

Molecular Complexity from Polyunsaturated Substrates: The Gold Catalysis Approach

LOUIS FENSTERBANK* AND MAX MALACRIA*
*Institut Parisien de Chimie Moléculaire (UMR CNRS 7201),
UPMC Univ-Paris 06 – Sorbonne Université 4 Place Jussieu,
C. 229, 75005 Paris, France*

RECEIVED ON OCTOBER 4, 2013

CONSPECTUS

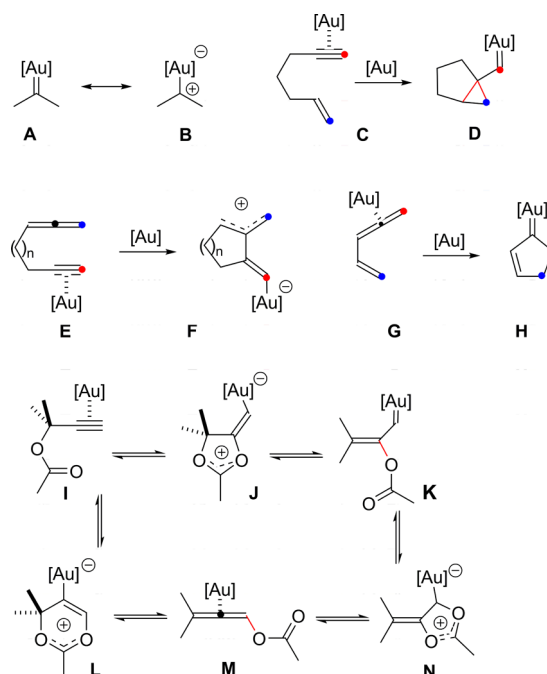
Over the last two decades, electrophilic catalysis relying on platinum(II), gold(I), and gold(III) salts has emerged as a remarkable synthetic methodology. Chemists have discovered a large variety of organic transformations that convert a great assortment of highly functionalized precursors into valuable final products. In many cases, these methodologies offer unique features, allowing access to unprecedented molecular architectures. Due to the mild reaction conditions and high function compatibility, scientists have successfully developed applications in total synthesis of natural products, as well as in asymmetric catalysis. In addition, all these developments have been accompanied by the invention of well-tailored catalysts, so that a palette of different electrophilic agents is now commercially available or readily synthesized at the bench.

In some respects, researchers' interests in developing homogeneous gold catalysis can be compared with the Californian gold rush of the 19th century. It has attracted into its fervor thousands of scientists, providing a huge number of versatile and important reports. More notably, it is clear that the contribution to the art of organic synthesis is very valuable, though the quest is not over yet. Because they rely on the intervention of previously unknown types of intermediates, new retrosynthetic disconnections are now possible.

In this Account, we discuss our efforts on the use of readily available polyunsaturated precursors, such as enynes, dienyne, allenynes, and allenenes to give access to highly original polycyclic structures in a single operation. These transformations transit via previously undescribed intermediates **A**, **B**, **D**, **F**, and **H** that will be encountered later on. All these intermediates have been determined by both ourselves and others by DFT calculations and in some cases have been confirmed on the basis of experimental data. In addition, dual gold activation can be at work in some of these transformations, for instance, from **E** to **F**.

Strikingly, we have found propargyl acetates to be particularly productive precursors. In a preliminary step upon electrophilic activation (complex **I**), they can lead to oxonium **J** or a vinylcarbenoid species **K** after 1,2-migration or complexed allenylester **M** from a formal 1,3-migration. All of them can serve as versatile entries for multievent processes. The propargyl cycle, sometimes called the golden carousel, involves species **I–N**, which lie in a close equilibrium. The control of this merry-go-round and its offshoots depends on the energy barriers associated with the subsequent reactions of these intermediates.

We illustrate these themes in this Account, focusing on the intriguing characteristics of gold catalysis.



1. Introduction

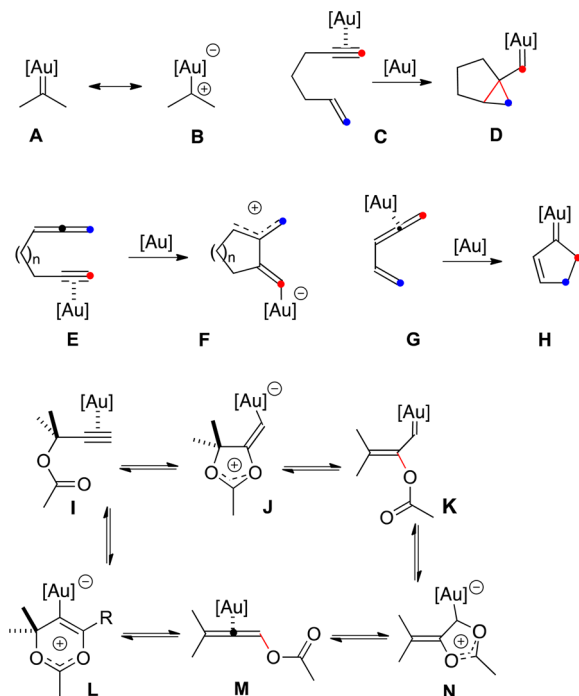
Consuming π -bonds to create σ -bonds is thermodynamically favorable. It is the foundation of a very vast number of synthetic transformations generally consisting of addition reactions. These addition processes to a π -component might involve highly reactive nucleophilic, electrophilic, or radical intermediates. They can also necessitate a catalytic activation of the π partner. Over the last two decades, we have concentrated some of our activity to the development of multiple σ -bonds formation sequences from readily available and highly modular precursors to reach molecular complexity in a one-pot operation. For that purpose, radical transformations have displayed a palette of valuable features. The addition of a radical intermediate to a π bond is generally an easy and fast process. It results in the generation of a new reactive radical intermediate, which can itself engage in a new homolytic process, and so on, yielding highly valuable cascade processes.¹ These can lead to polycyclic frameworks, including triquinanes,² as well heterocyclic platforms such as quinazolidones or guanidines,³ as shown in Scheme 1.

While working out these radical approaches, we also focused our attention on the development of PtCl_2 -catalyzed cycloisomerizations,⁴ which emerged in the 1990s with the seminal work of Chatani and Murai⁵ and were then followed by highly inspiring studies from the groups of Fürstner⁶ and Echavarren.⁷ Since that initiation time, this chemistry has fully bloomed providing remarkable entries for molecular complexity.⁸

In a collaborative project, with the group of Jose Marco-Contelles, we initially examined the behavior of polyunsaturated diene precursors **1** and **3** (two alkenes and one alkyne) bearing an oxygenated group at the propargylic position. We immediately stumbled into a fascinating dichotomy of reactivity. When exposed to 5 mol % PtCl_2 in toluene at 80 °C, methoxyether **1**, led in a single transformation creating four C–C bonds to a highly congested tetracyclic derivative **2** as a single diastereomer, which displays two fused cyclopropane moieties. In contrast, ester precursor **3** provided two products, **4** and **5**, with an untouched olefin moiety showing the 1,2-acetate migration accompanied by the formation of a cyclopropyl group (Scheme 2).⁹ Product **2** formally results from the transformation of the alkyne into two carbene intermediates, a reactivity reminiscent of previous work by Chatani and Murai.¹⁰

1,2-Ester migration products **4** and **5**, presumably involving the **I** to **N** golden carousel as calculated by Cavallo,¹¹

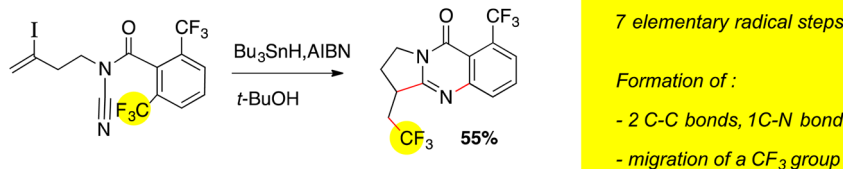
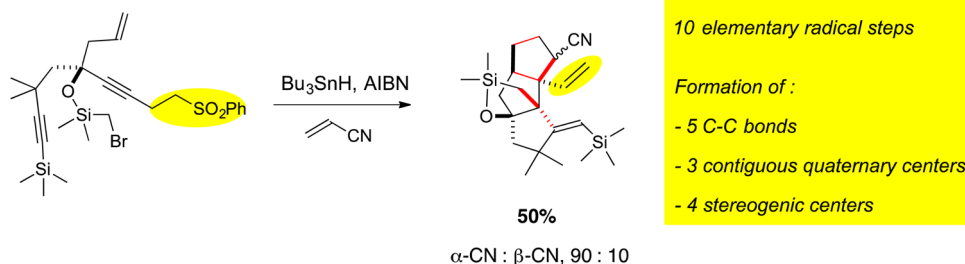
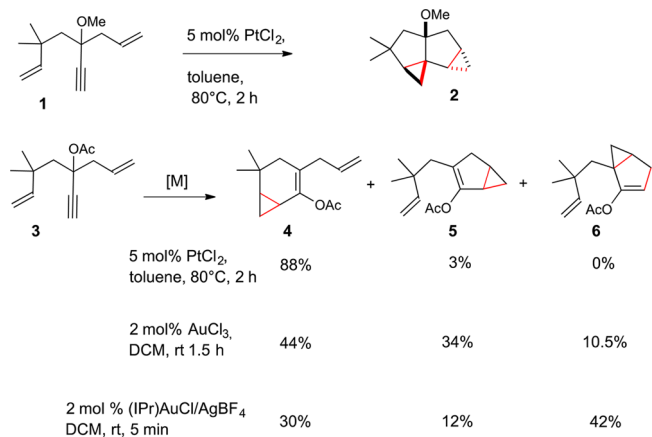
suggested a new and fecund type of transformations was available from this type of electrophilic catalysis. This proved to be completely confirmed.¹²



Additional examples of the ether–ester dichotomy were obtained from 5-en-1-yn-3-ol systems,¹³ as well as in the transannular cycloisomerization of cycloundec-5-en-1-yne precursors (*p*-nitrobenzoate ester **7** and methoxy ether **9**), giving regioisomeric keto derivatives (Scheme 3).¹⁴

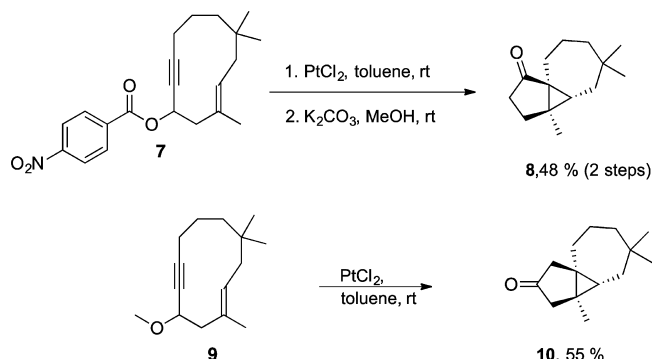
2. 1,2- or 1,3-Acetate Migration, a Versatile Entry to Molecular Complexity

2.1. Context. Interestingly, some intriguing, but barely quoted until the 2000s, literature precedents by Firmenich chemists Ohloff and Rautenstrauch showed that propargyl acetates could be easily activated with electrophilic metallic salts.¹⁵ In 1984, Rautenstrauch published a very seminal work describing the Pd(II)-catalyzed formation of cyclopentenones from 1-ethynyl-2-propenyl acetates as in **14** to **15**.¹⁶ This transformation is now coined as Rautenstrauch rearrangement or sometimes Ohloff–Rautenstrauch rearrangement to refer to another seminal work by Ohloff¹⁷ that describes the ZnCl_2 -mediated cycloisomerization of a 1,6-enynyl acetate system **11** (Scheme 4). The common element of these transformations is the intervention of a formal 1,2-*O*-acyl migration. Soon, after the renaissance of this chemistry with PtCl_2 and inspiring reports by Ohe and Uemura with ruthenium,¹⁸ it was rapidly established

SCHEME 1. Molecular Complexity via Radical Cascades That Consume π -Bonds and Create σ -Bonds**SCHEME 2.** The Ether–Ester Dichotomy in the $PtCl_2$ -Catalyzed of Dienes

by the groups of Toste¹⁹ and Fürstner,²⁰ just to name a few, that gold catalysis was highly powerful for Rautenstrauch-type rearrangements and of course for a myriad of transformations.²¹

Related to our initial findings with $PtCl_2$, and in collaboration with the group of Steven Nolan, we found that gold(I)–carbene complexes could alter the course of the reaction of **1** and favor a new rearrangement product **6**, already observed with $AuCl_3$ and ascribed to an increased stability of cationic intermediates brought by the NHC ligands on gold (Scheme 2).^{22,23} Concomitant to these developments, it was shown by us that internal alkynes bearing an acetate group at the propargylic position undergo a 1,3-OAc migration upon catalysis with $PtCl_2$, resulting in the formation of an allenyl ester derivative.²⁴ When flanked with a homoallyl

SCHEME 3. Regioisomeric Ketones from the Transannular Cycloisomerization of Macrocyclic 1,5-Enynes

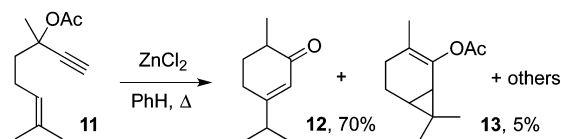
group, the latter undergo a [3,3]-rearrangement leading to triene derivatives.²⁵

The 1,3-OAc migration of propargyl acetates being used for decades with a variety of electrophilic metals (Ag^+ , Cu^+ , ...),²⁶ it was natural that gold electrophilic complexes could also catalyze this transformation as shown initially by Zhang.²⁷

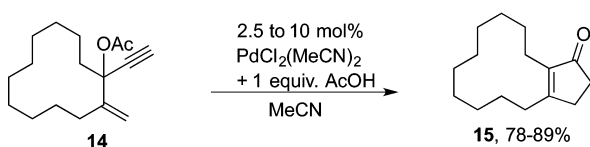
The mechanisms of the transformations of Scheme 2 have been at the center of intense debates. While the intervention of a platina- or an auro-cyclopropylcarbene intermediate of type **D** in the formation of **2** is probably admitted by everyone now on the basis of theoretical investigations and experimental evidence,^{7,28} the formation of acetate migration products (**4–6**) is still under analysis, presumably involving the **I–N** manifold. It would take too much space of this Account to discuss all the pertinent literature. Suffice it to say that there is no obvious answer, especially when considering the results of Scheme 5.

SCHEME 4. Seminal Works by Ohloff and Rautenstrauch

Ohloff, 1976



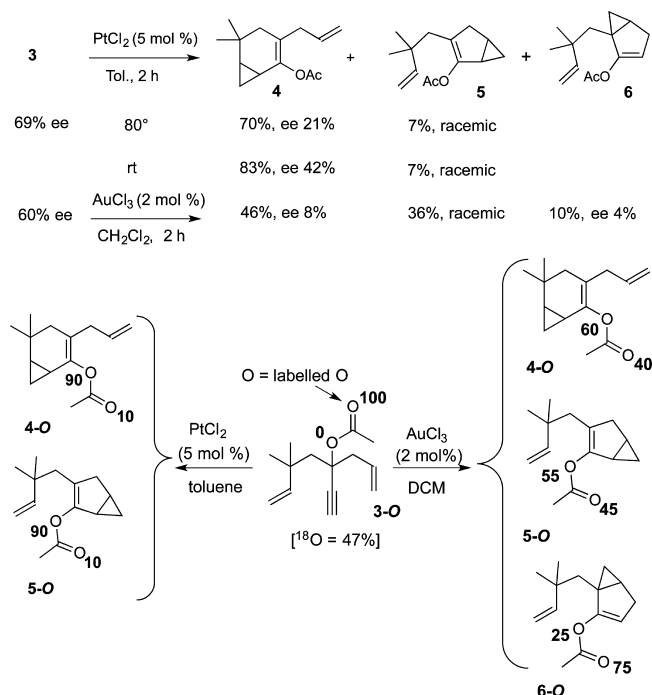
Rautenstrauch, 1984



A partial chirality transfer is observed in the formation of the cyclohexene ring **4**, while no ee was observed on the cyclopentene product **5**.²⁹ Thus, the intervention of a free carbene intermediate as first suggested is unlikely. A more concerted pathway such as an initial cycloproponation stereodirected by the acetate group and its migration or a nucleophilic attack of the vinyl function on the oxonium intermediate is presumably involved, which corroborates chirality transfer studies by the Toste, Fürstner, and Fehr groups on shorter enyne systems (1,4 and 1,5)³⁰ and calculations by de Lera³¹ and Marco-Contelles and Soriano.³² Moreover, O-labeling analyses from **3-O** illustrate all the complexity of these transformations. The PtCl_2 -catalyzed process suggests a relatively clean 1,2-transfer while gold-catalyzed ones are consistent with an important scrambling of the oxygen atoms in the acetate migration step.²⁹

2.2. Toward Polycyclic Assemblies. **2.2.1. Cyclic Propargyl Acetates As Partners.** Besides applications in the total synthesis of natural products,^{29,33,34} an attractive feature of these reactions is the opportunity to work out the straightforward preparation of polycyclic assemblies. Starting from easily accessible enynes **16** based on mixtures of diastereoisomeric cyclic templates, a completely stereoconvergent³⁵ process catalyzed by platinum(II) or gold(I) and gold(III) affords a variety of tricyclic derivatives **17** accompanied by allenylesters **18** as byproducts.³⁶ Also remarkable is the possibility to run some of these reactions in ionic liquids³⁷ and to build medium sized rings even in neat conditions as shown in entry 6 of Table 1.

2.2.2. Allenynes as Partners. In the context of the development of this electrophilic catalysis, allenyne substrates have been quite useful for us, from a synthetic point of view and as mechanistic probes.³⁸ This is illustrated in Scheme 6, which shows two cases of subtle change in the catalyst structure that dramatically alters the fate of a reaction. Thus,

SCHEME 5. Mechanistic investigations in the 1,2-OAc migration products formation

allenyne **19** will very selectively give hydriindene derivative **20** with halide containing gold and platinum catalysts, while halide free catalyst generally delivered Alder-ene products **21**.^{24,39} Both type of products presumably originate from a nucleophilic attack of the allene on the electrophilically activated alkyne moiety as in **E** to **F**. Another striking example of contrasted behavior is given with the cycloisomerization of allenynol **22**. Upon catalysis with PtCl_4 , a biscarbene reactivity as in the transformation of **9** into **10** (Scheme 3) is observed resulting from the activation of the alkyne partner and delivering fused bicyclic product **23**, while with a cationic gold catalyst, electrophilic activation of the allene partner is observed leading to a nucleophilic attack of the alcohol function to provide ether **24**.⁴⁰ Because these processes are still under investigation from a mechanistic point of view in collaboration with mass spectroscopists Yves Gimbert (Université Joseph Fourier) and Denis Lesage (UPMC),⁴¹ we have notably examined dual gold activation pathways.⁴² However, we will not cover this work in this Account, and we will focus on allenylesters partners.

Indeed, allenyl esters, whether they originate from a direct 1,3-migration or a double 1,2-migration, have proven to be highly valuable partners that can be activated with platinum or gold catalysts or act as nucleophiles with a preactivated partner such as an alkyne.

TABLE 1. Straightforward Access to Polycyclic Assemblies 17

Entry	Enyne 16	Cat. ^[a]	Products 17 and 18 and yield	
1		PtCl ₂ AuCl ₃ Au(I)	17a, 89% 63% 61%	18a, 0% 28% 31%
2		PtCl ₂ AuCl ₃ Au(I)	17b, 98% 55% 61%	18b, 0% 32% 32%
3		PtCl ₂ ^[b] AuCl ₃ Au(I)	17c, 50% 16% 11%	18c, 32% 68% 51%
4		PtCl ₂ AuCl ₃ Au(I)	17d, 98% 96% 58%	18d, 0% 0% 11%
5		PtCl ₂ AuCl ₃ Au(I)	17e, 82% ^[c] 94% -	18e, 0% 0% -
6		PtCl ₂ ^[b] AuCl ₃ Au(I)	17f, 66% 92% 53%	18f, 24% 0% 25%
	neat conditions:	PtCl ₂ , 80°C AuCl ₃ , rt	63% 46%	

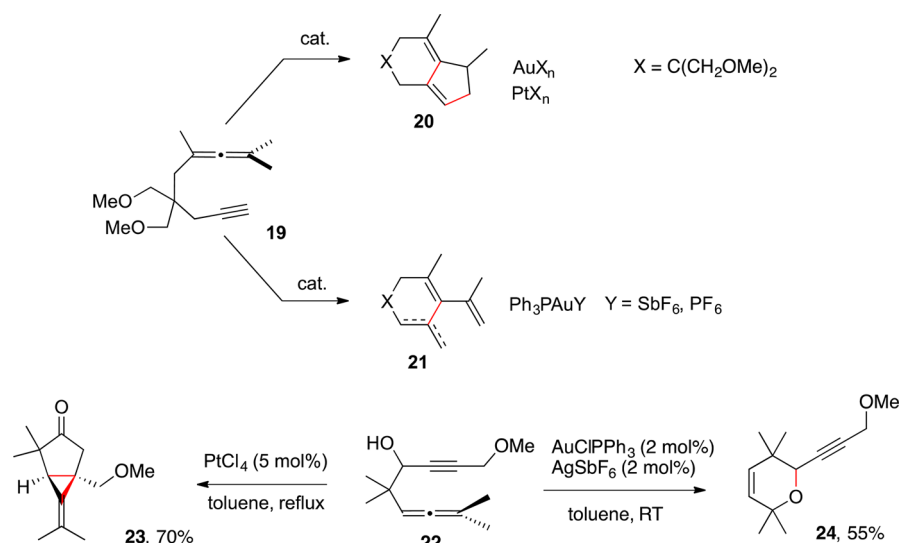
^aAu(I) refers to PPh₃AuSbF₆ generated *in situ* from an equimolar mixture of AgSbF₆ and AuSIPPh₃. Reactions were run at 80 °C in toluene with PtCl₂ (5 mol %) for 2 h and at rt in CH₂Cl₂ with gold catalysts (2 mol %) for 5–10 min. ^bReactions with PtCl₂ were run at rt for 24–48 h. ^cA minor diastereomer (<5%) was observed.

2.2.3. Entering the Equilibrium from Allenyl Esters. In a series of experiments, we could show that allenyl esters **25** and **26** are valuable precursors of previously described rearranged products **4–6** and **17b** as shown in Scheme 7. The ratio between **4** and **6** is altered, greatly favoring **6**, with the use of propargyl acetate **25** as the precursor (compare with Scheme 2). In some cases, with other cyclic templates, new rearrangement products were also observed. We could also engage allenyl ester **27** in an intermolecular cyclopropanation with styrene providing adduct **28** as a 3:1 mixture of diastereomers. All products, **4–6**, **17b**, and **28**, are further evidence of the **I–N** manifold. Other literature reports are also consistent with these findings.⁴³

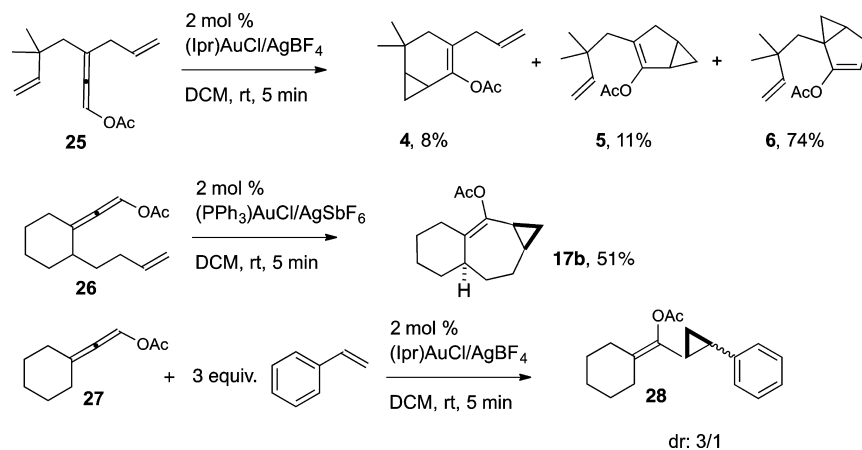
Our preliminary findings with allenene substrates of type **29** showed that these substrates can be efficiently activated upon gold catalysis as in **0** to yield to carbene intermediate

of type **H**, through a metallotropic Nazarov rearrangement. The carbene intermediate **H** has then the possibility to evolve through a hydrogen 1,2-migration delivering cyclopentadienyl substrates **30**⁴⁴ or to be trapped intramolecularly to give cyclopropyl moiety containing products **31** (Scheme 8).⁴⁵ Here also, it was judicious to apply a dual gold catalysis process starting from propargyl acetates to generate allenylester precursors, in order to limit the number of steps to reach the reactive allenene substrate. We could thus use this principle for the expedient synthesis of polyquinane systems from propargyl acetate substrates, and it also culminated in the total synthesis of the linear triquinane natural product capnellene from easily accessible precursor **32**. In a single reaction, using Echavarren's catalyst [**Au1**],⁴⁶ the tricyclic skeleton **33** of the natural product is assembled in high yield and completely stereoselectively. Following seven steps of

SCHEME 6. Various Patterns of Cycloisomerization from Allenyne Substrates



SCHEME 7. Electrophilic Activation of Allenyl Esters

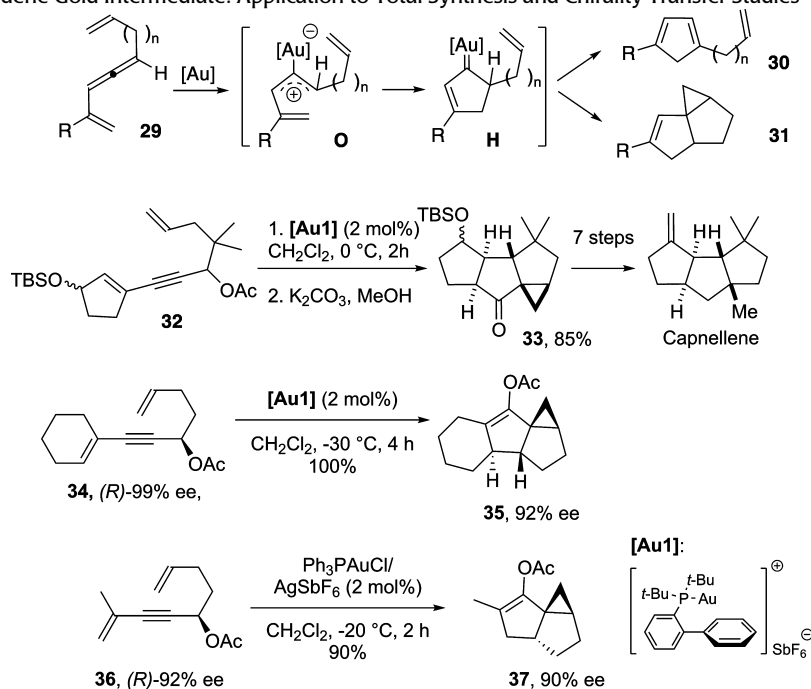


mainstream chemistry, the sesquiterpene natural product capnellene is obtained. Second, a simple enzymatic resolution of propargyl acetate substrates is possible furnishing precursors with a high enantiomeric enrichment. After a stereospecific 1,3-migration, vinylallenyl esters precursors are indeed obtained with high ee's. An interesting effect of the degree of substitution of the allenene partner was evidenced.⁴⁷ While disubstituted vinylallenes undergo the previously mentioned rearrangement with no chirality transfer,^{44a} trisubstituted allenenes stemming from precursors such as **34** and **36** provided the corresponding final products **35** and **37** with high to complete ee retention (Scheme 8).

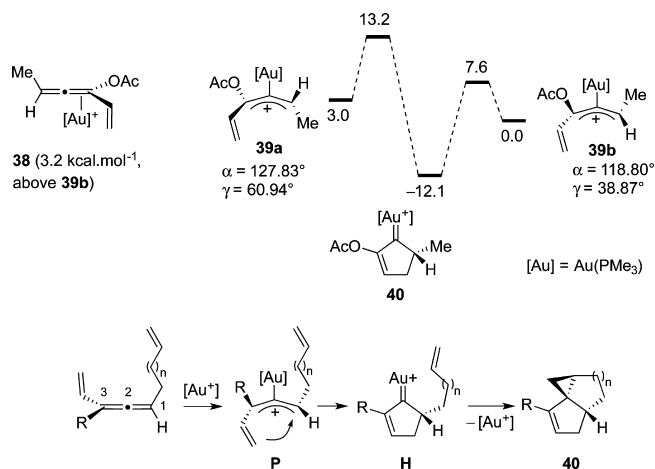
To rationalize this intriguing observation, Vincent Gandon ran DFT calculations.^{45,47,48} Coordination of gold to the central carbon of an allene may give rise to a so-called

"bent-allene" complex. An illustration of this is found in the modeling of the coordination of a cationic gold nucleus on trisubstituted vinylallenyl ester (Scheme 9). A minimum was found with twisted allylic cationic complex **39a**, compared with a diastereomeric form of it (complex **39b**) and η^2 -allene complex **38**. Very interestingly, no planar structure could be modeled in that case. This marks a sharp contrast with disubstituted allene substrates, which upon coordination with a cationic gold complex give birth to a fully delocalized allylic cation as minima. Thus, owing to allylic interactions, planar conformations of gold complexes of vinylallenes are disfavored compared with twisted ones. More importantly, the importance of bent allenes or twisted allylic cation intermediates lies in their ability to retain the chirality of the starting allene (Scheme 9). Indeed, inversion of

SCHEME 8. A Cyclopentenylidene Gold Intermediate: Application to Total Synthesis and Chirality Transfer Studies



SCHEME 9. Bent Allenes or Twisted Allylic Cations as Intermediates

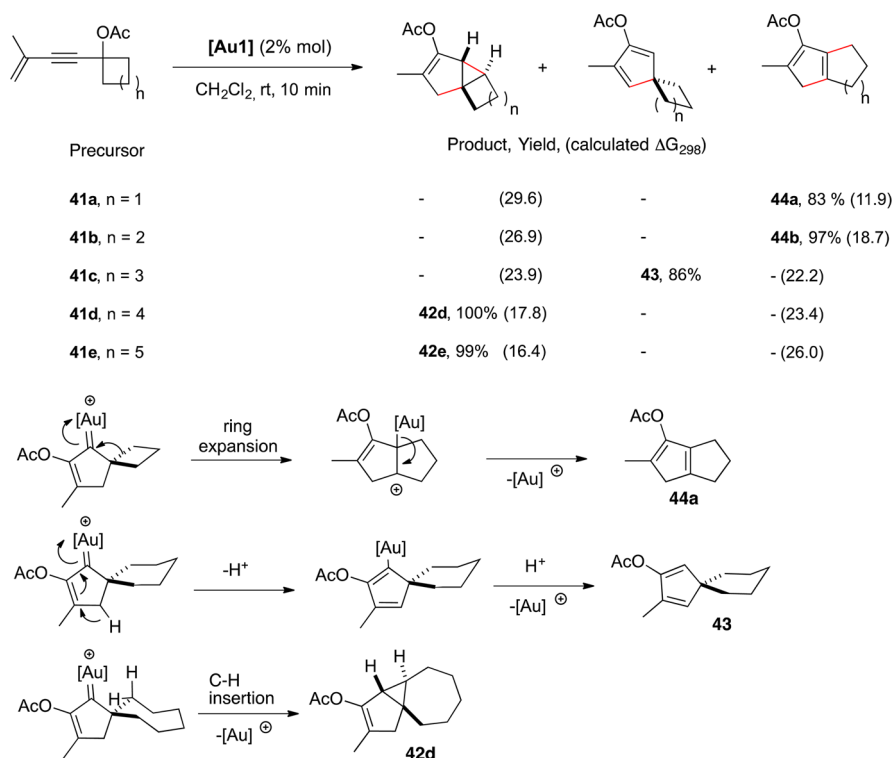


configuration of these species, and hence racemization of the substrate, would occur via planar transition states that are somehow difficult to reach if the starting allene is at least trisubstituted. In consequence, the metalla-Nazarov⁴⁹ pathway will take place with an attack of the vinyl group *anti* to the metal fragment on the configurationally stable intermediates **39b** and **P**, providing **40** and **H**, respectively. This theoretical insight is fully consistent with the experimental findings. Interestingly, we could also check that disubstituted allenes rapidly racemize in the reaction conditions.⁴⁷ Finally, it should be pointed out that transition metal complexes of tetraamino bent allenes have been isolated by Bertrand⁵⁰ and Fürstner⁵¹

and that bent allene intermediates have also been proposed in related transformations by the groups of Toste⁵² and Nevado.⁵³

We examined the possible evolution of carbenes of type **H** in the absence of a pendant olefin on cyclic precursors of type **41** (Scheme 10). The ring size proved to be a crucial factor. Thus, cyclobutyl and cyclopentyl precursors **41a** and **41b** provided bicyclic fused cyclopentadienes **44a** and **44b**. These can be rationalized by a 1,2-carbocationic rearrangement releasing ring strain and leading to ring expansion. In sharp contrast, cycloheptyl and cyclooctyl templates **41d** and **41e** provided tricyclic cyclopropyl containing products **42d** and **42e** as single diastereomers. The latter presumably originate from a rare gold catalyzed 1,3 C–H insertion process,^{54,55} presumably driven by entropic factors. Interestingly, with a six-membered ring, spiro product **43** has been obtained resulting from a prototropy sequence. In this case, no ring strain triggers the enthalpy demanding C–H insertion or the ring expansion leading to a cycloheptyl derivative, which is disfavored by both entropic and enthalpic factors. This proton shift was not possible to model; however DFT calculations were conducted on the ring expansion and ring fusion (C–H insertion) steps.

It is remarkable that the calculated energies of activation match perfectly the experimental findings. Notably, as n

SCHEME 10. Evolution of the Cyclopentenylidene Intermediate Adjacent to a Cyclic Moiety

increases, the energy to reach the ring fusion transition state decreases from 29.6 to 16.4 kcal·mol⁻¹. Conversely, the ring expansion activation energies increase from 11.9 to 26 kcal·mol⁻¹. For $n = 3$ (precursor **41c**), both processes require activation energies above 22 kcal·mol⁻¹, favoring the elimination pathway. All these evolutions also illustrate a continuum between a carbocation and a carbene in the nature of intermediates of type **B** and **H**, which has been the matter of intense debate.⁵⁶

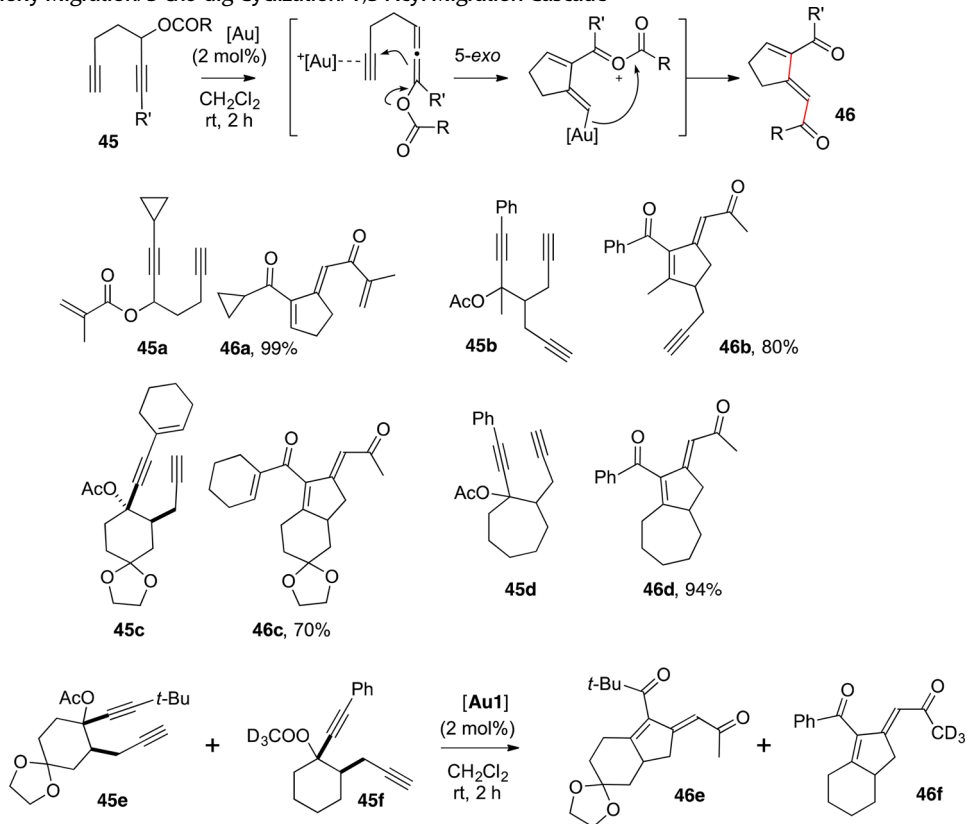
Unsymmetrical 1,6-diyne precursors **45** bearing an acetate group at the 3-propargylic position allowed confirmation of the higher reactivity of η^2 -alkyne gold complexes toward nucleophilic attack compared with other unsaturated partners (alkenes, allenes). An interesting bonus in this system is the possibility to trap an acylium cation by a vinyl gold intermediate, resulting in an overall 1,3-acyloxy migration/5-*exo*-dig cyclization/1,5-acyl migration cascade, which delivers enones **46** (Scheme 11).^{57,58}

The scope of this sequence proved to be wide as demonstrated by the efficient transformation of precursors **45a–d**. The reaction of the labeled compound **45f**, in the presence of **45e**, did not lead to any deuterium scrambling on products **46e,f** suggesting an intramolecular acylium shift. This was consistent with DFT calculations, which justified the *E* configuration of the exocyclic olefin.

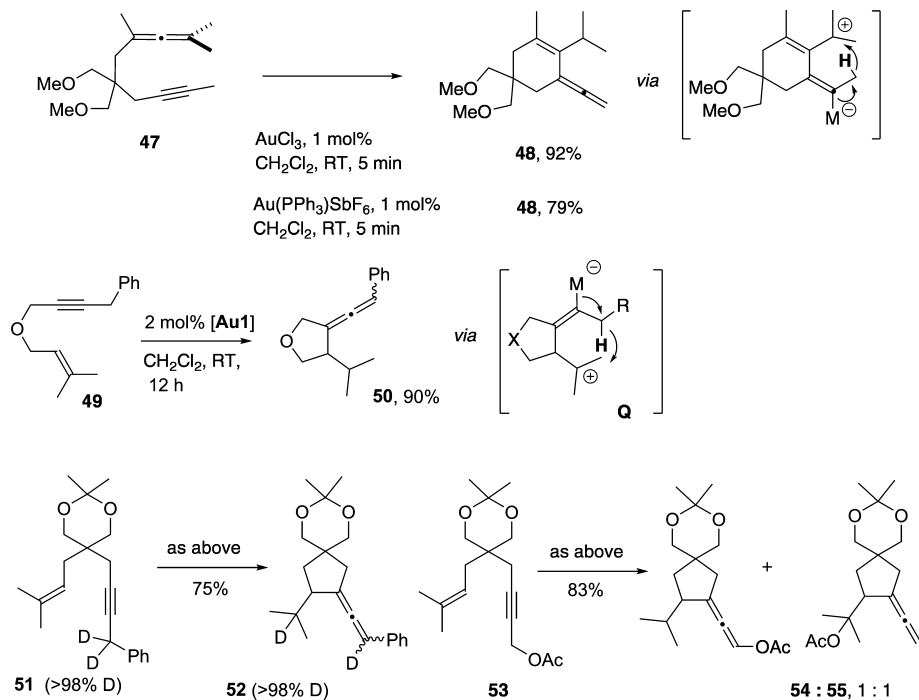
3. Other Opportunities for Molecular Complexities

3.1. Hydride Migration. 3.1.1. Allenyne Precursors. In the course of the exemplification of the platinum and gold catalyzed cycloisomerization of allenyne substrates, we encountered a very unique reactivity of precursors bearing a disubstituted alkyne moiety such as **47** (Scheme 12). An unprecedented formation of an exocyclic allene derivative (product **48**) was observed. Deuterium labeling studies²² suggested a hydride migration from the methyl group to the allylic cation originating from the nucleophilic attack of the allene onto the activated alkyne partner as in **Q**. This 1,5-hydride shift was also supported by DFT calculations. We could transpose this type of reactivity to enyne systems bearing a prenyl group for which stabilization of a carbocation is fully operating. A series of exocyclic allenes has been synthesized (products **50**, **52**, and **54**).⁵⁹ In the case of propargyl acetates, a competing 1,5-acetate migration may take place giving allene **55**.⁶⁰ Synthetically valuable hydride transfers have also been disclosed by the group of Gagosz,⁶¹ Helaja,⁶² Hashmi,⁶³ and Alcaide and Almendros,⁶⁴ and they have been applied, for instance, to the preparation of allenes.⁶⁵

3.2. Alkyl Migration. The gold-capped carbocationic intermediates of type **B** have been known to engage in different types of alkyl migration based rearrangements.

SCHEME 11. 1,3-Acyloxy Migration/5-*exo*-dig Cyclization/1,5-Acyl Migration Cascade

SCHEME 12. 1,5-Hydride Migration on 1,5-Prenylenyne To Provide Cyclic Allenes



As shown in Scheme 10, ring strain release is a good driving force for this type of evolution. On the basis of this principle

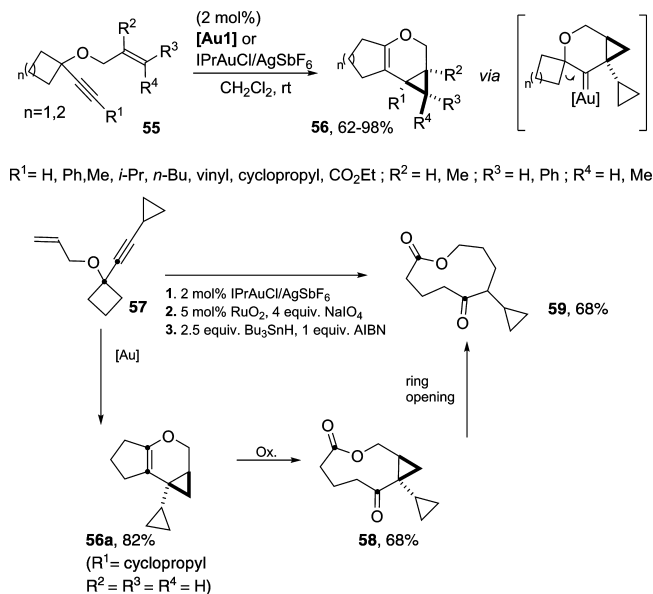
and illustrative literature reports,⁶⁶ we could devise a three step synthetic sequence leading to macrocyclic lactones

from *O*-tethered 1,6-enynes containing a strained ring at the 3-position (Scheme 13).⁶⁷ Thus, cyclobutyl or cyclopentyl precursors **55** upon cationic gold(I) catalysis reacted via intermediate ring expansion to efficiently provide fused tricyclic products **56**. The latter easily undergo oxidative cleavage of the alkene function to provide ketolactone **58**. Selective cyclopropyl ring-opening based on the intermediate

formation a *O*-stannyl ketyl radical allows the homologation of the macrocycle **59** to give **60**.

Due to its high compatibility with heteroatoms and the mild reaction conditions required, gold catalysis is a valuable methodology for the preparation of various heterocyclic systems.^{68,69} As illustrated before, allenes can be cleanly activated by cationic gold catalysts. We thought of taking advantage of this property with the use of nitrogen-based nucleophiles to provide a new synthetic access to pyrroles which remain interesting targets. We found that β -allenyl hydrazones were the proper substrates to undergo this transformation as shown by the full conversion tosylhydrazone precursor **60** in microwave conditions in the presence of Gagosz' catalyst (Scheme 14). Electrophilic activation of the allenyl moiety triggers the nucleophilic attack of the nitrogen atom. The resulting carbocationic center α to the nitrogen atom (intermediate **R**) evolves through selective alkyl migration either ethyl vs methyl (as in product **64**), phenyl vs methyl (as in product **66**), or ring expansion (as in fused bicycle **68**) to provide intermediate **62**, which delivers the aromatic *N*-aminopyrrole system after prototropy.⁷⁰

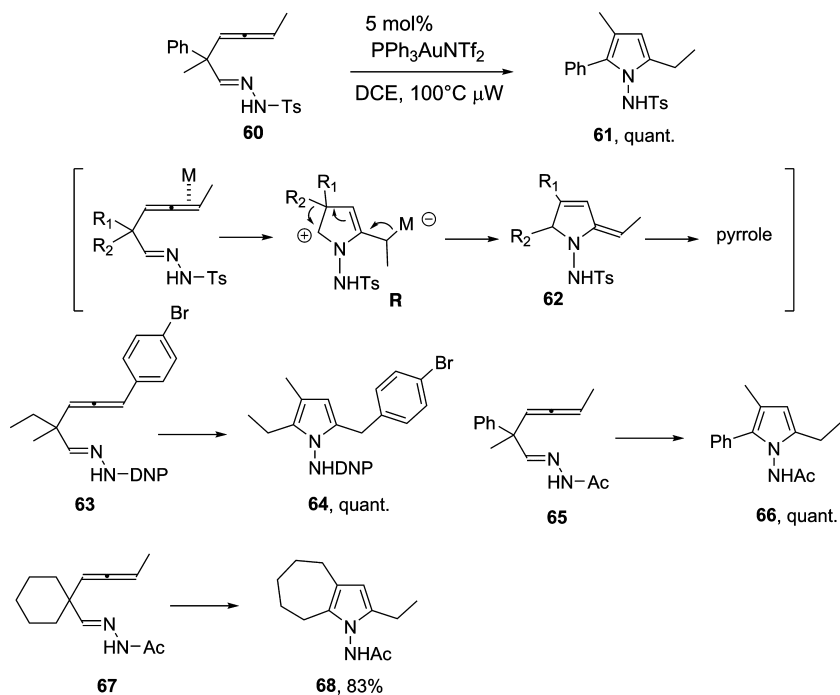
SCHEME 13. Macrolactones by Gold-Catalyzed Ring Expansions



4. Concluding Remarks

In this Account, we have focused on the utilization of gold catalysts to produce highly functionalized and complex molecular scaffolds from readily available polyunsaturated

SCHEME 14. Allenylhydrazones as Precursors of Pyrroles



starting materials. Most of these reactions have shown high efficiency and selectivity. Their mechanisms are reasonably well-understood, notably thanks to DFT modeling. Applications in heterocyclic chemistry, natural product synthesis, and asymmetric synthesis have been disclosed. Because substrate dependence is still very prominent in gold catalyzed transformation, some refinement in the control of the reactions is required. Essential progress in gold catalysis will be on ligand design in order to answer the frequent question: which catalyst for which reaction? More sustainable catalytic systems, which notably reduce the loading or allow recycling, are also highly desirable. Recent results along these lines such as the use polyoxometalate-based,⁷¹ organometallic-platform-based,⁷² and NHC-cyclodextrin-based gold catalysts⁷³ have been published by us in the context of collaborative works with the teams of Bernold Hasenknopf, Hani Amouri, and Matthieu Sollogoub, respectively, at UPMC.

We are grateful to the following funding agencies and institutions: UPMC, CNRS, ANR, IUF. Funding from Sanofi, Pierre Fabre, and Servier laboratories is also greatly acknowledged. We warmly thank all our collaborators who have participated in the electrophilic catalysis epic and whose names have appeared in the quoted publications and notably research associates from our team: Corinne Aubert, Mylène Augé, Marion Barbazanges, Erica Benedetti, Christophe Blaszykowski, Christian Brazel, Franck Brebion, Kevin Cariou, Laure-Lise Chapellet, Jean-Manuel Cloarec, Saloua Chelli, Julien Coulomb, Christine Courillon, Anne-Lise Dhimane, Nathalie Dupré, Vincent Gandon, Pierre Garcia, Jean-Philippe Goddard, Youssef Harrak, Louis-Jeanne Julien, Emmanuel Lacôte, Gilles Lemièrre, Juan Manuel Lopez Romero, Malika Makhoulf Brahmi, Rocio Martinez Mallorquin, Emily Mainetti, Frédéric Marion, Nicolas Marion, Xavier Moreau, Virginie Mouriès-Mansuy, Cyril Ollivier, Antoine Simonneau, and Serge Thorimbert.

BIOGRAPHICAL INFORMATION

Louis Fensterbank obtained his Ph.D. in 1993 from SUNY Stony Brook with Scott Sieburth. After a temporary lecturer position at UPMC in 1994, he was appointed Chargé de Recherche CNRS in 1995 in Max Malacria's team. In 2004, he obtained a professorship position at UPMC, and in 2008, he was nominated junior member of the Institut Universitaire de France.

Max Malacria obtained his Ph.D. from the University of Aix-Marseille III with Prof. Marcel Bertrand and was appointed Assistant in 1974 at the University of Lyon I with Prof. J. Goré. He was a postdoctoral fellow with Prof. K. P. C. Vollhardt at the University of California at Berkeley before moving back to the University of Lyon I in 1983. In 1988, he became a Full Professor at the UPMC. In 1991,

he joined the Institut Universitaire de France. Since 2011, he has been the director of the ICSN in Gif sur Yvette.

FOOTNOTES

*E-mail: louis.fensterbank@upmc.fr.

*Fax: (+33) 1-4427-7360. E-mail: max.malacria@upmc.fr.

The authors declare no competing financial interest.

The manuscript was written through contributions of both authors. Both authors have given approval to the final version of the manuscript.

REFERENCES

- For a recent review on radical cascades, see: Baralle, A.; Baroudi, A.; Daniel, M.; Fensterbank, L.; Goddard, J.-P.; Lacôte, E.; Larraufie, M.-H.; Maestri, G.; Malacria, M.; Ollivier, C. Radical Cascade Reactions. In *Encyclopedia of Radicals in Chemistry, Biology and Materials*; Studer, A., Chatgililoglu, C., Eds.; John Wiley & Sons: Chichester, U.K., 2012; Vol. 2, pp 729–766.
- (a) Devin, P.; Fensterbank, L.; Malacria, M. From Acyclic Precursors to Linear Triquinanes through a Diastereoselective One-Pot Process. A New Illustration of the Synthetic Power of Radical Cascades. *J. Org. Chem.* **1998**, *63*, 6764–6765. (b) Dhimane, A.-L.; Aïssa, C.; Malacria, M. Transannular Radical Cascade as an Approach to the Diastereoselective Synthesis of Linear Triquinane. *Angew. Chem., Int. Ed.* **2002**, *41*, 3284–3287.
- (a) Larraufie, M.-H.; Courillon, C.; Ollivier, C.; Lacote, E.; Malacria, M.; Fensterbank, L. Radical Migration of Substituents of Aryl Groups on Quinazolinones Derived from N-Acyl Cyanamides. *J. Am. Chem. Soc.* **2010**, *132*, 4381–4387. (b) Larraufie, M.-H.; Ollivier, C.; Fensterbank, L.; Malacria, M.; Lacôte, E. Radical Synthesis of Guanidines from N-Acyl Cyanamides. *Angew. Chem., Int. Ed.* **2010**, *49*, 2178–2181.
- For reviews, see: (a) Zhang, L.; Sun, J.; Kozmin, S. Gold and Platinum Catalysis of Enyne Cycloisomerization. *Adv. Synth. Catal.* **2006**, *348*, 2271–2296. (b) Fürstner, A.; Davies, P. W. Catalytic Carbophilic Activation: Catalysis by Platinum and Gold π Acids. *Angew. Chem., Int. Ed.* **2007**, *46*, 3410–3449. (c) Michelet, V.; Toulllec, P. Y.; Genêt, J.-P. Cycloisomerization of 1,n-Enynes: Challenging Metal-Catalyzed Rearrangements and Mechanistic Insights. *Angew. Chem., Int. Ed.* **2007**, *47*, 4268–4315.
- Chatani, N.; Morimoto, T.; Muto, T.; Murai, S. Highly Selective Skeletal Reorganization of 1,6- and 1,7-Enynes to 1-Vinylcycloalkenes Catalyzed by $[\text{RuCl}_2(\text{CO})_3]_2$. *J. Am. Chem. Soc.* **1994**, *116*, 6049–6050. (b) Chatani, N.; Furukawa, N.; Sakurai, H.; Murai, S. PtCl_2 -Catalyzed Conversion of 1,6-, 1,7-Enynes to 1-Vinylcycloalkenes. Anomalous Bond Connection in Skeletal Reorganization of Enynes. *Organometallics* **1996**, *15*, 901–903.
- Fürstner, A.; Stelzer, F.; Szillat, H. Platinum-Catalyzed Cycloisomerization Reactions of Enynes. *J. Am. Chem. Soc.* **2001**, *123*, 11863–11869.
- Mendez, M.; Munoz, M. P.; Nevado, C.; Cardenas, D. J.; Echavarren, A. M. Cyclizations of Enynes Catalyzed by PtCl_2 or Other Transition Metal Chlorides: Divergent Reaction Pathways. *J. Am. Chem. Soc.* **2001**, *123*, 10511–10520.
- Fürstner, A. Gold and Platinum Catalysis—a Convenient Tool for Generating Molecular Complexity. *Chem. Soc. Rev.* **2009**, *38*, 3208–3221.
- (a) Mainetti, E.; Mouriès, V.; Fensterbank, L.; Malacria, M.; Marco-Contelles, J. The Effect of a Hydroxy Protecting Group on the PtCl_2 -Catalyzed Cyclization of Dienynes—A Novel, Efficient, and Selective Synthesis of Carbocycles. *Angew. Chem., Int. Ed.* **2002**, *41*, 2132–2135. (b) Marco-Contelles, J.; Arroyo, N.; Anjum, S.; Mainetti, E.; Marion, N.; Cariou, K.; Lemièrre, G.; Mouriès, V.; Fensterbank, L.; Malacria, M. PtCl_2 - and PtCl_4 -Catalyzed Cycloisomerization of Polyunsaturated Precursors. *Eur. J. Org. Chem.* **2006**, 4618–4633.
- Chatani, N.; Kataoka, K.; Murai, S.; Furukawa, N.; Seki, Y. Construction of Novel Polycyclic Ring Systems by Transition-Metal-Catalyzed Cycloisomerization of Ene-Ene-Ynes. Interception of a Carbenoid Intermediate in Skeletal Reorganization of Enynes. *J. Am. Chem. Soc.* **1998**, *120*, 9104–9105.
- Correa, A.; Marion, N.; Fensterbank, L.; Malacria, M.; Nolan, S. P.; Cavallo, L. Golden Carousel in Catalysis: The Cationic Gold/Propargylic Ester Cycle. *Angew. Chem., Int. Ed.* **2008**, *47*, 718–721.
- For reviews, see: (a) Marco-Contelles, J.; Soriano, E. Recent Developments in the Metal-Catalyzed Reactions of Metallocarbenoids from Propargylic Esters. *Chem.—Eur. J.* **2007**, *13*, 1350–1357. (b) Marion, N.; Nolan, S. P. Propargylic Esters in Gold Catalysis: Access to Diversity. *Angew. Chem., Int. Ed.* **2007**, *46*, 2750–2752.
- Harrak, Y.; Blaszykowski, C.; Bernard, M.; Cariou, K.; Mainetti, M.; Mouriès, V.; Dhimane, A. L.; Louis Fensterbank, L.; Malacria, M. PtCl_2 -Catalyzed Cycloisomerizations of 5-En-1-yn-3-ol Systems. *J. Am. Chem. Soc.* **2004**, *126*, 8656–8657.
- Blaszykowski, C.; Harrak, Y.; Gonçalves, M.-H.; Cloarec, J.-M.; Anne-Lise Dhimane, A.-L.; Fensterbank, L.; Malacria, M. PtCl_2 -Catalyzed Transannular Cycloisomerization of 1,5-Enynes: A New Efficient Regio- and Stereocontrolled Access to Tricyclic Derivatives. *Org. Lett.* **2004**, *6*, 3771–3774.
- Note that the Firmenich tradition of electrophilic activation of acetylenes has been pursued by Charles Fehr who recently retired from these laboratories. See refs **30c** and **33c**.

- 16 Rautenstrauch, V. 2-Cyclopentenones from 1-Ethynyl-2-propenyl Acetates. *J. Org. Chem.* **1984**, *49*, 950–952.
- 17 Strickler, H.; Davis, J. B.; Ohloff, G. Zur Cyclisierung von Dehydrolinalylacetat in Gegenwart von Zinkchlorid. *Helv. Chim. Acta* **1976**, *59*, 1328–1332.
- 18 (a) Miki, K.; Ohe, K.; Uemura, S. A New Ruthenium-Catalyzed Cyclopropanation of Alkenes Using Propargylic Acetates As a Precursor of Vinylcarbenoids. *Tetrahedron Lett.* **2003**, *44*, 2019–2022. (b) Miki, K.; Ohe, K.; Uemura, S. Ruthenium-Catalyzed Cyclopropanation of Alkenes Using Propargylic Carboxylates as Precursors of Vinylcarbenoids. *J. Org. Chem.* **2003**, *68*, 8505–8513.
- 19 Shi, X.; Gorin, D. J.; Toste, F. D. Synthesis of 2-Cyclopentenones by Gold(I)-Catalyzed Rautenstrauch Rearrangement. *J. Am. Chem. Soc.* **2005**, *127*, 5802–5803.
- 20 Mamane, V.; Gress, T.; Krause, H.; Fürstner, A. Platinum- and Gold-Catalyzed Cycloisomerization Reactions of Hydroxylated Enynes. *J. Am. Chem. Soc.* **2004**, *126*, 8654–8655.
- 21 There has been a huge number of valuable reviews on gold catalysis. For a recent monograph covering most aspects of gold catalysis, see: *Modern Gold Catalyzed Synthesis*; Hashmi, A. S. K., Toste, F. D., Eds.; Wiley VCH: Weinheim, Germany, 2012.
- 22 Marion, N.; de Frémont, P.; Lemièrre, G.; Stevens, E. D.; Fensterbank, L.; Malacria, M.; Nolan, S. P. Au(I)-Catalyzed Cycloisomerization of 1,5-Enynes Bearing a Propargylic Acetate: Formation of Unexpected Bicyclo[3.1.0]hexene. *Chem. Commun.* **2006**, 2048–2050.
- 23 For a review on the benefits brought by NHCs in homogenous gold catalysis, see: Gatineau, D.; Goddard, J.-P.; Mouries-Mansuy, V.; Fensterbank, L. When NHC Ligands Make a Difference in Gold Catalysis. *Isr. J. Chem.* **2013**, *53*, 892–900.
- 24 Cadran, N.; Cariou, K.; Hervé, G.; Aubert, C.; Fensterbank, L.; Malacria, M.; Marco-Contelles, J. PtCl₂-Catalyzed Cycloisomerizations of Allenynes. *J. Am. Chem. Soc.* **2004**, *126*, 3408–3409.
- 25 Cariou, K.; E. Mainetti, E.; Fensterbank, L.; Malacria, M. Tandem PtCl₂ Catalyzed —Thermal [3,3] Rearrangements of Enyne Acetates. *Tetrahedron* **2004**, *60*, 9745–9755.
- 26 For reviews, see: (a) Shu, X.-Z.; Shu, D.; Schienebeck, C. M.; Tang, W. Rhodium-Catalyzed Acyloxy Migration of Propargylic Esters in Cycloadditions, Inspiration from the Recent “Gold Rush”. *Chem. Soc. Rev.* **2013**, *41*, 7698–7711. (b) Shiroodi, R. K.; Gevorgyan, V. Metal-Catalyzed Double Migratory Cascade Reactions of Propargylic Esters and Phosphates. *Chem. Soc. Rev.* **2013**, *42*, 4991–5001.
- 27 Zhang, L. Tandem Au-Catalyzed 3,3-Rearrangement-[2 + 2] Cycloadditions of Propargylic Esters: Expedient Access to Highly Functionalized 2,3-Indoline-Fused Cyclobutanes. *J. Am. Chem. Soc.* **2005**, *127*, 16804–16805.
- 28 (a) Soriano, E.; Ballesteros, P.; Marco-Contelles, J. Theoretical Investigation on the Mechanisms of the PtCl₂-Mediated Cycloisomerization of Polyfunctionalized 1,6-Enynes. 1. Role of the Propargylic Substituents. *Organometallics* **2005**, *24*, 3172–3181. (b) Witham, C. A.; Mauleon, P.; Shapiro, N. D.; Sherry, B. D.; Toste, F. D. Gold(I)-Catalyzed Oxidative Rearrangements. *J. Am. Chem. Soc.* **2007**, *129*, 5838–5839.
- 29 Marion, N.; Lemièrre, G.; Correa, A.; Costabile, C.; Ramon, R. S.; Moreau, X.; de Frémont, P.; Dahmane, R.; Hours, A.; Lesage, D.; Tabet, J.-C.; Goddard, J.-P.; Gandon, V.; Cavallo, L.; Fensterbank, L.; Malacria, M.; Nolan, S. P. Gold- and Platinum-Catalyzed Cycloisomerization of Enynyl Esters versus Allenenyl Esters: An Experimental and Theoretical Study. *Chem.—Eur. J.* **2009**, *15*, 3243–3260.
- 30 (a) Shi, X.; Gorin, D. J.; Toste, F. D. Synthesis of 2-Cyclopentenones by Gold(I)-Catalyzed Rautenstrauch Rearrangement. *J. Am. Chem. Soc.* **2005**, *127*, 5802–5803. (b) Fürstner, A.; Hannen, P. Platinum- and Gold-Catalyzed Rearrangement Reactions of Propargylic Acetates: Total Syntheses of (–)- α -Cubebene, (–)-Cubebol, Sesquicarene and Related Terpenes. *Chem.—Eur. J.* **2006**, *12*, 3006–3019. (c) Fehr, C.; Galindo, J. Synthesis of (–)-Cubebol by Face-Selective Platinum-, Gold-, or Copper-Catalyzed Cycloisomerization: Evidence for Chirality Transfer. *Angew. Chem., Int. Ed.* **2006**, *45*, 2901–2904.
- 31 Nieto Faza, O.; Carlos Silva Lopez, C.; Alvarez, R.; de Lera, A. R. Mechanism of the Gold(I)-Catalyzed Rautenstrauch Rearrangement: A Center-to-Helix-to-Center Chirality Transfer. *J. Am. Chem. Soc.* **2006**, *128*, 2434–2437.
- 32 Soriano, E.; Ballesteros, P.; Marco-Contelles, J. Theoretical Investigation on the Mechanisms of the PtCl₂-Mediated Cycloisomerization of Polyfunctionalized 1,6-Enynes. 2. Propargylic Carboxylates. *Organometallics* **2005**, *24*, 3182–3191.
- 33 (a) Anjum, S.; Marco-Contelles, J. PtCl₂-Mediated Cycloisomerization of Unsaturated Propargylic Carboxylates. *Tetrahedron* **2005**, *61*, 4793–4803. (b) Fürstner, A.; Hannen, P. Carene Terpenoids by Gold-Catalyzed Cycloisomerization Reactions. *Chem. Commun.* **2004**, 2546–2547. (c) Fehr, C.; Vuagnoux, M.; Buzas, A.; Arpagaus, J.; Sommer, H. Gold- and Copper-Catalyzed Cycloisomerizations towards the Synthesis of Thujopsanone-Like Compounds. *Chem.—Eur. J.* **2011**, *17*, 6214–6220.
- 34 For a review, see: Rudolph, M.; Hashmi, A. S. K. Gold Catalysis in Total Synthesis—An Update. *Chem. Soc. Rev.* **2012**, *41*, 2448–2462.
- 35 An exception to the stereoconvergent nature of this was found with 6-membered ring templates to make decalin product: Harrak, Y.; Makhlof, M.; Azzaro, S.; Mainetti, E.; Lopez Romero, J. M.; Cariou, K.; Gandon, V.; Goddard, J.-P.; Malacria, M.; Fensterbank, L. New Elements in the Gold(I)-Catalyzed Cycloisomerization of Enynyl Ester Derivatives Embedding a Cyclohexane Template. *J. Organomet. Chem.* **2011**, *696*, 388–399.
- 36 Moreau, X.; Goddard, J.-P.; Bernard, M.; Lemièrre, G.; López-Romero, J. M.; Mainetti, E.; Marion, N.; Mouries, V.; Thorimbert, S.; Fensterbank, L.; Malacria, M. Gold- vs. Platinum-Catalyzed Polycyclizations by O-Acyl Migration. Solvent-Free Reactions. *Adv. Synth. Catal.* **2008**, *350*, 43–48.
- 37 Moreau, X.; Hours, A.; Fensterbank, L.; Goddard, J.-P.; Malacria, M.; Thorimbert, S. Use of Ionic Liquids in the Platinum- And Gold-Catalyzed Cycloisomerization of Enyne Systems. *J. Organomet. Chem.* **2009**, *694*, 561–565.
- 38 Aubert, C.; Fensterbank, L.; Garcia, P.; Malacria, M.; Simonneau, A. The Transition Metal Catalyzed Cycloisomerizations of 1,n-Allenynes and -Allenenes. *Chem. Rev.* **2011**, *111*, 1954–93.
- 39 Lemièrre, G.; Gandon, V.; Agenet, N.; Goddard, J.-P.; de Kozak, A.; Aubert, C.; Fensterbank, L.; Malacria, M. Gold(I)- and gold(III)-catalyzed cycloisomerization of allenynes. *Angew. Chem., Int. Ed.* **2006**, *45*, 7596–7599.
- 40 Zriba, R.; Gandon, V.; Aubert, C.; Fensterbank, L.; Malacria, M. Alkyne versus Allene Activation in Platinum- and Gold-Catalyzed Cycloisomerization of Hydroxylated 1,5-Allenynes. *Chem.—Eur. J.* **2008**, *14*, 1482–1491.
- 41 For recent examples of mechanistic studies, see: (a) Simonneau, A.; Jaroschik, F.; Lesage, D.; Karanik, M.; Guillot, R.; Malacria, M.; Tabet, J.-C.; Goddard, J.-P.; Fensterbank, L.; Gandon, V.; Gimbert, Y. Tracking Gold Acetylides in Gold(I)-Catalyzed Cycloisomerization Reactions of Enynes. *Chem. Sci.* **2011**, *2*, 2417–2422. (b) Baumgarten, S.; Lesage, D.; Gandon, V.; Goddard, J.-P.; Malacria, M.; Tabet, J.-C.; Gimbert, Y.; Fensterbank, L. The Role of Water in Platinum-Catalyzed Cycloisomerization of 1,6-Enynes: A Combined Experimental and Theoretical Gas Phase Study. *ChemCatChem* **2009**, *1*, 138–143. (c) Gimbert, Y.; Fensterbank, L.; Gandon, V.; Goddard, J.-P.; Lesage, D. Ligand Effect in Platinum-Catalyzed Cycloisomerization of 1,6-Enynes: Water or Carbon Monoxide, a Similar Role despite Distinct Electronic Properties? *Organometallics* **2013**, *32*, 374–376.
- 42 For dual gold activation on 1,5-allenynes, see: (a) Cheong, P. H.-Y.; Morganelli, P.; Luzung, M. R.; Houk, K. N.; Toste, F. D. Gold-Catalyzed Cycloisomerization of 1,5-Allenynes via Dual Activation of an Ene Reaction. *J. Am. Chem. Soc.* **2008**, *130*, 4517–4526. For a review on dual gold activation, see: (b) Braun, I.; Asiri, A. M.; Hashmi, A. S. K. Gold Catalysis 2.0. *ACS Catal.* **2013**, *3*, 1902–1907.
- 43 Gung, B. W.; Bailey, L. N.; Craft, D. T.; Barnes, C. L.; Kirschbaum, K. Preparation and Characterization of Two New N-Heterocyclic Carbene Gold(I) Complexes and Comparison of Their Catalytic Activity to (IPr)AuCl. *Organometallics* **2010**, *29*, 3450–3456.
- 44 For similar approaches, see: (a) Lee, J. H.; Toste, F. D. Gold(I)-Catalyzed Synthesis of Functionalized Cyclopentadienes. *Angew. Chem., Int. Ed.* **2007**, *46*, 912–914. (b) Funami, H.; Kusama, H.; Iwasawa, N. Preparation of Substituted Cyclopentadienes through Platinum(II)-Catalyzed Cyclization of 1,2,4-Trienes. *Angew. Chem., Int. Ed.* **2007**, *46*, 909–911. (c) Zhang, L.; Wang, S. Efficient Synthesis of Cyclopentenones from Enynyl Acetates via Tandem Au(I)-Catalyzed 3,3-Rearrangement and the Nazarov Reaction. *J. Am. Chem. Soc.* **2006**, *128*, 1442–1443.
- 45 (a) Lemièrre, G.; Gandon, V.; Cariou, K.; Fukuyama, T.; Dhimane, A.-L.; Fensterbank, L.; Malacria, M. Tandem Gold(I)-Catalyzed Cyclization/Electrophilic Cyclopropanation of Vinyl Allenes. *Org. Lett.* **2007**, *9*, 2207–2211. (b) Lemièrre, G.; Gandon, V.; Cariou, K.; Hours, A.; Fukuyama, T.; Dhimane, A.-L.; Fensterbank, L.; Malacria, M. Generation and Trapping of Cyclopentenylidene Gold Species: Four Pathways to Polycyclic Compounds. *J. Am. Chem. Soc.* **2009**, *131*, 2993–3006.
- 46 Herrero-Gomez, E.; Nieto-Oberhuber, C.; Lopez, S.; Benet-Buchholz, J.; Echavarren, A. M. Cationic η^1/η^2 -Gold(I) Complexes of Simple Arenes. *Angew. Chem., Int. Ed.* **2006**, *45*, 5455–5459.
- 47 Gandon, V.; Lemièrre, G.; Hours, A.; Fensterbank, L.; Malacria, M. The Role of Bent Acyclic Allene Gold Complexes in Axis-to-Center Chirality Transfers. *Angew. Chem., Int. Ed.* **2008**, *47*, 7534–7538.
- 48 Fensterbank, L.; Malacria, M.; Gandon, V. Activation of Allenes by Gold Complexes: a Theoretical Standpoint. In *Computational Mechanisms of Au and Pt Catalyzed Reactions*; Soriano, E., Marco-Contelles, J., Eds.; Topics in Current Chemistry; Springer-Verlag: Berlin: Heidelberg, 2011; Vol. 302, pp 1–26.
- 49 (a) For a recent allene Nazarov reaction, see: (a) Alcaide, B.; Almendros, P.; Alonso, J. M.; Fernandez, I. Carbocyclization versus Oxycyclization on the Metal-Catalyzed Reactions of Oxyallenyl C3-Linked Indoles. *J. Org. Chem.* **2013**, *78*, 6688–6701. For a recent review, see: (b) Tius, M. A. Allene ether Nazarov cyclization. *Chem. Soc. Rev.* **2014**, *1039/c3cs60333d*.
- 50 Dyker, A. C.; Lavallo, V.; Donnadiu, B.; Bertrand, G. Synthesis of an Extremely Bent Acyclic Allene (A “Carbodicarbene”): A Strong Donor Ligand. *Angew. Chem., Int. Ed.* **2008**, *47*, 3206–3209.
- 51 Fürstner, A.; Alcarazo, M.; Goddard, R.; Lehmann, C. W. Coordination Chemistry of Ene-1,1-diamines and a Prototype “Carbodicarbene”. *Angew. Chem., Int. Ed.* **2008**, *47*, 3210–3214.
- 52 Mauleon, P.; Krinsky, J. L.; Toste, F. D. Mechanistic Studies on Au(I)-Catalyzed [3,3]-Sigmatropic Rearrangements using Cyclopropane Probes. *J. Am. Chem. Soc.* **2009**, *131*, 4513–4520.
- 53 Garayalde, D.; Enrique Gomez-Bengoa, E.; Huang, X.; Goeke, A.; Nevado, C. Mechanistic Insights in Gold-Stabilized Nonclassical Carbocations: Gold-Catalyzed Rearrangement of 3-Cyclopropyl Propargylic Acetates. *J. Am. Chem. Soc.* **2010**, *132*, 4720–4730.

- 54 For a review on gold-mediated C–H activation processes, see: de Haro, T.; Nevado, C. On Gold-Mediated C–H Activation Processes. *Synthesis* **2011**, 2530–2539.
- 55 For other relevant examples of 1,3 C–H insertion gold-catalyzed insertion processes, see: (a) Horino, Y.; Yamamoto, T.; Ueda, K.; Kuroda, S.; Toste, F. D. Au(I)-Catalyzed Cycloisomerizations Terminated by sp^3 C–H Bond Insertion. *J. Am. Chem. Soc.* **2009**, *131*, 2809–2811. (b) Escribano-Cuesta, A.; Lopez-Carrillo, V.; Janssen, D.; Echavarren, A. E. Gold-Catalyzed Reactions of 1,5- and 1,6-Enynes with Carbonyl Compounds: Cycloaddition vs. Metathesis. *Chem.—Eur. J.* **2009**, *15*, 5646–5650. (c) Chunia, S.; Liu, R.-S. Gold-Catalyzed 1,3-Addition of a sp^3 -Hybridized C–H Bond to Alkenylcarbenoid Intermediate. *J. Am. Chem. Soc.* **2008**, *130*, 16488–16489.
- 56 (a) Hashmi, A. S. K. "High Noon" in Gold Catalysis: Carbene versus Carbocation Intermediates. *Angew. Chem., Int. Ed.* **2008**, *47*, 6754–6756. (b) Echavarren, A. M. Carbene or Cation. *Nat. Chem.* **2009**, *1*, 431–433. (c) Seidel, G.; Mynott, R.; Fürstner, A. Elementary Steps of Gold Catalysis: NMR Spectroscopy Reveals the Highly Cationic Character of a "Gold Carbenoid". *Angew. Chem., Int. Ed.* **2009**, *48*, 2510–2513. (d) Benitez, D.; Shapiro, N. D.; Tkatchouk, E.; Wang, Y.; Goddard, W. A.; Toste, F. D. A Bonding Model for Gold(I) Carbene Complexes. *Nat. Chem.* **2009**, *1*, 482–486.
- 57 Leboeuf, D.; Simonneau, A.; Aubert, C.; Malacria, M.; Gandon, V.; Fensterbank, L. Gold-Catalyzed 1,3-Acyloxy Migration/5-exo-dig Cyclization/1,5-Acyl Migration of Diynyl Esters. *Angew. Chem., Int. Ed.* **2011**, *50*, 6868–6871.
- 58 For some recent work on 1,6-diynes acetates, see: (a) Rao, W.; Koh, M. J.; Li, D.; Hirao, H.; Chan, P. W. H. Gold-Catalyzed Cycloisomerization of 1,6-Diyne Carbonates and Esters to 2,4a-Dihydro-1H-fluorenes. *J. Am. Chem. Soc.* **2013**, *135*, 7926–7932. (b) Lauterbach, T.; Gatzweiler, S.; Nösel, P.; Rudolph, M.; Rominger, F.; Hashmi, A. S. K. Carbene Transfer — A New Pathway for Propargylic Esters in Gold Catalysis. *Adv. Synth. Catal.* **2013**, *355*, 2481–2487.
- 59 Harrak, Y.; Simonneau, A.; Malacria, M.; Gandon, V.; Fensterbank, L. Gold(I)-Catalyzed Cycloisomerisation of 1,6-Enynes into Functionalised Allenes. *Chem. Commun.* **2010**, *46*, 865–867.
- 60 For a gold-catalyzed sequence involving a 1,6-OAc migration, see: Hashmi, A. S. K.; Yang, W.; Yu, Y.; Hansmann, M. M.; Rudolph, M.; Rominger, F. Gold-Catalyzed Formal 1,6-Acyloxy Migration Leading to 3,4-Disubstituted Pyrrolidin-2-ones. *Angew. Chem., Int. Ed.* **2013**, *52*, 1329–1332.
- 61 Jurberg, I. D.; Odabachian, Y.; Gagosz, F. Hydroalkylation of Alkynyl Ethers via a Gold(I)-Catalyzed 1,5-Hydride Shift/Cyclization Sequence. *J. Am. Chem. Soc.* **2010**, *132*, 3543–3552.
- 62 Melchionna, M.; Martin Nieger, M.; Helaja, J. Isolation of a Zwitterionic Diene Gold Complex Intermediate in the Direct Conversion of Enyne–Amines to Cyclopentadienes. *Chem.—Eur. J.* **2010**, *16*, 8262–8267.
- 63 Hashmi, A. S. K.; Braun, I.; Nösel, P.; Schädlich, J.; Wieteck, M.; Rudolph, M.; Rominger, F. Simple Gold-Catalyzed Synthesis of Benzofulvenes—gem-Diaurated Species as "Instant Dual-Activation" Precatalysts. *Angew. Chem., Int. Ed.* **2012**, *51*, 4456–4460.
- 64 Alcaide, B.; Almendros, P.; Cembellin, S.; Martínez del Campo, T.; Fernández, I. Gold-Catalyzed Tuning of Reactivity in Allenes: 9-endo Hydroarylation versus Formal 5-exo Hydroalkylation. *Chem. Commun.* **2013**, *49*, 1282–1284.
- 65 Bolte, B.; Odabachian, Y.; Gagosz, F. Gold(I)-Catalyzed Rearrangement of Propargyl Benzyl Ethers: A Practical Method for the Generation and in Situ Transformation of Substituted Allenes. *J. Am. Chem. Soc.* **2010**, *132*, 7294–7296.
- 66 For a review, see: Garayalde, D.; Nevado, C. Synthetic Applications of Gold-Catalyzed Ring Expansions. *Beilstein J. Org. Chem.* **2011**, *7*, 767–780.
- 67 Simonneau, A.; Harrak, Y.; Jeanne-Julien, L.; Lemièrre, G.; Mouriès-Mansuy, V.; Goddard, J.-P.; Malacria, M.; Fensterbank, L. Ring Expansions Within the Gold-Catalyzed Cycloisomerization of O-Tethered 1,6-Enynes. Application to the Synthesis of Natural-Product-like Macrocycles. *ChemCatChem* **2013**, *5*, 1096–1099.
- 68 For reviews, see: (a) Rudolph, M.; Hashmi, A. S. K. Heterocycles from Gold Catalysis. *Chem. Commun.* **2011**, 6536–6544. (b) Shen, H. C.; Graham, T. H. Gold-Catalyzed Formation of Heterocycles — an Enabling New Technology for Medicinal Chemistry. *Drug Discovery Today: Technol.* **2013**, *10*, e3–e14.
- 69 For heterocycles synthesis catalyzed by platinum or gold from our group, see: (a) Cariou, K.; Ronan, B.; Mignani, S.; Fensterbank, L.; Malacria, M. From $PtCl_2$ - and Acid-Catalyzed to Uncatalyzed Cycloisomerization of 2-Propargyl Anilines: Access to Functionalized Indoles. *Angew. Chem., Int. Ed.* **2007**, *46*, 1881–1884. (b) Simonneau, A.; Garcia, P.; Goddard, J.-P.; Mouriès-Mansuy, V.; Malacria, M.; Fensterbank, L. Combination of Gold Catalysis and Selectfluor for the Synthesis of Fluorinated Nitrogen Heterocycles. *Beilstein J. Org. Chem.* **2011**, *7*, 1379–1386.
- 70 Benedetti, E.; Lemièrre, G.; Chapellet, L.-L.; Penoni, A.; Palmisano, G.; Malacria, M.; Goddard, J.-P.; Fensterbank, L. Gold(I)-Catalyzed Cyclization of β -Allenylhydrazones: An Efficient Synthesis of Multisubstituted N-Aminopyrroles. *Org. Lett.* **2010**, *12*, 4396–4399.
- 71 Dupré, N.; Brazel, C.; Fensterbank, L.; Malacria, M.; Thorimbert, S.; Hasenknopf, B.; Lacôte, E. Self-Buffering Hybrid Gold-Polyoxometalate Catalysts for the Catalytic Cyclization of Acid-Sensitive Substrates. *Chem.—Eur. J.* **2012**, *18*, 12962–12965.
- 72 Dubarle-Offner, J.; Barbazanges, M.; Augé, M.; Desmarests, C.; Moussa, J.; Axet, M. R.; Ollivier, C.; Aubert, C.; Fensterbank, L.; Gandon, V.; Malacria, M.; Gontard, G.; Amouri, H. Gold Compounds Anchored to a Metalated Arene Scaffold: Synthesis, X-ray Molecular Structures, and Cycloisomerization of Enyne. *Organometallics* **2013**, *32*, 1665–1673.
- 73 Guitet, M.; Zhang, P.; Marcelo, F.; Tugny, C.; Jiménez-Barbero, J.; Buriez, O.; Amatore, C.; Mouriès-Mansuy, V.; Goddard, J.-P.; Fensterbank, L.; Zhang, Y.; Roland, S.; Ménand, M.; Sollogoub, M. NHC-Capped Cyclodextrins (ICyDs): Insulated Metal Complexes, Commutable Multicoordination Sphere, and Cavity-Dependent Catalysis. *Angew. Chem., Int. Ed.* **2013**, *52*, 7213–7218.