowed us to obtain precursors **47**–**49**. Silylation of



Scheme 2.16 Efficient and selective 1,5-hydride shift



Scheme 2.17 Gung's study on a related system: importance of the prenyl substituent

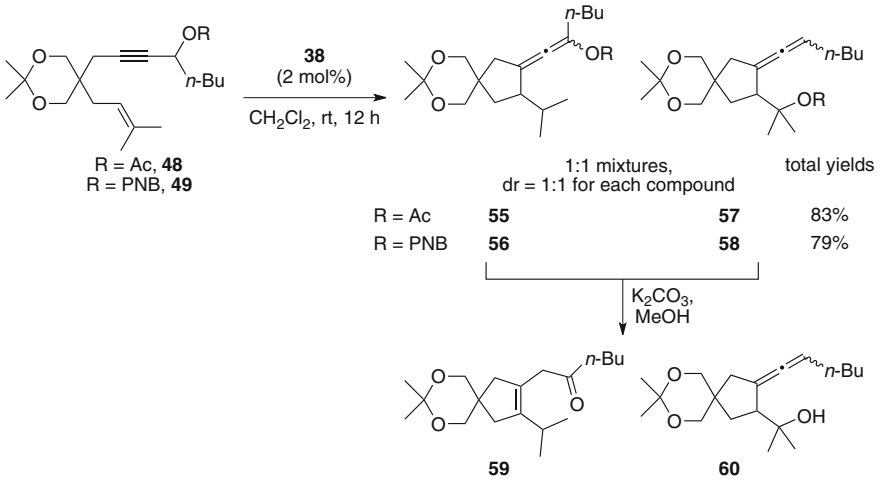
31 under classical conditions led to compound **50**. Alkylethers were not explored, as we assumed the risk to see them react similarly to benzylether derivatives upon platinum catalysis [26].

We then submitted precursors **47**–**50** to our reaction conditions. We were pleased to find that substrate **47** gave selectively the product of 1,5-hydride shift **51** in a satifying 75 % yield and in a 1:1 diastereomeric ratio (Scheme 2.16).

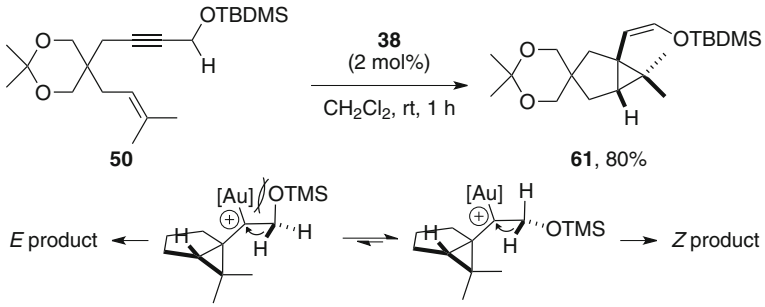
The preferred nucleophilic attack of the double bond over acetate migration is quite surprising, but consistent with the observation made by Gung on similar substrate **52** [27]. In his case, the olefin is monosubstituted and formation of cyclopropylcarbene prevails over any acyloxy migration process.[7] A 1,2-OAc shift ends the catalytic cycle, thus delivering bicyclo[3.1.0]hexane compound **53** (Scheme 2.17). Therefore, the importance of using prenyl substituents is decisive to render the 1,5-hydride shift favourable rather than 1,2-OAc shift.

Secondary esters **48** and **49** both led to unseparable 1:1 mixtures of compounds resulting of either a 1,5-hydride shift (**55** and **56**) or a 1,5-carbonyloxy shift (**57** and **58**). As it was anticipated in Scheme 2.10, when the propargylic substituent is a good leaving group, competition between hydride or the latter migration could take place. Each product of the mixture was separated after methanolysis of the ester groups, leading to the corresponding ketone **59** or alcohol **60** (Scheme 2.18). Finally, no products that could arise from an initial rearrangement of the

[7] However, as discussed in Chap. 1, Sect. 1.5.1, formation of **53** can also arise from a 1,2-OAc shift/cyclopropanation sequence, but it was not evoked by the authors.



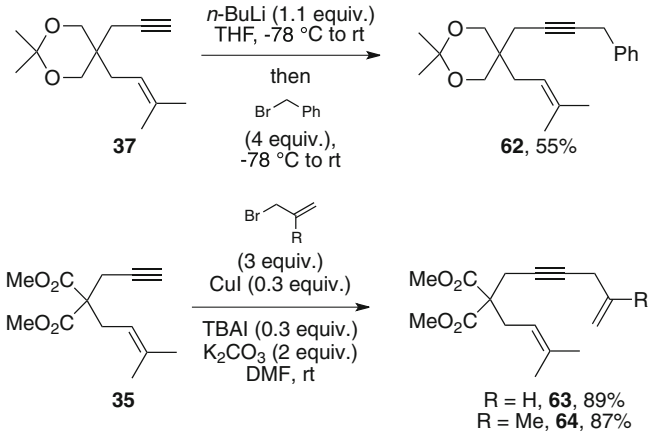
Scheme 2.18 Competition between 1,5-hydride or 1,5-carbonyloxy shift



Scheme 2.19 Bicyclo[3.1.0]hexane compound formation from silyl-protected precursor **164**

propargylic ester (refer to Chap. 1, Sect. 1.5.1) were observed in the reactions of compounds **47** and **49**.

Silyl-protected substrate **50** did not undergo any 1,5-migration process, but selectively rearranged into bicyclo[3.1.0]hexane derivative **61** bearing a double bond of (*Z*) configuration (Scheme 2.19). This time, the 1,2-hydride shift/gold elimination process seems kinetically more favourable than any other process. This result could have been foreseen in view of Michelet's study with closely similar precursor, nonetheless with platinum(II) catalysis [26]. The selectivity toward the (*Z*) isomer is also consistent with her study, although she did not give any explanation for this phenomenon. It can reasonably be assumed that it resides in steric factors according to the model depicted in Scheme 2.19. In view of the above described results, a fine tuning between the leaving ability and the electron



Scheme 2.20 Synthesis of 1,6-enynes bearing allyl and benzyl acetylenic substituents

withdrawing character of the protected hydroxy group at the external propargylic position seems to be the key to selectively perform a 1,5-hydride shift.

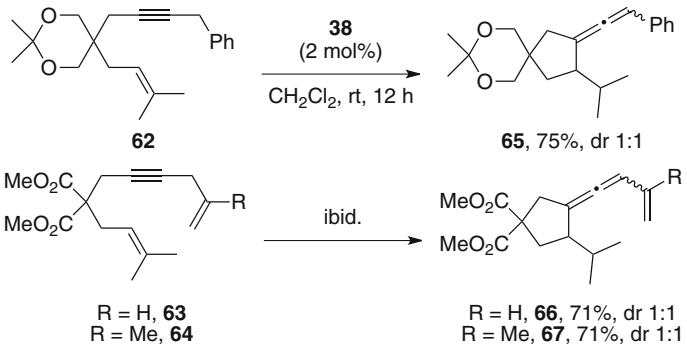
We then thought about benzyl and allyl as acetylenic substituents. They are clearly not leaving groups, and delocalization of their π-electrons into the σ-antibonding orbital of the vinylic or benzylic C-H bond could maybe help to the realization of a 1,5-hydride migration process.

2.2.3 Vinyl and Benzyl Groups as Propargylic Substituents

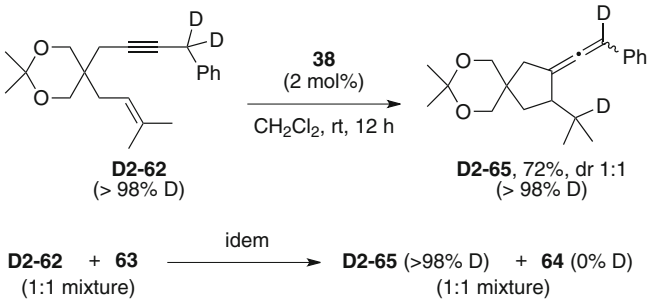
Benzyl derivative **62** was synthesized by treatment of 1,6-enyne **37** with *n*-butyllithium followed by addition of benzyl bromide. We also synthesized allyl and methallyl precursors **63** and **64** starting from malonate-tethered enyne **63** through palladium-free Sonogashira conditions (Scheme 2.20) [28].

We were pleased to find that submission of substrates **62–64** to catalytic amounts of **38** resulted in a clean conversion to the corresponding aryl- and vinylallenes **65–67** arising from a gold-catalyzed cyclization/1,5-hydride shift process (Scheme 2.21). Again, no diastereoselectivity was attained. Intriguingly, whereas vinylallenes of type **67** have been shown in the literature to undergo a Nazarov-type reaction upon gold or platinum catalysis, leading to cyclopentene derivatives [18, 29, 30], a prolonged reaction time of **67** resulted only in a complex mixture of unidentified products.

To further validate our proposed mechanism, we synthetized the deuterated analogue of **62**, **D2-62**, by reaction of 1,1-dideuteroallyl bromide with the corresponding lithium acetylide of **62** (60 % yield). When this substrate was reacted with 2 mol% of **38**, fully deuterated products **D2-65** was obtained. We also performed a deuterium scrambling experiment to confirm the intramolecular nature:



Scheme 2.21 Synthesis of aryl- and vinyl-allenes by a Au-catalyzed cyclization/1,5-H shift tandem reaction



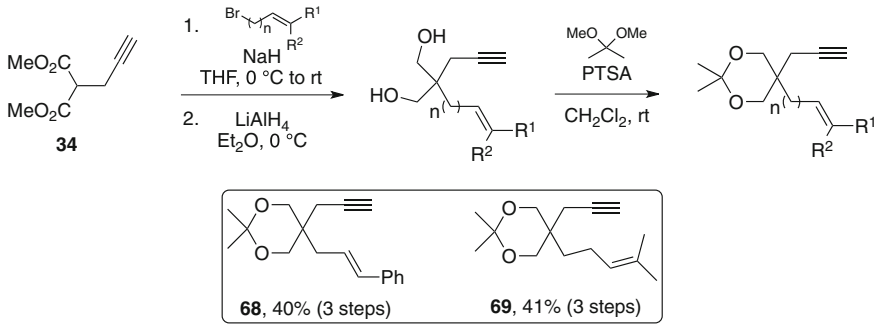
Scheme 2.22 Deuterium-labelling experiments

equimolar amounts of substrates **D2-62** and **63** were mixed together in a dichloromethane solution and submitted to the gold catalyst. A 1:1 mixture of product **D2-65** and **66** was obtained, the latter exhibiting no deuterium incorporation while it was superior than 98 % for **D2-65**, thus proving the intramolecular character of the migration process (Scheme 2.22).

2.3 Substrate Scope and Limitations

2.3.1 Carbon-Tethered Enynes

Encouraged by our preliminary results with carbon-tethered enynes, we next attempted to extend the scope of this new rearrangement to styryl precursors and 1,7-enynes. For this purpose we synthetized enynes **68** and **69** from propargylmalonate **34** through a similar sequence of organic reactions than for the synthesis of **37** (Scheme 2.23).



Scheme 2.23 Synthesis of substrates **68** and **69**

Enynes **68** and **69** were alkylated under classical conditions using *n*-butyllithium followed by addition of valeraldehyde. Subsequent acetylation furnished acetate precursors **70** and **71** (Table 2.1).

A benzyl derivative was also synthetized by alkylation with benzyl bromide, delivering 1,7-enyne precursor 72 (Scheme 2.24).

When submitted to cationic gold(I) catalyst **38** in dichloromethane at rt, styryl precursor **70** was totally recovered after 12 h. The use of harscher conditions resulted in full conversion of the starting material within 5 h, but unfortunately a complex mixture of unseparable products was obtained (Scheme 2.25).

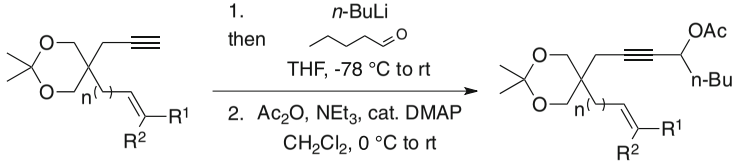
1,7-enynes precursors **71** and **72** both gave disappointing results. When submitted to catalyst **38**, substrate **71** led to a complex, unseparable mixture of unidentified compounds. Lowering the temperature to 0 °C slowed down conversion, but a mixture was still obtained. Precursor **72** was unreactive under the normal conditions. Harscher ones (dichloroethane, 60 °C) allowed full conversion of the starting material within 4 h, however NMR of the crude mixture revealed a complete decomposition of the starting material (Scheme 2.26).

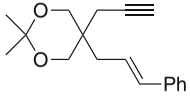
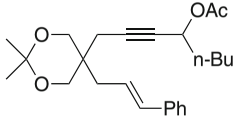
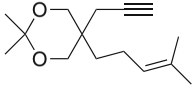
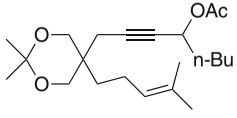
Clearly, the 1,5-migration process is strongly limited by the length of the tether and the nature of the double bond. The 1,5-relationship of the hydride toward its acceptor seems to be determinant, as suggest our results on 1,7-enynes **71** and **72**. The disappointing reactivity of styryl precursor could find explanations in steric repulsions avoiding the hydride and the benzylic cation to have the requisite geometry for the 1,5-migration process. Carbon-tethered enynes were abandoned, and we next focused our study on heteroatom-tethered enynes.

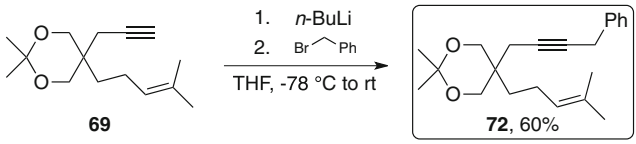
2.3.2 Heteroatom-Tethered 1,6-enynes

As a starting point to the synthesis of heteroatom-tethered enynes, we synthetized various propargyl alcohols or amines. The precursor of N-tethered enynes we used

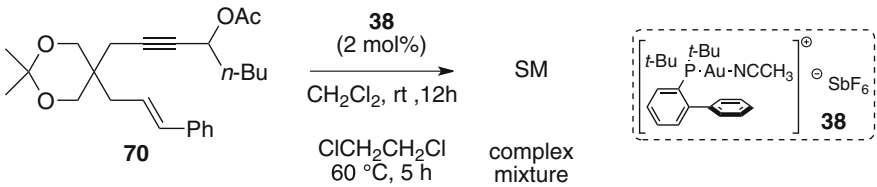
Table 2.1 Synthesis of 1,6-enynes **70** and **71**



Entry	Enyne		Product (yield, 2 steps)	
1		**68**		**70**, 84%
2		**69**		**71**, 81%

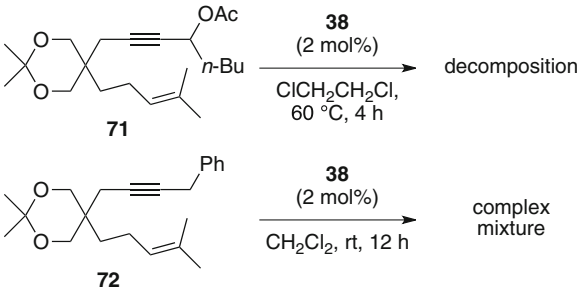


Scheme 2.24 Synthesis of benzyl-substituted 1,7-enyne precursor **72**

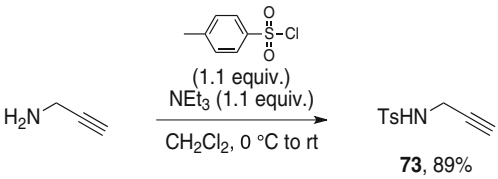


Scheme 2.25 Failure to promote the cycloisomerization of styryl precursor **70** through 1,5-migration

Scheme 2.26 Failed attempts to promote 1,5-migration on 1,7-enynes



Scheme 2.27 Synthesis of *N*-tosyl propargyl amine **73**

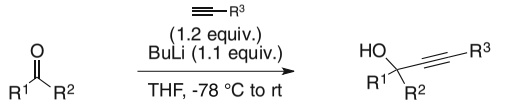


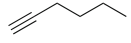
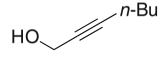
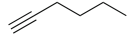
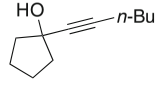
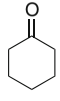
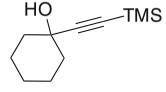
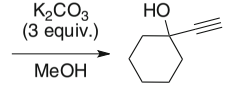
was N-tosyl propargyl amine **73** obtained in one step in 89 % yield by tosylation of commercially available propargyl amine (Scheme 2.27).

Propargyl alcohols **74–76** were prepared in excellent yields by addition of lithium acetylides onto aldehydes or ketones. Propargyl alcohol **76** was subsequently desilylated under classical methanolysis conditions to give precursor **77** (Table 2.2).

Propargyl amine and alcohols **73–75** and **77** were next alkylated by treatment with sodium hydride and an allyl bromide in 73–83 % yield. 1,6-Enynes **78–80** bearing a terminal alkyne can be further functionalized at the acetylenic position. Precursor **81** displays an alkyl-substituted triple bond, so that we can check the

Table 2.2 Synthesis of propargylic alcohols **74**–**77**



Entry	Aldehyde/Ketone	Alkyne	Product (yield)
1			 **74**, 91%
2			 **75**, 94%
3			 **76**, quant.  **77**, quant.

possibility of a 1,5-hydride shift without the assistance of an adjacent π-donor group. Enyne **82**, bearing a mono-substituted olefin, will allow us to test the limit of the 1,5-migration process as well (Table 2.3).

Terminal alkynes in enynes **78–80** were alkylated with valeraldehyde upon treatment with *n*-butyllithium, and subsequent acetylation furnished cyclization precursors **83–85**, the latter bearing a quaternary propargylic center (Table 2.4).

Benzyl derivatives **86** and **87** were also synthetized starting from enynes **79** and **80**, respectively (Table 2.5).

Finally, substrate **88** with a methylene cyclohexane moiety was synthetized. Wittig-Horner olefination of cyclohexanone followed by reduction using LAH furnished allylic alcohol **89**. Alkylation of the latter with propargyl bromide and subsequent alkylation of the acetylenic position gave enyne precursor **88** (Scheme 2.28).

We then assessed the reactivity of substrates **81–88** when submitted to catalytic amounts of catalyst **38**. *n*-Butyl precursors **81** and **82** both rearranged into bicyclo[4.10]heptene skeletons **90** and **91**, the latter with ring expansion of the cyclopentane framework (Scheme 2.29).

The cycloisomerization of **81** into **89** clearly demonstrates that the presence of an adjacent π-donor group is critical to perform the 1,5-hydride shift. Thus, it is not surprising that enyne **82**, bearing a mono-substituted olefin, reacts in a similar manner. The mechanism of this transformation is detailed in the box of Scheme 2.29 and involves an *endo* cyclopropylcarbene **92** (refer to Sect. 1.3.3 of Chap. 1). The latter would then undergo a 1,2-alkyl shift/ring expansion followed by gold elimination consistent with precedents in the 1,6- and 1,5-enynes series (ibid.).

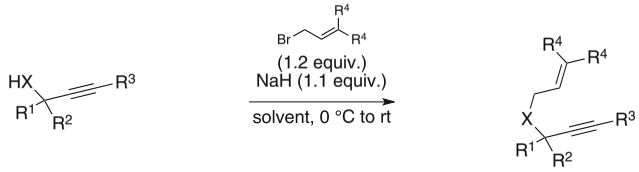
O-acyl precursors **83–85** gave contrasting results. N-tethered substrate **83** was unreactive under the classical gold catalysis conditions. When switching to harscher ones (refluxing dichloroethane), a complex mixture of unseparable products was obtained (Scheme 2.30).

O-tethered substrate **84** led selectively upon cationic gold(I) catalysis to allene **93** arising from a 1,5-acetate shift process. This is in sharp contrast with carbon-tethered substrate **47** also bearing a primary acetate at the external propargylic position that gave selectively a 1,5-hydride shift product (Scheme 2.16). This example is a nice illustration of a mechanistic divergence directed by the tether (Scheme 2.31).

Enyne **85** bearing a quaternary propargylic center exhibited a particular reactivity when submitted to catalyst **38**, as diene **94** was obtained in quantitative yield with a (*E*)/(*Z*) ratio of 1:0.4 (Scheme 2.32).

As we detected a downfield signal in the ^{1}H NMR of the crude mixture, we assumed that this product could arise from a gold-triggered elimination of 3,3-dimethylacrolein. This process would be possible if a 1,5-hydride shift occurs from the allylic position onto the external carbon of the triple bond, leading to vinylgold oxonium **95**. Gold elimination would then take place concomitant with elimination of 3,3-dimethylacrolein, to lead to allene **96**. A 3,3-sigmatropic shift, probably gold-catalyzed, would finally deliver the mixture of dienes **92** through dioxonium intermediate **97** (Scheme 2.33).

Table 2.3 Synthesis of 1,6-enynes **78**–**82**



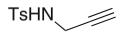
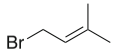
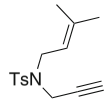
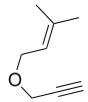
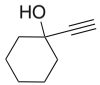
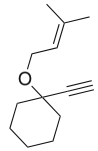
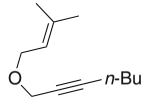
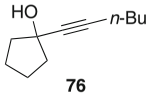
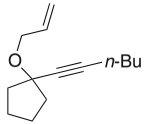
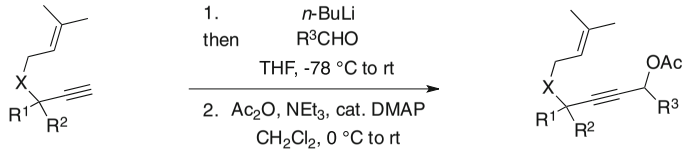
Entry	Propargyl amine/alcohol	Bromide	Solvent	Product (yield)
1	 **73**		DMF	 **78** (79%)
2		idem	THF	 **79** (83%)
3	 **77**	idem	idem	 **80** (72%)
4	**74**	idem	idem	 **81** (79%)
5	 **76**		idem	 **82** (73%)

Table 2.4 Synthesis of 1,6-enynes **83**–**85**



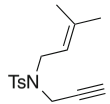
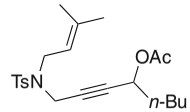
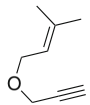
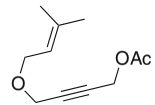
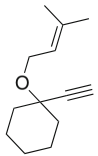
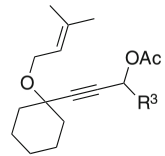
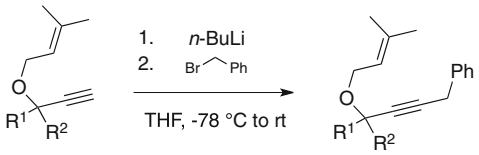
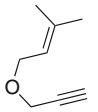
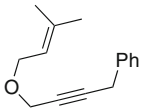
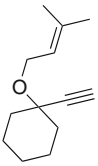
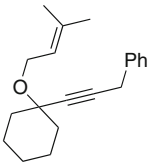
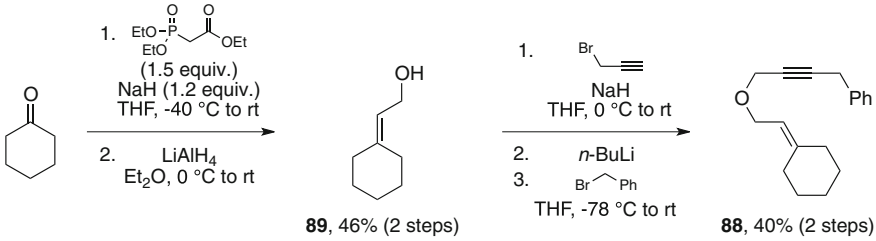
Entry	Enyne		R^3	Product (yield, 2 steps)	
1		**78**	*n*-Bu		**83** (77%)
2		**79**	H		**84** (82%)
3		**80**	*n*-Bu		**85** (56%)

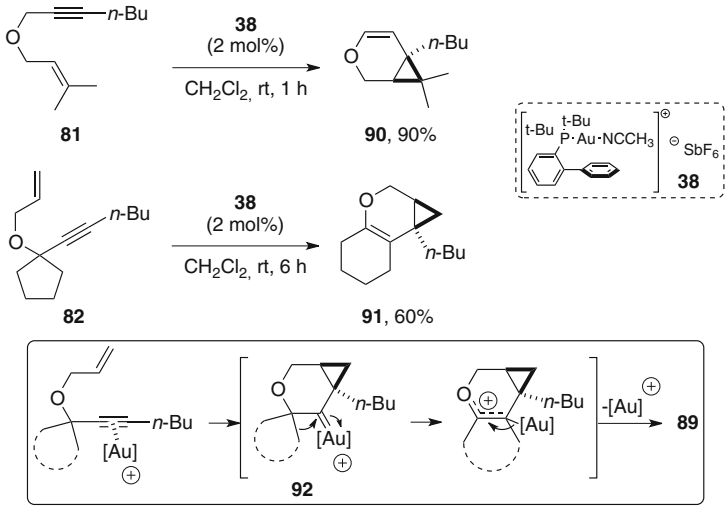
Table 2.5 Benzylation of the acetylenic position of enynes **79**–**80**



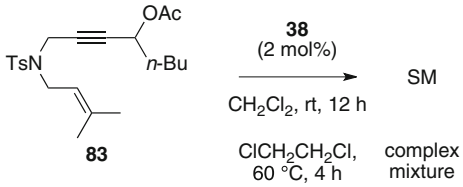
Entry	Enyne	Product (yield)
1	 **79**	 **86** (56%)
2	 **80**	 **87** (56%)



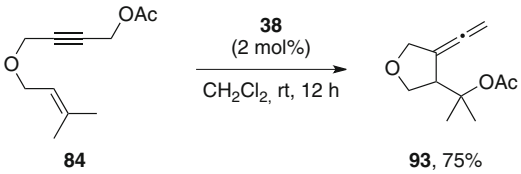
Scheme 2.28 Synthesis of substrate **88** bearing a methylene cyclohexane



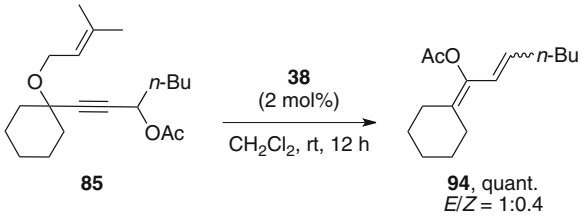
Scheme 2.29 Cycloisomerization of enynes **81** and **82** into fused polycyclic compound **90** and **91**



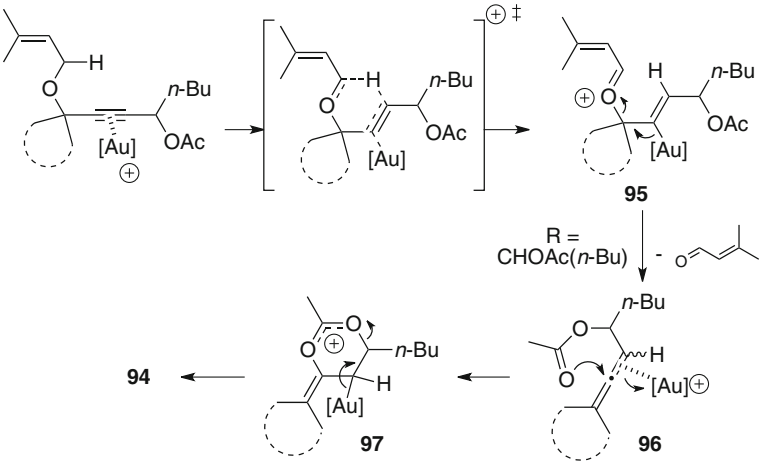
Scheme 2.30 Failed attempts to cyclize *N*-tethered precursor **83**



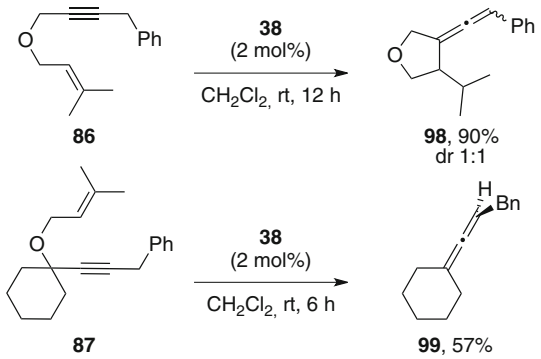
Scheme 2.31 Cyclization of *O*-tethered enyne **84** through a 1,5-OAc shift process



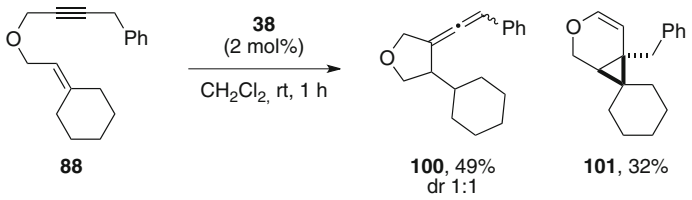
Scheme 2.32 Particular reactivity of substrate **85** bearing a quaternary propargylic center



Scheme 2.33 Mechanistic hypothesis accounting for the formation of product **92**



Scheme 2.34 Reactivity of benzyl derivatives **86** and **87**



Scheme 2.35 Competition between *endo* cyclization and 1,5-hydride shift in the cycloisomerization of **88**

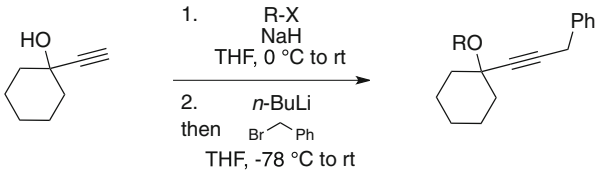
Gratifyingly, benzyl derivative **86** was cleanly converted to cyclized compound **98** through a 1,5-hydride shift upon gold catalysis, in 90 % yield. However, enyne **87** bearing a quaternary propargylic center selectively rearranged into allene **99**. This product presumably arise from a mechanistic sequence similar to the one leading to allene **96** in the rearrangement of enyne **85** into diene **94** (Scheme 2.34).

These examples show that two 1,5-hydride shift processes can compete when using *O*-tethered enynes, one leading to compounds **94** or **99**, the other leading to **98**. The nature of the internal propargylic center has a dramatic influence in the overcoming of one pathway over the other.

When reacted with a catalytic amount of **38**, substrate **88** led, within a short reaction time, to a 3:2 mixture exocyclic allene **100** and *endo* cyclization product **101**, the allene derivative being, once more, obtained as a 1:1 mixture of diastereoisomers (Scheme 2.35).

This last example suggests that using trisubstituted, sterically hindered double bond may rise issues of selectivity, *endo* cyclization becoming competitive with 1,5-hydride migration.

Table 2.6 Synthesis of propargyl ethers **102** and **103**



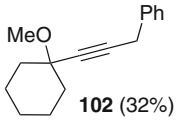
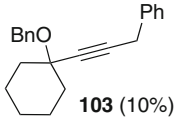
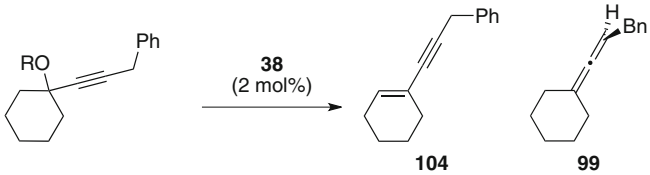
Entry	R-X	Product (yield, 2 steps)
1	MeI	 **102** (32%)
2		 **103** (10%)

Table 2.7 Reactivity of propargyl ethers **87**, **102** and **103** toward gold catalysis

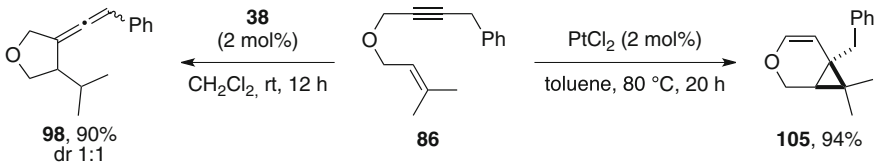


Propargyl ether	Conditions	Yield	
102, R = Me	$ClCH_2CH_2Cl$, 80 °C, 5 h	70%	-
103, R = Bn	CH_2Cl_2, rt, 12 h	-	47% (90% brsm)
87, R =	CH_2Cl_2, rt, 6 h		57%

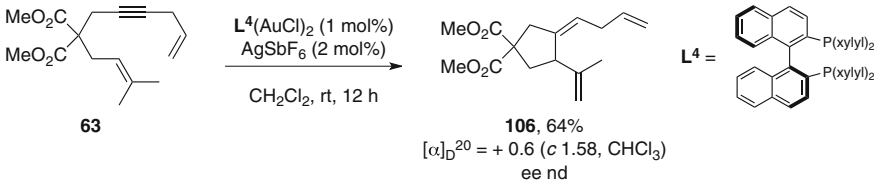
2.3.3 Rearrangement of Propargyl Ethers into Allenes

Another 1,5-hydride migration process was disclosed, leading to diene **94** or allene **99** (vide supra). A study of its scope was started with propargyl ethers **102** and **103** bearing a quaternary propargylic center. They were synthetized from propargyl alcohol **77** through a Williamson reaction/alkylation sequence (Table 2.6).

The reactivity of propargyl ethers **102** and **103** and **87** when submitted to catalyst **38** are summarized in Table 2.7. Precursor **102** was unreactive under room-temperature conditions. Running the reaction in refluxing dichloroethane led to **104** resulting from methanol elimination as the single product (70 % yield). Benzyl ether **103** cleanly afforded allene **99** in 47 % yield, however conversion



Scheme 2.36 Distinct mechanistic pathways between **38** and $PtCl_2$



Scheme 2.37 Alder-ene product reaction upon catalysis with a chiral bimetallic gold complex

was incomplete. As a matter of comparison, dimethallyl precursor **87** reacted faster under room-temperature conditions.

During the course of this study, another team reported the direct formation of allenes from benzyl propargyl ethers with cationic gold(I) catalysts through the same process as described above (Scheme 2.5) [12]. Therefore, we did not go further into the examplification of this reactivity.

2.3.4 Conclusions and Perspectives

This overall study has shown that the gold catalyst could promote different, substrate-dependant rearrangements on the enyne precursors that have been tested. These rearrangements can enter in competition as illustrated by the example depicted in Scheme 2.35. The tether, the external propargylic substituent and the nature of the double bond have an influence on the reactivity preference of a considered substrate. One study still have to be done, dealing with the catalyst's influence. For example, we noticed that enyne **86** behaved differently in the presence of a platinum catalyst (Scheme 2.36).

In an attempt to render the 1,5-hydride shift process enantioselective with a chiral bimetallic gold complex [31], a formal Alder-ene product was selectively obtained (Scheme 2.37). This clearly shows that the nature of the catalyst is also at stake in these processes.

2.4 Synthetic Strategy Toward Macrolactones Based on a Gold-Catalyzed Enyne Cycloisomerization

2.4.1 Generality of the Endo Cyclization/Ring Expansion of Oxygen-Tethered 1,6-enynes

2.4.1.1 Catalyst Optimization

We briefly looked at the scope of the reactivity displayed by enynes **81** and **82** upon gold catalysis. First, we optimized the reaction of **82** with cationic gold(I) catalyst **38**, running it on a larger scale within a shorter time. We also screened other catalysts, and intriguingly, platinum chloride salts showed no activity toward this cycloisomerization process (Table 2.8, entries 1–3), as well as neutral gold(I) and gold(III) salts, giving sometimes elimination product **121** (entries 4–5).

Pentamethylcyclopentadienyl iridium chloride dimer, which was recently shown by our group to perform *endo* cycloisomerization of nitrogen- and oxygen-tethered enynes, [32] was also inactive (entry 11). However, other cationic gold(I) complexes were able to promote *endo* cyclization. Among them, catalyst **38** and $\mathbf{L^5}Au^+$ with a bulky donor ligand, the latter being generated by chloride abstraction in presence of silver hexafluoroantimonate, were found to be the most efficient. It is worth noting that bulkiness of the ligand seems to play a role, as tri-*tert*-butylphosphine allows the reaction to proceed with efficiency. According to these results, we kept either **38** or $\mathbf{L^5}Au^+$ as catalysts of choice to perform this rearrangement.

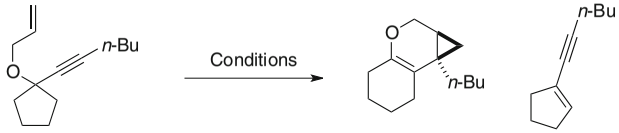
2.4.1.2 Reaction Scope

We then synthetized a series of oxygen-tethered 1,6-enynes starting from different commercial cycloalkanones. A two-step sequence consisting of addition of a lithium acetylide onto the carbonyl moiety of the cycloalkanone followed by alkylation with an alkyl bromide in refluxing THF furnish the targeted enyne. According to this procedure, 1,6-enynes **108–114** were synthetized from either cyclobutanone (Scheme 2.38, **108–110**) or cyclopentanone (**111–114**) in yields ranging from 63 to 86 %. We first focus on precursors bearing non terminal alkyne, substituted by various alkyl groups, such as *n*-butyl (**109** and **110**), cyclopropyl (**108**, **111–113**) and isopropyl (**114**).

Four membered-ring precursors **108–110** reacted well when submitted to catalyst **38**, and cleanly afforded compounds **115–117** in good yields (Table 2.9).

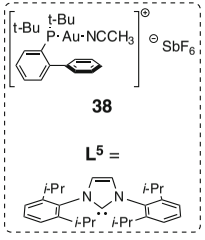
Enyne **108** and **110** cleanly afforded in good isolated yields fused tricyclic compounds **115** and **117**, respectively (entries 1 and 3). Cycloisomerization product of **109**, **116** was isolated in a lower yields (entry 2). Apolar by-products, which were not isolated, formed during the reaction. The poor diastereoselectivity

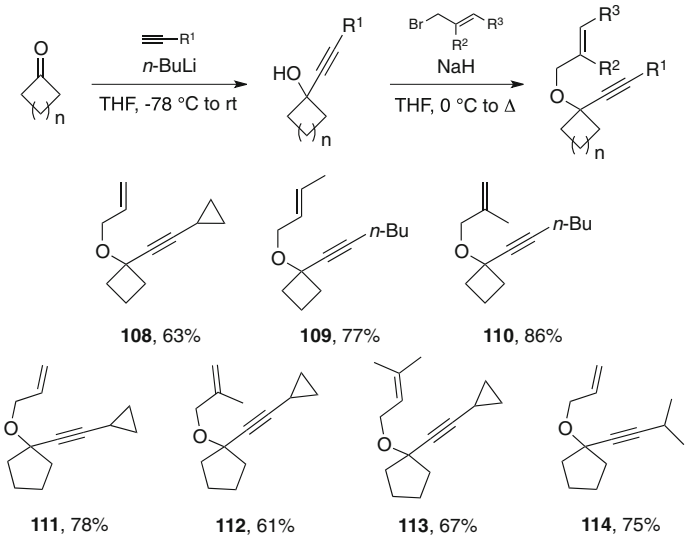
Table 2.8 Catalyst optimization



82 **91** **107**

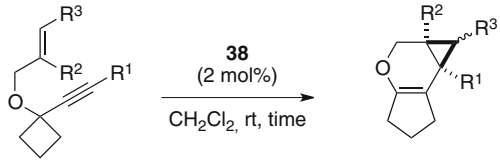
Entry	Conditions	Product(s)
1	$PtCl_2$ (5 mol%), toluene, 80 °C, 5 h	SM
2	$PtCl_2$ (5 mol%), toluene, Δ, 15 h	SM
3	$PtCl_4$ (5 mol%), toluene, 80 °C, 5 h	SM
4	AuCl (2 mol%), CH_2Cl_2, rt, 27 h	SM
5	$AuCl_3$ (2 mol%), CH_2Cl_2, rt, 27 h	SM + **107**, 33%
6	$Ph_3PAuCl/AgSbF_6$ (2 mol%), CH_2Cl_2, rt, 30 min	**82**, 50%
7	$(t\text{-}Bu)_3PAuCl/AgSbF_6$ (2 mol%), CH_2Cl_2, rt, 1 h 30	**82**, 75%
8	$[Ph_3PAu]NTf_2$ (2 mol%), CH_2Cl_2, rt, 30 min	**82**, 49%
9	**38** (2 mol%), CH_2Cl_2, rt, 1 h 30	**82**, 84%
10	$\mathbf{L^5}AuCl/AgSbF_6$ (2 mol%), CH_2Cl_2, rt, 1 h 30	**82**, 85%
11	$[IrCp^*Cl_2]_2$ (5 mol%), $ClCH_2CH_2Cl$, Δ, 12 h	SM

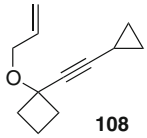
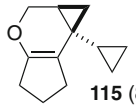
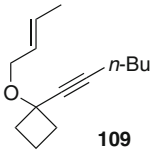
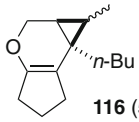
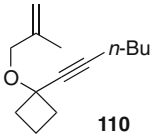
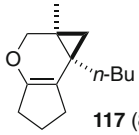




Scheme 2.38 Synthesis of enynes precursors with a quaternary propargylic center

Table 2.9 Cycloisomerization/ring expansion of enynes **108**–**110** catalyzed by cationic gold(I)



Entry	Enyne	Time	Product (yield)
1	 **108**	4 h	 **115** (81%)
2	 **109**	6 h	 **116** (51%, dr 3:2)
3	 **110**	6 h	 **117** (85%)

in this last example suggests that a planar carbocation corresponding to an opened form of the intermediate *endo* cyclopropylcarbene might be involved (see Chap. 1, Sect. 1.3.3).

On the opposite, five-membered ring derivatives **111–114** gave contrasting results. For these enyne precursors, catalyst $\mathbf{L^5}Au^+$ with a NHC ligand gave better results than catalyst **38** (Table 2.10). While enyne **114** reacted well in the presence of catalyst $\mathbf{L^5}Au^+$ (77 % yield, entry 4), substrates with acetylenic cyclopropyl substituents were more capricious. For example product **119** issued from the cycloisomerization of **112** was formed with unidentified polar by-products and was isolated in a poor 37 % yield (entry 2).

In only 2 h, **111** led to a mixture of products from which a major one was isolated and assigned to structure **137** after full-NMR analysis. A mechanistic proposal accounting for the formation of **118** would involve a vinyl cyclopropane rearrangement [33–37][8] on cycloisomerization compound **123** leading to the strained tricyclic intermediate **124**. An elimination step would finally lead to compound **118** (Scheme 2.39).

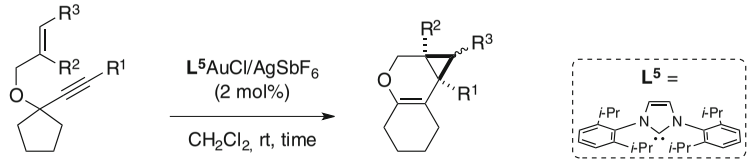
Why this divergence in the reaction outcome is observed remains unanswered. Probably the poor yield of **119** could result from this side reaction, however the related alcohol was not isolated. Regarding to precursor **113**, a considerable amount of allene **121** was detected in the crude reaction mixture after 2 h at room temperature with catalyst $\mathbf{L^5}Au^+$, starting material being totally consumed. It is likely that this by-product arise from the 1,5-hydride shift/aldehyde elimination reaction that was discussed above (Sect. 1.2.2). This process might be favored in the presence of a prenyl double bond. Only 12 % of the desired cycloisomerized product **120** was isolated (Table 2.10, entry 3). Formation of allenes could possibly be responsible for the moderate yield obtained in the cycloisomerization of enyne **109** (Table 2.9, entry 2).

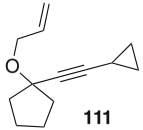
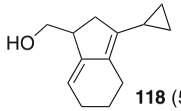
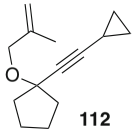
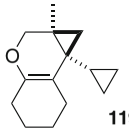
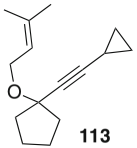
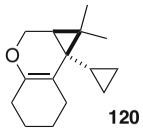
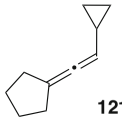
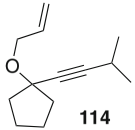
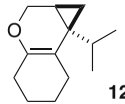
We next turned our attention to precursors remaining unsubstituted at the acetylenic position. We synthetized enynes **125–127** starting from commercially available cycloalkanones (Table 2.11). Alkynylation using *n*-butyllithium in the presence of trimethylsilyl acetylene followed by desilylation under classical methanolysis afforded propargyl alcohols **128–130**. This two steps sequence worked quite well except the addition onto indanone (entry 2) which proved to be difficult (41 % yield), probably because dehydration of alcohol **129** might occur. Final alkylation in DMF delivered the *O*-tethered 1,6-enynes **125–127**. In the case of substrates **125** and **126**, an impurity remained after column chromatography that could be eliminated by Kugelrohr distillation, but seriously decreasing the overall yield (entries 1 and 2).

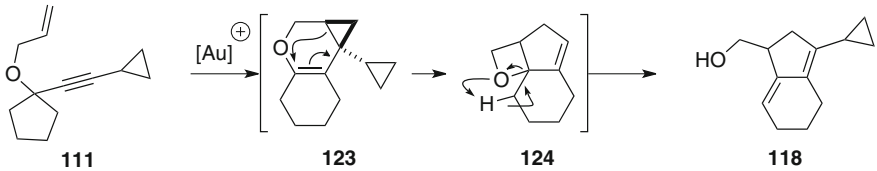
The results of the gold-catalyzed rearrangements of enynes **125–127** are summarized in Table 2.12. Gold-catalyzed reaction of **125** led to a mixture of

[8] See also: [37].

Table 2.10 Cycloisomerization/ring expansion of enynes **111**–**114** catalyzed by cationic gold(I)



Entry	Enyne	Time	Product (yield)
1	 **111**	2 h	 **118** (50%)
2	 **112**	18 h	 **119** (37%)
3	 **113**	2 h	 **120** (12%)  **121** (48%)
4	 **114**	5 h	 **122** (77%)



Scheme 2.39 Mechanistic rationale for the cycloisomerization of **111**

cyclopropanation/ring expansion product **130** and skeletal rearrangement product **131** (entry 1). Enyne **126** produced an unseparable mixture of several compounds when submitted to catalyst **38**, in which the ring expansion product **132** was the major component. Purification by flash column chromatography did not allowed the isolation of pure **132**, but the yield could be assessed by ^{1}H NMR of the fraction containing the cyclized compound (entry 2). The crude reaction mixture resulting from submission of enyne **127**, bearing a prenyl double bond, to catalyst **38**, did not reveal any ring expansion product at all. In place, skeletal rearrangement compounds **133** and **134** were isolated in 11 and 58 % yield, respectively (entry 3).

These results clearly indicate that skeletal rearrangement enters in competition with *endo* cyclopropanation for 1,6-enynes bearing no acetylenic substituents (entries 1 and 3). They are sometimes exclusive as demonstrated with the cycloisomerization of **127**, bearing a prenyl double bond (entry 3).[9]

2.4.2 Access to Ketomacrolactones from Ring-Expansion Products

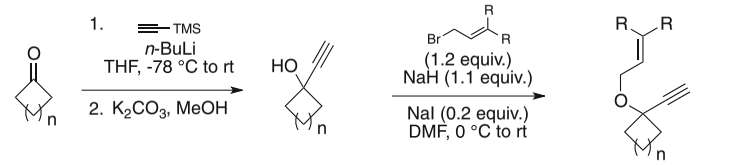
The platinum- and gold-catalyzed cycloisomerization of 1,6-enynes into bicyclo[3.1.0]heptene derivatives, through an endocyclic cyclopropylcarbene, was rarely applied to natural and/or biologically active compounds [39–41]. By our side, we envisionned the possible access to ketomacrolatones from of cycloisomerization/ring expansion products by realizing first the oxidative cleavage of the enol ether, followed by cyclopropane opening (Scheme 2.40).

It is worth noting that the 5-ketodecalactone skeleton we could obtain by this synthetic sequence is found in some natural products of biological interest, such as diplodialide D, sporostatin and xestodecalactone A (Scheme 2.41).

In order to validate our approach, we chose **91** as a model substrate. The oxidative cleavage of its enol ether moiety was successfully realized using either pyridinium chlorochromate [42] or a combination of ruthenium dioxide and sodium periodate, [43] and 10-membered ring lactone **136** was isolated in similar yields (Table 2.13).

[9] For a study where prenyl double bonds showed distinct behaviors, see Ref. [38].

Table 2.11 Synthesis of 1,6-enynes **125–127**



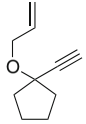
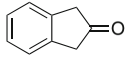
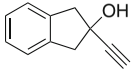
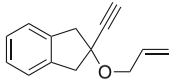
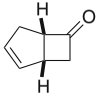
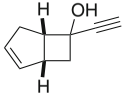
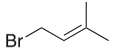
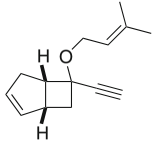
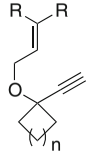
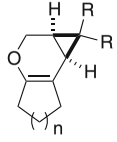
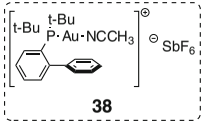
Entry	Ketone	Propargyl alcohol	Bromide	Product (yield, 3 steps)
1		**128**		 **125** (43%)
2		 **129**	idem	 **126** (22%)
3		 **130** dr > 25:1		 **127** (67%) dr > 25:1

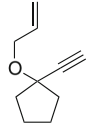
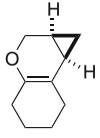
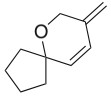
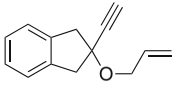
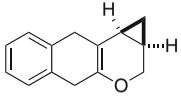
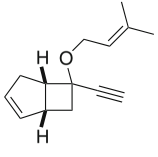
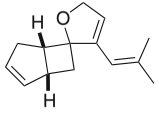
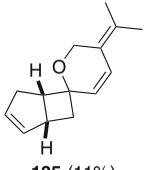
Table 2.12 Cycloisomerization/ring expansion of enynes **125**–**127** catalyzed by cationic gold(I)

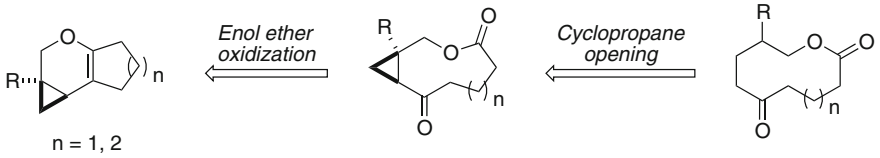


38
(2 mol%)
CH_2Cl_2, rt, time



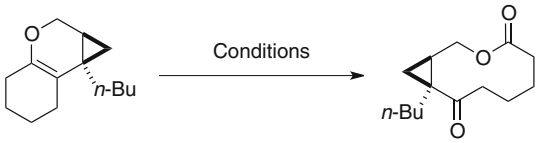


Entry	Enyne	Time	Product (yield)	
1	 **125**	1 h	 **131** (65%)	 **132** (18%)
2	 **126**	2 h	 **133** (62%, NMR yield)	
3	 **127** dr > 25:1	2 h	 **134** (58%) dr > 25:1	 **135** (11%) dr > 25:1



Scheme 2.40 Envisionned approach to the 5-ketodecalactone and 6-ketoundecalactone skeletons

Table 2.13 Oxidative cleavage of enol ether **91**



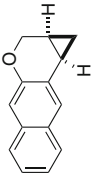
91		**136**
	PCC (4 equiv.), Celite CH_2Cl_2, rt	58%
	RuO_2 (5 mol%), $NaIO_4$ (4 equiv.) CCl_4/H_2O 1:1	59%

Encouraged by these results, we applied these oxidation conditions to the mixture from which we were not able to isolate **133**, the cycloisomerization product of **126**. We expected that the polar ketolactone thus obtained could be easily separated from the other unidentified components of the mixture. However, a totally different outcome was reached with enol ether **133**, and aromatized naphthyl derivative **136** was obtained, in excellent yield with ruthenium dioxide. When ozone was used as the oxidant, only a mixture of products from which **137** could be isolated in poor yield. To the best of our knowledge, such reaction had never been reported. It seems that aromaticity of the final compound may act as a driving force that discriminates oxidative cleavage of the double bond in favor of aromatization (Table 2.14).

We then tried several methods to open the cyclopropane in compound **136**. We assumed that the presence of a carbonyl group in α position might facilitate its opening through radical-based methodologies. We first tried a photochemical procedure consisting in irradiation in the presence of NEt_3 and $LiClO_4$, reported by Cossy et al. [44]. Unfortunately, in these conditions, the starting material was totally recovered (Scheme 2.42).

Several reports describe samarium diiodide as a good reductor of cyclopropyl ketones. We tried the conditions reported by the team of Motherwell (SmI_2, HMPT in THF) [45] and this time the starting material was fully consumed, but led to the linear carboxylic acid derivative **138** (Scheme 2.43).

Table 2.14 Oxidation of cyclized compound **133**

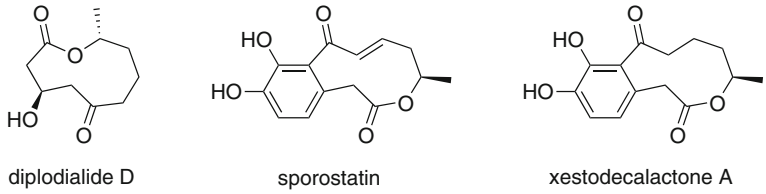


126 **133** **137**

62% (NMR yield) 54%

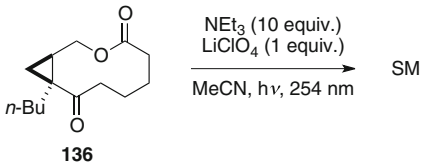
82%

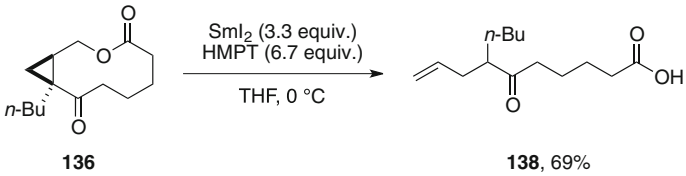
22%



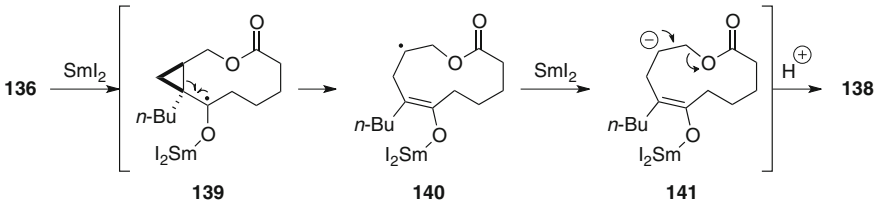
Scheme 2.41 Natural products exhibiting the 5-ketodecalactone skeleton

Scheme 2.42 Failed attempt to open cyclopropane in **136** photochemically





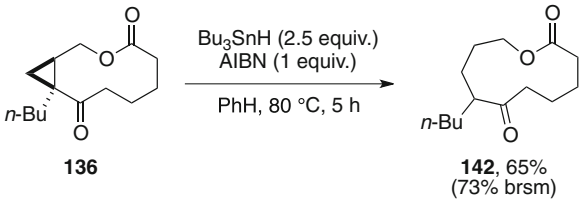
Scheme 2.43 Reaction of cyclopropylketolactone **136** with SmI_2



Scheme 2.44 Mechanism accounting for the formation of **138**

Although the cyclopropane was indeed opened, product **138** was certainly not the one expected. The following mechanism can account for the formation of this product: first, reaction of samarium diiodide with the keto group generates ketyl radical **139**, and cyclopropane opening led to the corresponding enolate **158**. A fast reduction of the secondary radical then occurs, accompanied by departure of the carboxylate group to lead, after protonation, to acid derivative **156** (Scheme 2.44).

Clearly the fast reduction of radical **158** must be avoided to get selectively the product of cyclopropane opening. This could be achieved if a good hydrogen donor is present in the reaction mixture. For this purpose the use of the combination of tributyltin hydride and azo-isobutyronitrile (AIBN) appeared as a



Scheme 2.45 Successful opening of cyclopropane **136** to the 5-ketoundecalactone skeleton

satisfying option [46]. Application of these reaction conditions to **136** gratifyingly led to the desired 11-membered ring lactone **142**. Let us underline that full conversion was not reached, but the reaction conditions have not been optimized to date (Scheme 2.45). Thus, our approach was validated starting from model substrate **91**.

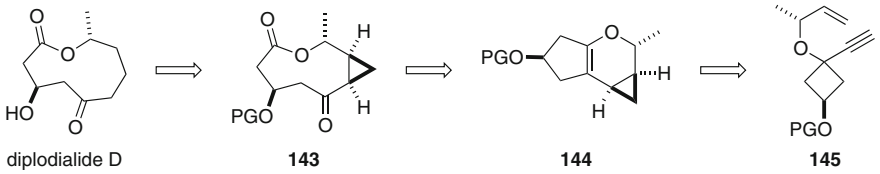
2.4.3 Perspective: Toward the Total Synthesis of Diplodialide D

We envisioned a possible total synthesis of diplodialide D through the below depicted retrosynthetic analysis: the aimed 5-ketodecalactone could be built from cyclopropyl ketone **143** by a sequence of deprotection and cyclopropane opening steps. **143** would result from the oxidative cleavage of enol ether **144**, the latter coming from the gold-catalyzed cyclosomerization of enyne **145** (Scheme 2.46).

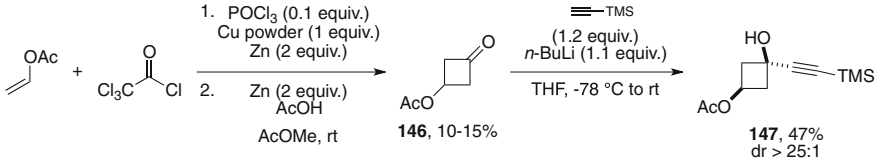
Therefore, we started the synthesis of enyne **163.** Cyclobutanone **164** was first synthetized through a one-pot procedure by reaction of trichloroacetyl chloride and vinyl acetate in the presence of copper and zinc [47]. Addition of trimethylsilyl lithium acetylide furnished alcohol **165** in an acceptable yield, which relative *syn* configuration was addressed according to literature precedents (Scheme 2.47) [48–50].

The functionalization of alcohol **147–145** proved to be difficult. Classical conditions involving deprotonation of the alcohol and alkylation with an alkyl bromide were dispelled as competitive SN_2' could lead to a mixture of products. Several methodologies based on Lewis acid-assisted propargylic substitution were reported in the literature, but either sodium tetrachloroaurate, [51] copper bromide [52] or bismuth chloride [53] resulted in recovery of the starting material, even at higher temperature than used in the original reports. Another procedure was reported by the team of Toste that did not rely on a Lewis acid activation but is supposed to proceed through an allenic intermediate resulting from the 3,3-sigmatropic shift of an oxopropargyloxyrhenium species [54]. Unfortunately, these new conditions failed to give the desired product (Scheme 2.48).

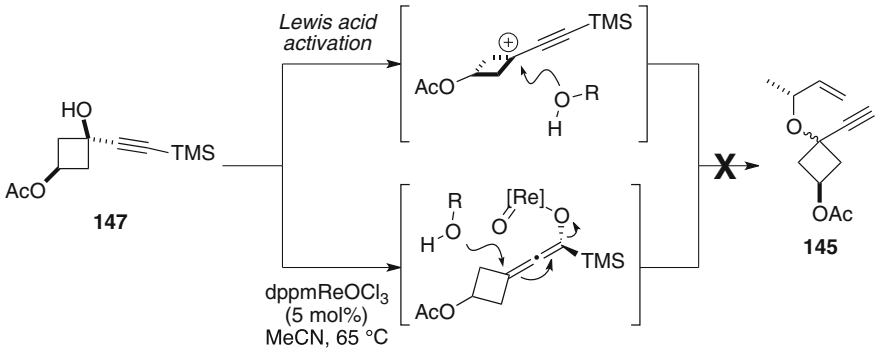
Other possibilities could be enviosionned for the synthesis of **145**: other Lewis, and even Brønsted acid could be assessed, and the Nicholas reaction could also be a solution. Otherwise, direct allylation via a π-allyl transition metal complex can



Scheme 2.46 Retrosynthetic analysis of diplodialide D



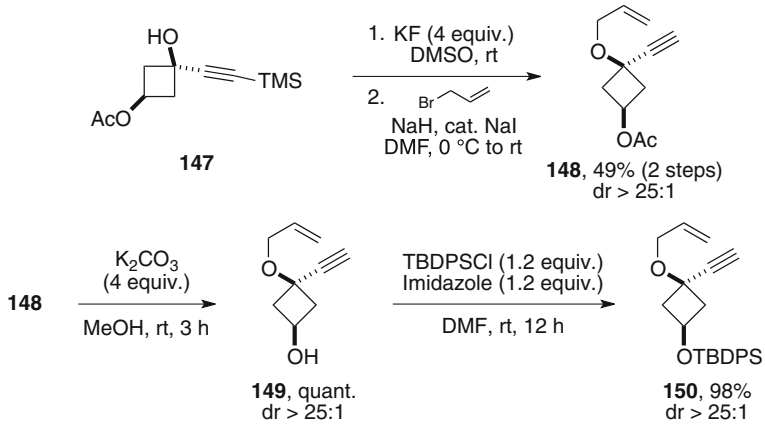
Scheme 2.47 Toward the synthesis of enyne **147**



Scheme 2.48 Failed attempts to realize the last step in the synthesis of **145**

also be envisionned. For time reason, all these methods have not been tried. However, to get an idea of the behaviour of enynes of type **145** bearing a substituted cyclobutane ring, we synthetized enynes **148**–**150**. Propoargyl alcohol was first desilylated using potassium fluoride, and classic alkylation in the presence of sodium hydride furnished enyne **148**. Further steps allowed variation of the hydroxy protecting group (Scheme 2.49).

The submission of these precursors to gold catalysts gave unfortunately disappointing results (Table 2.15). Hydroxy-protected enynes **148** and **150** reacted slowly, and gave skeletal reorganization products **151** and **152** in moderate yields (entries 1 and 3). Catalyst **38** was inactive toward enyne **150**, but cationic gold(I) catalyst $[Ph_3PAu]NTf_2$ led to complete conversion overnight. Only traces of cyclopropanic products could be observed in the crude reaction mixtures of **148** and **150** that we did not manage to isolate. Regarding enyne **149**, its reaction with



Scheme 2.49 Synthesis of 1,6-enynes **148–150**

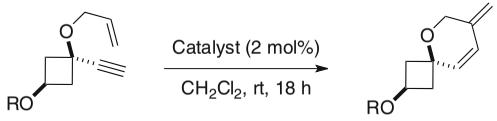
cationic phosphinegold(I) catalyst **38** led to an unseparable, complex mixture of unidentified compounds (Table 2.15).

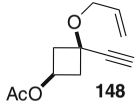
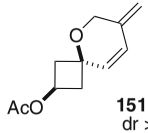
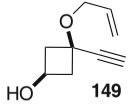
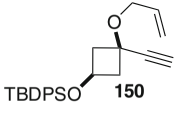
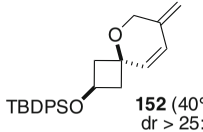
These results predict a consequent work of optimization for the gold-catalyzed key-step en route to diplodialide D. A fine tuning between the catalyst, the hydroxy-protecting group and the reaction conditions should be found to promote the desired, selective cyloisomerization of these cyclobutane-based enynes.

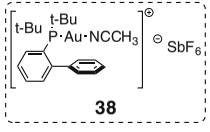
2.5 Conclusion and Perspectives

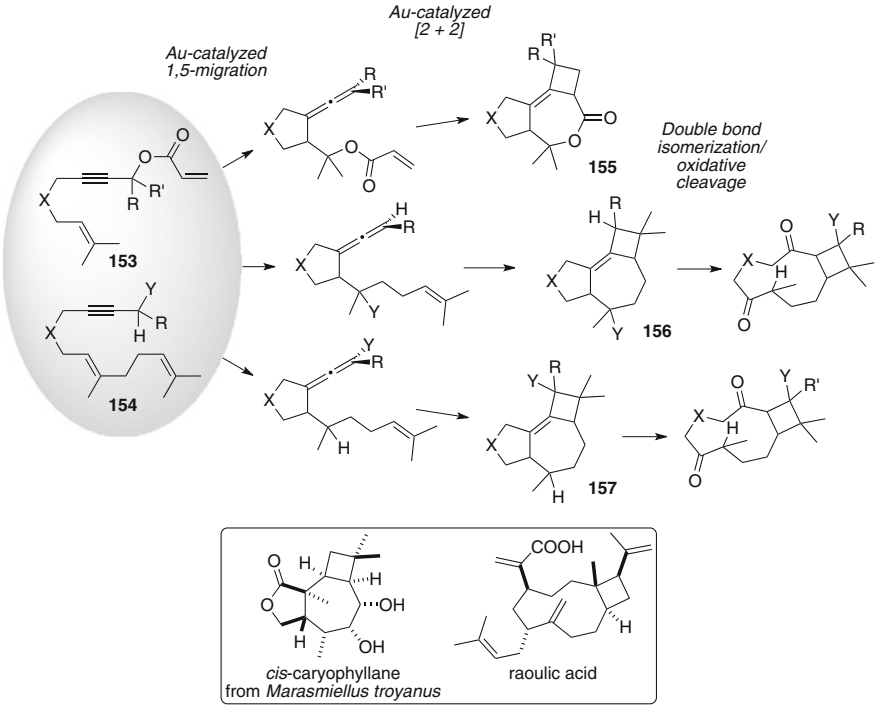
This work on 1,6-enynes enlightens and illustrates well the "substrate dependency" frequently met in the cycloisomerizations of enynes upon carbophilic activation. It is further amplified if working with substrates decorated with various functional groups inserted at key position in the enyne backbone. To our part, we disclosed that donor groups at the external propargylic position could promote a 1,5-migration process triggered by the 5-*exo* cyclization of a prenyl double bond onto the gold-activated alkyne. Interesting findings were also done with oxygen-tethered enynes: with prenyl double bonds, a 1,5-hydride shift followed by dimethylacrolein elimination can give rise to allene, while inserting a strained cycloalkane at the internal propargylic position can lead to products of *endo* cyclization with expansion of the strained ring. Synthetic value was brought to these products, as they were efficiently transformed into ketomacrolactones. A total synthesis of natural product diplodialide D was begun. To put an end to this chapter, we would like to give a prospect for the 1,5-migration process. Considering acrylate derivative **153** or geraniol-based enyne **154**, a gold-catalyzed 1,5-migration should give rise to the corresponding 1,7-allenene compounds (Scheme 2.50). Gold is also known to promote the [2 + 2] cycloaddition of

Table 2.15 Cycloisomerization reactions of enynes **148**–**150**



Entry	Enyne	Catalyst	Product (yield)
1	 **148**	**38**	 **151** (53%) dr > 25:1
2	 **149**	idem	complex mixture
3	 **150**	$[Ph_3PAu]NTf_2$	 **152** (40%) dr > 25:1





Scheme 2.50 Perspective: a tandem, gold-catalyzed 1,5-migration/[2 + 2] cycloaddition reaction

allenenes. It would be therefore possible that, at this stage, these allenenes underwent a [2 + 2] cycloaddition, thus leading to tricyclic compounds **155–157**, which skeletons resemble to those of some members of the caryophyllane family (Scheme 2.50, box). To go further, it would be also possible after isomerization and oxidative cleavage of the double bond to access the bicyclo[8.2.0]dodecane skeleton of raoulic acid (Scheme 2.50, box).

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