ChemPubSoc Europe
DOI: 10.1002/cctc.201801201
CHEMCATCHEM Reviews

VIP *Very Important Paper*

Generation of Gold(I) Carbenes by Retro-Buchner Reaction: From Cyclopropanes to Natural Products Synthesis

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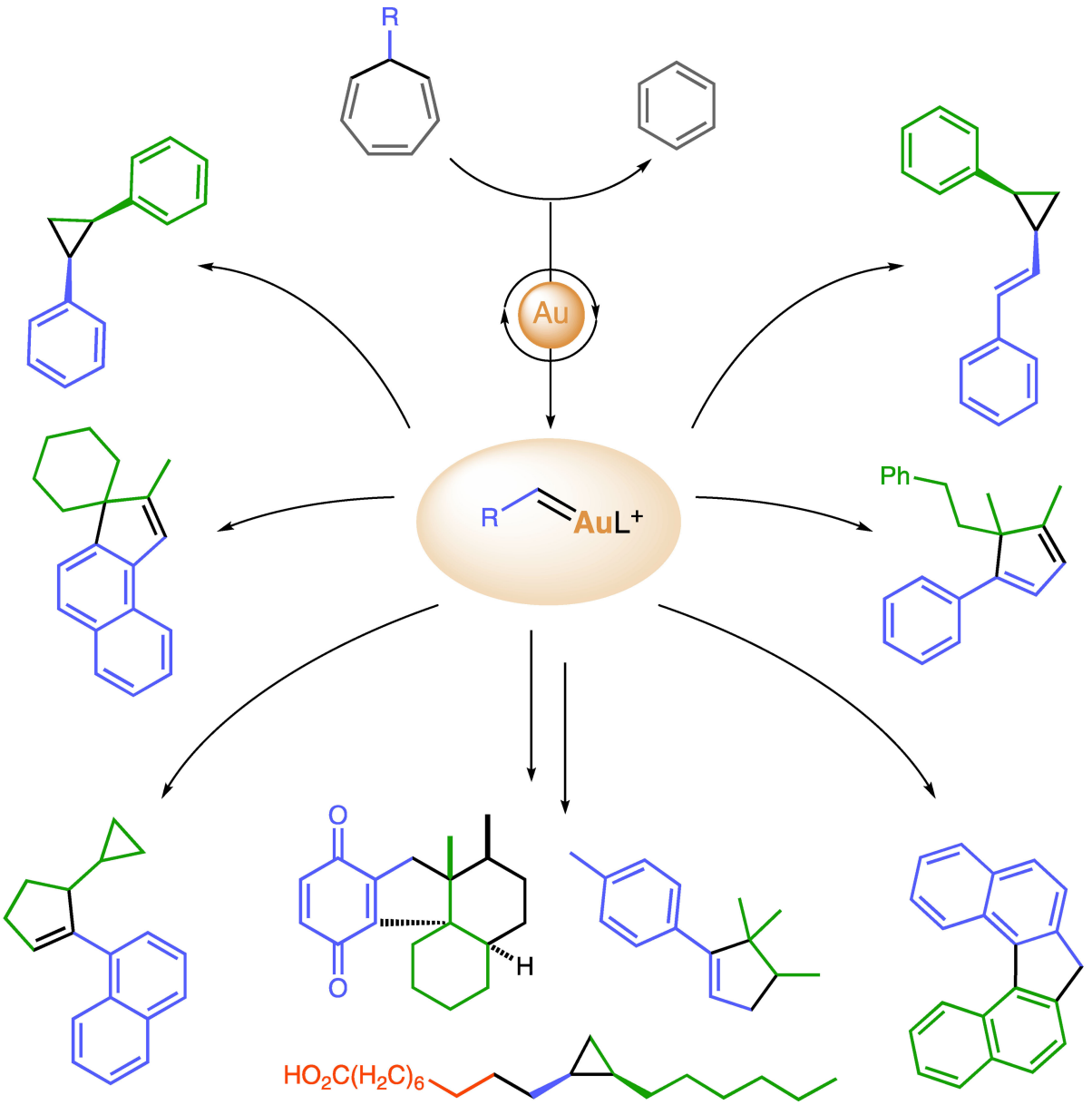


The gold(I)-catalyzed retro-Buchner (decarbenation, retrocyclopropanation) reaction of 7-substituted cycloheptatrienes has emerged as a safe and powerful alternative for the generation of gold(I) carbenes. These carbenes can cyclopropanate alkenes, take part in intramolecular reactions, or engage in higher cycloadditions with different partners, giving rise to a wide range of relevant structures. This review covers the developments made on the generation of gold(I) carbenes *via* decarbenation reactions, and the applications of these reactions in organic synthesis.

1. Introduction

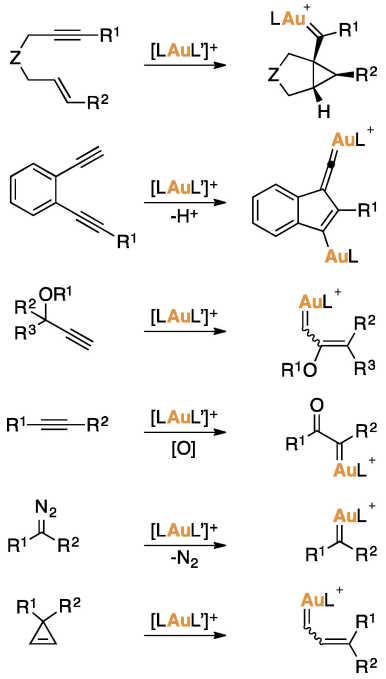
Over the past two decades, homogeneous gold(I) catalysis has arisen as one of the most powerful tools for the construction of molecular complexity. Since its dawn in 1998, when a groundbreaking report on the gold(I)-catalyzed hydration of alkynes was published,[1] gold catalysis became a hot topic in organic chemistry. Due to its π-Lewis acidity, cationic gold(I) complexes have been extensively used to selectively activate π C–C bonds, especially alkynes, triggering chemical transformations that give rise to complex structures that are difficult to access by other means, in an atom-economic fashion.[2] The total synthesis of biologically relevant products stands out among the applications that have been found for these new methodologies based on homogeneous gold catalysis.[3]

Many gold(I)-catalyzed transformations have been proposed to proceed *via* highly electrophilic cationic gold(I) carbenes as intermediates (Scheme 1).[2,4,5] Despite the importance of these

Scheme 1. Carbocation and carbene resonance forms used to describe gold (I) carbenes. L = phosphines, phosphites or NHC carbene ligands among others.

intermediates, their structure is somewhat controversial and has been interpreted by different authors as gold(I)-stabilized carbocations or gold(I) carbenes (Scheme 1).[6,7] The extension of the π-backbonding interaction, which is at the core of the discussion, influences the relative contributions of the carbene and the carbocation resonance forms, and therefore, the reactivity of these electrophilic species. These different interpretations can be understood because it was not until recently that examples of well-defined cationic gold(I) carbenes were spectroscopically and structurally characterized.[8,9] These recent findings have provided new insight into the electronic structure of the Au–C bond in these key gold(I) intermediates. Ultimately, experimental and theoretical work has shown that the nature of gold(I) carbenes is better accounted for as a continuum that ranges from metal-stabilized singlet carbenes to metal-coordinated carbocations.[6c,7]

Gold(I) carbenes can be generated through different methods in catalytic transformations (Scheme 2). Among these



Scheme 2. General methods for the catalytic generation of gold(I) carbenes.

strategies, the cycloisomerization of 1,*n*-enynes has attracted special attention to the synthetic community, and has been extensively explored in many different contexts.[2f,h,j,10]

Other examples include the cycloaddition of diene-allenes to form gold vinylidene intermediates,[11] the 1,2-acyloxy migration of propargylic carboxylates or ethers,[12] and the nucleophilic addition of *N*-oxides or sulfoxides to electrophilic (η^2-alkyne)gold(I) complexes.[13,14] In addition to reactions involving alkynes, transformations based on gold(I)-catalyzed decomposition of diazocompounds,[5,15] and opening of cyclopropenes[16] have also been proposed to form these highly electrophilic species.

Driven by the high interest of the scientific community on the plethora of transformations that are proposed to take place

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This manuscript is part of the Anniversary Issue in celebration of 10 years of ChemCatchem.

through metal carbene intermediates, great efforts have been made to generate them in an efficient manner. In spite of this fact, most strategies present limitations, such as lack of generality (very specific substrates are employed, such as 1,*n*-enynes), the requirement of potentially undesired functional groups that end up in the reaction products, or the preparation and handling of potentially dangerous materials, such as diazo compounds.

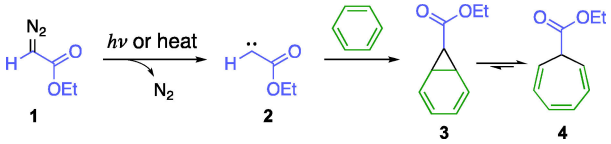
In 2008, Chen and coworkers observed for the first time the formation and reactivity of a gold carbene *via* retro-cyclopropanation in gas phase, using electrospray ionization tandem mass spectroscopy.[17,18] Two years later, our group reported the first formation of gold(I) carbenes in solution *via* retro-cyclopropanation reaction.[19] Soon after, based on this initial finding, a general methodology for the cyclopropanation of olefins based on the retro-Buchner reaction of 7-aryl-1,3,5-cycloheptatrienes was developed.[20] This retro-cyclopropanation (decarbenation) process represents a safe and general way of generating gold(I) carbenes without the need of introducing stabilizing or undesired functional groups.

Following these initial results, a wide range of synthetic methodologies were developed based on the generation of gold(I) carbenes by retro-cyclopropanation. In this review, we cover the different transformations that were discovered over the past 10 years through the generation of gold(I) carbenes *via* retro-cyclopropanation, especially using the retro-Buchner reaction of 7-substituted cycloheptatrienes.

2. Historical Perspective

2.1. The Buchner Ring Expansion

The Buchner ring expansion is the reaction of a diazo compound, originally ethyl diazoacetate (**1**), with an arene, such as benzene, to form a cycloheptatriene (Scheme 3). This



Scheme 3. Buchner ring expansion of benzene.

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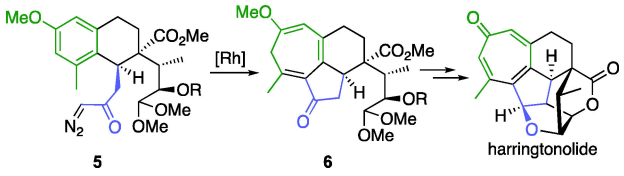
Cristina García-Morales was born in Moguer (Huelva, Spain) in 1990. After a one-year period as an Erasmus student at Strathclyde University (Glasgow, United Kingdom), she received her B.S. degree in Chemistry from Universidad de Huelva (Huelva, Spain) in 2013. After earning her MSc at the Universitat Rovira i Virgili (Tarragona, Spain) she has been a PhD student in the group of Prof. Antonio M. Echavarren at the Institute of Chemical Research of Catalonia (ICIQ), where she works on enantioselective gold(I) catalysis and the characterization of highly reactive gold(I) carbenes.

Prof. Dr Antonio M. Echavarren was born in Bilbao (Spain) and received his PhD at the Universidad Autónoma de Madrid (UAM, 1982) with Prof. Francisco Fariña. After a postdoctoral stay in Boston College with Prof. T. Ross Kelly, he joined the UAM as an Assistant Professor. Following a two years period as a NATO-fellow with Prof. John K. Stille in Fort Collins (Colorado State University), he joined the Institute of Organic Chemistry of the CSIC in Madrid. In 1992 he returned to the UAM as a Professor of Organic Chemistry and in 2004 he moved to Tarragona as a Group Leader at the Institute of Chemical Research of Catalonia (ICIQ). He has been Liebig Lecturer (Organic Division, German Chemical Society, 2006), Abbot Lecturer in Organic Chemistry (University of Illinois at Urbana-Campaign, 2009), Schulich Visiting Professor (Technion, Haifa, 2011), Sir Robert Robinson Distinguished Lecturer (University of Liverpool, 2011), Novartis Lecturer in Organic Chemistry (Massachusetts Institute of Technology, 2015) and Kurt Alder Lecturer 2017 (University of Cologne). In 2012 he got a European Research Council Advanced Grant. Prof. Echavarren is a member of the International Advisory Board of Organic & Biomolecular Chemistry, Chemical Society Reviews, Advanced Synthesis and Catalysis, and Organic Letters, member of the Editorial Board of Chemistry European Journal, and Associate Editor of Chemical Communications. He is a Fellow of the Royal Society of Chemistry. He received the 2004 Janssen-Cylag Award in Organic Chemistry and the 2010 Gold Medal of the Royal Spanish Chemical Society and an Arthur C. Cope Scholar Award from the ACS. He is the President of the Spanish Royal Society of Chemistry (RSEQ).

reaction was first reported by Eduard Buchner (not to be confused with Ernst Büchner, the industrial chemist that invented the Büchner funnel)[21] and Theodor Curtius, in 1885.[22] The original reaction involves first a thermal or photochemical decomposition of the diazo compound generating a free carbene (**2**) while nitrogen is released. This carbene can cyclopropanate benzene giving a norcaradiene derivative (**3**), which undergoes a 6-electron disrotatory electrocyclic opening to form a cycloheptatriene (**4**).

Nowadays, the aforementioned harsh thermal or photochemical conditions are usually avoided, and instead, metal-based catalytic systems are employed, using mainly copper or rhodium complexes.[23] The use of this strategy allows for an excellent control of the regioselectivity during the carbene addition, resulting in the exclusive formation of the kinetic non-conjugated 7-substituted-1,3,5-cycloheptatriene.[22c,23]

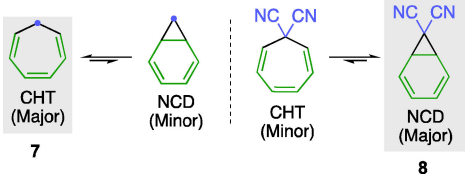
The Buchner reaction has found different applications in synthesis over the years.[24] An excellent example was reported by Mander and coworkers, who used a rhodium-catalyzed Buchner ring expansion to accomplish the total synthesis of (+)-hainanolidol and (+)-harringtonolide, two diterpenoids that display a tropone ring in their skeleton (Scheme 4).[25]



Scheme 4. Buchner reaction for the total synthesis of harringtonolide.

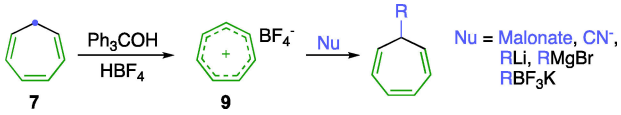
2.2. Cycloheptatrienes and its Valence Tautomerism

1,3,5-Cycloheptatriene (CHT) is an organic compound that has recurrently interested chemists since its first preparations from tropine or from cycloheptanone more than 100 years ago.[26] Even though cycloheptatrienes have found some uses in organic synthesis,[27] photochemistry,[28] and as ligands in coordination chemistry,[29] one of the main appeals to the scientific community has been the study of their valence tautomerism. Monocyclic cycloheptatrienes are in equilibrium with their corresponding norcaradiene (NCD) tautomers, through a thermally allowed disrotatory electrocyclic ring opening (Scheme 5).[30]



Scheme 5. The cycloheptatriene–norcaradiene equilibrium.

The position of this equilibrium is largely dictated by the nature of the substituents on the different positions of the cycloheptatriene or norcaradiene ring. Thus, for example, while simple 1,3,5-cycloheptatriene **7** is almost exclusively in the CHT form under standard conditions, the introduction of two CN groups at the 7-position gives rise to a thermodynamically stable norcaradiene (**8**).[30b] The nature of the different substituents also determines the geometry of cycloheptatrienes, which is usually non-planar and undergoes interconversion between two boat conformations. On the other hand, the ion that results from the abstraction of a hydride from 1,3,5-cycloheptatriene, the tropylium cation, is a planar, 6π electron-aromatic species that forms stable salts with different counter-anions.[31] These salts, especially tropylium tetrafluoroborate (**9**), are easily prepared[32] and can be used to synthesize cycloheptatriene derivatives (Scheme 6).[33] The reaction of tropylium

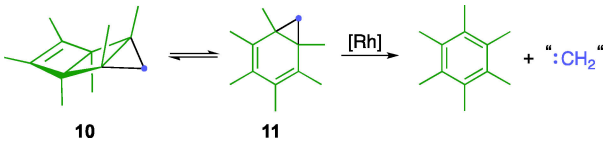


Scheme 6. Preparation and general reactivity of tropylium tetrafluoroborate.

tetrafluoroborate with carbon-based nucleophiles such as enolates of acetylketones or malonate esters,[34] inorganic cyanides,[35] or organometallic reagents[20] gives easy access to a wide range of non-conjugated 7-substituted-1,3,5-cycloheptatrienes.

2.3. First Examples of the Generation of Carbenes from Cycloheptatrienes

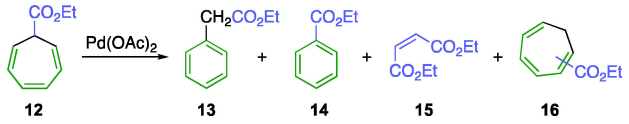
Previous to our discovery of the gold(I)-catalyzed retro-Buchner reaction, there were very few examples in which carbenes were released from cycloheptatriene or norcaradiene derivatives. Thus, it was shown in 1973 that 1,2,4,5,6,7-hexamethyltricyclo [3.2.0.0^{2,4}]hept-6-ene **10**, which is in equilibrium with its norcaradiene tautomer **11**, reacts in the presence of $[Rh(CO)_2Cl]_2$ to give hexamethylbenzene quantitatively (Scheme 7).[36]



Scheme 7. Rh-catalyzed retro-cyclopropanation releasing hexamethylbenzene.

The carbene released on this process could be trapped to some extent with cyclohexene. Other less methylated substrates were unsuccessful in affording the corresponding arene, and the possibility of using the released methylene carbene in any kind of synthetically useful manner was not clear by the time.

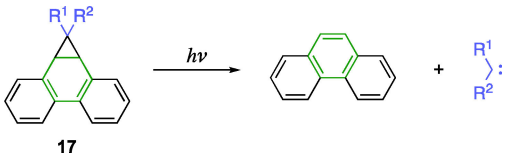
Twenty years later, as part of a study on the palladium(II)-promoted isomerization of 7-substituted 1,3,5-cycloheptatrienes *via* hydrogen-shift, it was found that the treatment of 7-ethoxycarbonyl-1,3,5-cycloheptatriene (**12**) with 1 equiv. of $Pd(OAc)_2$ gave ring-contraction products (**13** and **14**), along with isomerization products of the starting cycloheptatriene (**16**).[37] Interestingly, it was possible to detect traces (4% yield) of diethyl maleate **15**, a product that could have presumably been formed by the dimerization of the released palladium carbene (Scheme 8).



Scheme 8. Different products detected after the treatment of **12** with $Pd(OAc)_2$.

Additionally, Gassman and Johnson reported in 1976 the cleavage of cyclopropanes to form metal carbenes with low efficiency by using highly electrophilic $PhWCl_3/RAlCl_2$ (R = Et, Cl), demonstrating the possibility of carrying out a cyclopropane–olefin cross-metathesis.[38] Furthermore, it was also possible to carry out a retro-cyclopropanation of highly strained bicyclo[1.1.0]butanes with Ni(0) or Rh(I) *via* oxidative addition reactions.[39]

Without the need of transition metals, free carbenes could also be generated by retro-cyclopropanation of phenanthrene derivatives such as **17** under photochemical conditions (Scheme 9).[40]



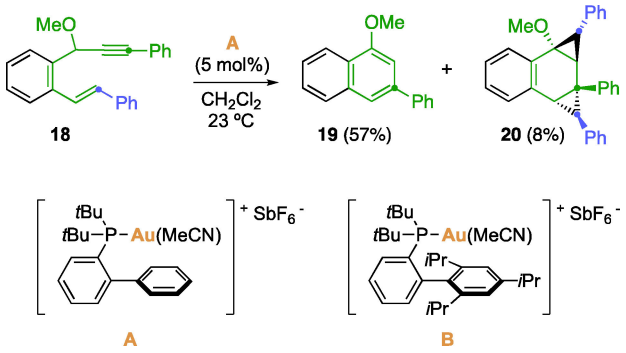
Scheme 9. Generation of carbenes from phenanthrene derivatives under photochemical conditions.

This retro-cyclopropanation reaction resembles a special case of a retro-Buchner process, in which the starting cycloheptatriene derivative is fused to two aromatic rings (**17**), releasing phenanthrene instead of a simple arene. These reactions have been further studied recently by other groups, using both experimental and theoretical methods.[41] However, the difficulty of the preparation of this type of phenanthrene derivatives makes this way of generating carbenes impractical for its application in organic synthesis. It was not until homogeneous gold(I) catalysis came into play that the generation of carbenes *via* retro-Buchner reaction could be applied in the development of new useful synthetic methodologies.

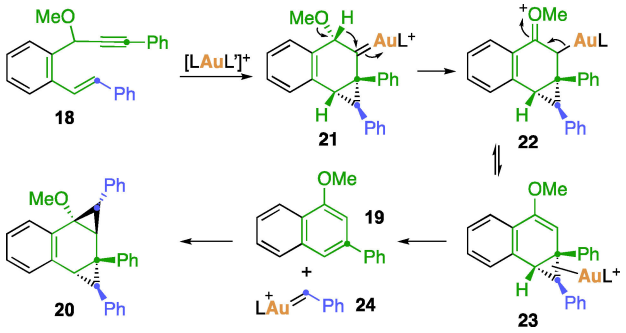
3. Generation of Gold(I) Carbenes by Retro-Cyclopropanation

3.1. Gold(I)-Carbenes by Retro-Buchner Reaction

In 2010, when we were studying the cycloisomerization of phenyl-linked 1,6-enynes (**18**), our group discovered a high yielding synthesis of naphthalenes (**19**) through an annulation/fragmentation process, together with the formation of **20**, a product containing two arylcyclopropane rings (Scheme 10).[19]



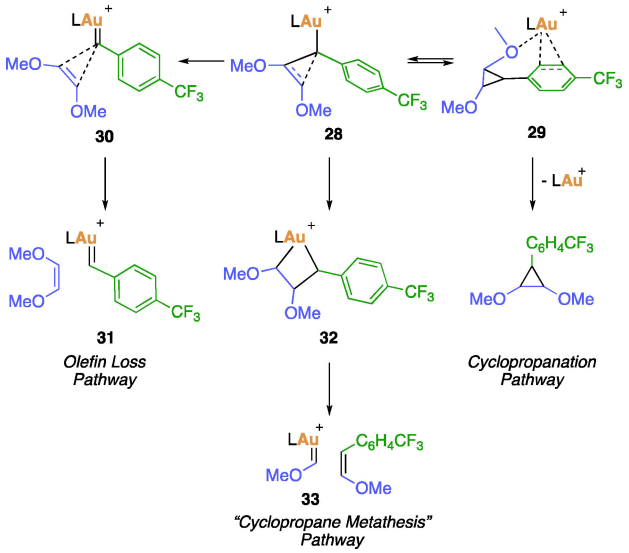
Scheme 10. Synthesis of naphthalenes by annulation–fragmentation of phenyl-linked 1,6-enynes. Structure of the two cationic phosphine complexes usually employed in the gold(I)-catalyzed retro-Buchner reaction.



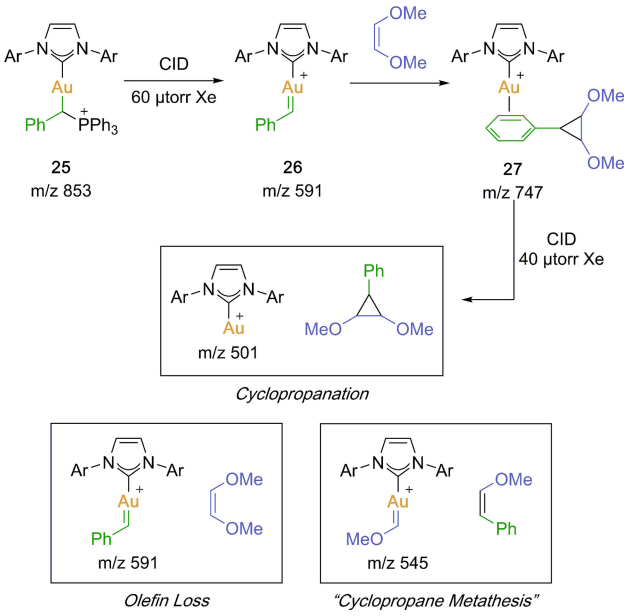
Scheme 11. Annulation–fragmentation mechanism of 1,6-enynes. [LAuL']$^+$ = **A**.

These results are consistent with a mechanism proceeding through a 6-*endo*-dig cyclization of the 1,6-enyne promoted by gold to form cyclopropyl gold(I) carbene **21** (Scheme 11), followed by a 1,2-H shift to form alkenyl gold(I) complex **22**, which after protodeauration is in equilibrium with **23**.[19] This intermediate, which can also be considered as a benzo-fused electron-rich norcaradiene, then undergoes a retro-cyclopropanation process, releasing the main reaction product (naphthalene **19**) and aryl gold(I) carbene **24**. The free gold(I) carbene **24** may then cyclopropanate another unit of **23**, delivering the corresponding biscyclopropane.

This mechanism was further supported by the synthesis and isolation of metal-free intermediate **23** and its treatment with 5 mol% of cationic gold(I) complex [(JohnPhos)Au(MeCN)]SbF_6,



Scheme 13. Mechanisms proposed for the three reaction pathways found for benzylidene gold(I) complexes in gas phase.



Scheme 12. Generation and reactivity of aryl gold(I) carbene **26** in gas phase.

giving 45% yield of naphthalene **19** and 38% yield of biscyclopropane **23**.[19] These results demonstrated, for the first time, the feasibility of generating gold(I) carbenes in solution from cycloheptatriene/norcaradiene derivatives. Furthermore, in 2015, Hashmi and coworkers reported a rearrangement of diynes to give naphthalenes, which presumably proceeds though a cycloisomerization phase, an alkyl migration, and finally a decarbenation (retro-Buchner) of a benzo-fused norcaradiene.[42]

3.2. Gold(I)-Carbenes by Retro-Cyclopropanation in Gas Phase

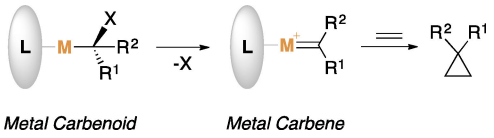
In an effort to gain insight into the nature of benzylidene gold (I) species, Chen and coworkers reported characterization of $[(IMes)AuCHPh]^+$ in the gas phase.[17] This cationic species was generated from a phosphonium ylide complex (**25**) as a suitable gold(I) carbene precursor *via* collision-induced dissociation of PPh_3 (Scheme 12). To complete the structural assignment, they investigated the reactivity displayed by this species in the presence of alkenes, demonstrating that **26** presents a typical metallocarbene behavior by promoting cyclopropanation, alkene loss and, even more interestingly, "cyclopropane metathesis".

To further understand the three reaction pathways, the group of Chen prepared a family of *p*-substituted gold benzylidene complexes, $[(IMes)AuCHAr]^+$ (Ar = *p*-XC_6H_4, where X = OMe, Me, Ph, F, H, Cl, Br, CO_2Me, CF_3, CN, SO_2Me) in gas phase.[43] Experimental data, kinetic studies, and DFT calculations supported that the open chain species **28** was a common intermediate for all the processes (Scheme 13).[44] Complex **28** can further undergo cyclopropane ring-closing, generating stable (η^2-cyclopropane)gold(I) complexes (**29**). The cyclopropane dissociation from **29** only took place upon collision activation and, in fact, this step was found to be rate determining of the cyclopropanation reaction. Instead of releasing cyclopropane, after collision activation, complex **29** can return to open-chain intermediate **28**, from which two different events can occur. First, it can revert to the initial adduct **30** that can further release the initial alkene. Alternatively, ring closing leading to the formation of a metallacyclobutane species **32** can take place. After a few internal rearrangements, a new gold(I) carbene **33** is generated together with an alkene resulting from a formal alkene metathesis reaction. To be more precise, the authors named this process "cyclopropane metathesis" and represents the first example of the generation of gold(I) carbenes *via* gold(I)-promoted retro-cyclopropanation in the gas-phase. The so-called "cyclopropane metathesis" resembles the gold(I)-catalyzed retrocyclopropanation that takes place in the retro-Buchner reaction reported by our group (Scheme 10).[19] In the following years, both the groups of Chen and Gronert demonstrated that the same reactivity patterns were displayed by gold(I) benzylidenes bearing other ancillary ligands.[45]

3.3. Alternative Methods for the Generation of Aryl Gold(I) Carbenes in Solution

Carbenoids are species structurally related to metallocarbenes. More precisely, they contain a sp^3 carbon bound both to a metal and to a leaving group (Scheme 14).[7a,46] After removal of the leaving group, a formal metallocarbene is generated, which can transfer the carbene moiety onto a substrate.

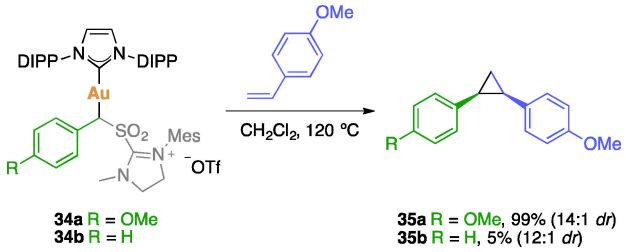
The first examples of gold(I) carbenoids were reported 30 years ago.[47] At that time, it was shown that carbenoids were able to take part on typical metal carbene reactions upon



Scheme 14. Structural relationship between metal carbenoids and metal carbenes. L = ligand.

release of the leaving group in solution. Since then, the studies regarding these species have been mainly focused on complexes of the type [LAuCH$_2$X] and their reactivity.[48]

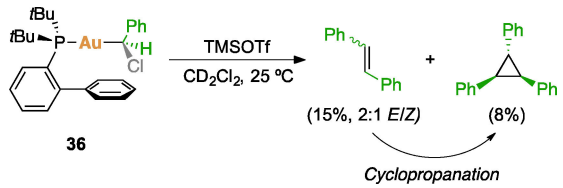
As descried in the previous section, Chen developed a strategy to generate [LAuCHAr]$^+$ carbenes in gas-phase based on the loss of PPh_3 from their [LAuCHArPPh$_3$]$^+$ counterparts (Scheme 12).[17,43,44,45] To transfer this approach to solution, they installed a SO_2-imidazolylidene moiety as leaving group, which undergoes thermal dissociation to release SO_2 gas and imidazolylidene (Scheme 15).[49] Following this methodology,



Scheme 15. Stoichiometric cyclopropanation of *p*-methoxystyrene with gold (I) carbene precursors. DIPP = 2,6-diisopropylphenyl.

they prepared a family of complexes bearing NHC and JohnPhos ligands. The formation of aryl gold(I) carbenes from these precursors was tested in the presence of *p*-methoxystyrene at 120 °C. The expected cyclopropanes (as *cis* and *trans* mixtures in different ratios) were obtained, supporting the formation of carbene intermediates at high temperatures.

In 2017, as part of a study on chloromethyl gold(I) carbenoids, our group reported the preparation of a chlorobenzyl gold(I) complex bearing JohnPhos as ligand (**36**).[48] Upon chloride abstraction with TMSOTf at 25 °C, the carbenoid was completely consumed through a bimolecular coupling generating *cis*- and *trans*-stilbene together with 1,2,3-triphenylcyclopropane, which arises from the cyclopropanation of the previously formed alkenes (Scheme 16).



Scheme 16. Activation of aryl gold(I) carbenoids with TMSOTf in solution.

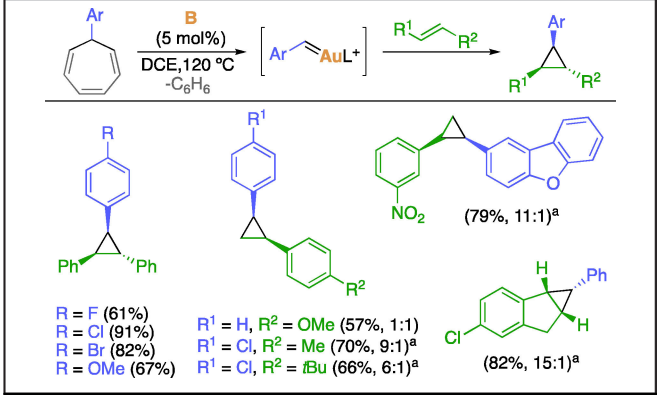
4. Cyclopropanation *via* Retro-Buchner Reaction of Cycloheptatrienes

4.1. Cyclopropanation with Aryl Gold(I) Carbenes

Cyclopropanes have attracted much attention from the scientific community, not only because of its applications as reactive intermediates in synthetic chemistry,[50] but also because they can be found in many biologically relevant natural or synthetic products.[51] Cyclopropanes are often prepared by trapping carbenes with alkenes, using different transition metals as catalysts, including gold.[52]

In 2011, our group reported a general method for the cyclopropanation of styrenes and stilbenes *via* gold(I)-catalyzed generation of carbenes by retro-Buchner reaction of 7-aryl-1,3,5-cycloheptatrienes (Table 1).[20]

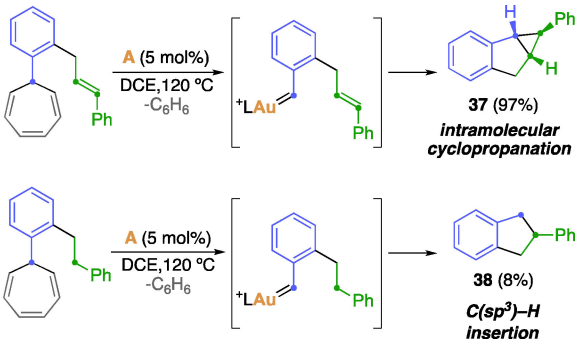
Table 1. Selected examples of the aryl-cyclopropanation reaction. [a] The *cis* or *endo* diastereoisomer was obtained as major product.



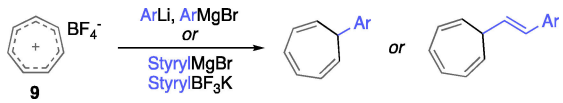
A variety of substituents are tolerated in both the aryl cycloheptatriene and in the alkene. This provides an access to 1,2,3-trisubstitued cyclopropanes, which are not easily prepared by other methods. When styrenes are employed, poor to good diastereoselectivities can be achieved favoring the *cis* product in most cases.

Additionally, it was possible to perform the same cyclopropanation intramolecularly, giving the expected cyclopropylindane **37** in quantitative yield, exclusively as the *exo* diastereoisomer (Scheme 17, upper reaction).[20] Using a related substrate (Scheme 17, bottom reaction), 8% yield of intramolecular C(sp^3)–H insertion product of the corresponding aryl gold(I) carbene was observed (**38**) under the same reaction conditions.

In regards to the starting substrates, a wide range of 7-aryl-1,3,5-cycloheptatrienes can be easily prepared by reaction of Grignard (ArMgBr) or organolithium reagents (ArLi) with commercially available tropylium tetrafluoroborate (Scheme 18).[33]



Scheme 17. Intramolecular cyclopropanation and C–H insertion.

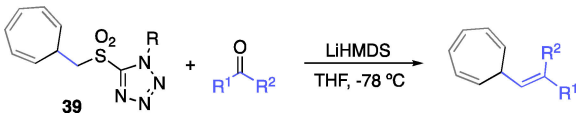


Scheme 18. Procedure for the synthesis of 7-aryl- or 7-styrylcycloheptatrienes.

4.2. Cyclopropanation with Vinyl Gold(I) Carbenes

Among all cyclopropanes, vinylcyclopropanes are of special interest because of their rich downstream chemistry,[50] undergoing rearrangements to cyclopentenes, cycloadditions, and other metal-catalyzed transformations.[53] They are also common motifs in natural products and active pharmaceuticals.[54]

Although some 7-styryl-1,3,5-cycloheptatrienes can be prepared using tropylium tetrafluoroborate as shown in Scheme 18, a more reliable and general method is based on the use of the Julia-Kocienski olefination employing sulfone **39** (Scheme 19).[55]

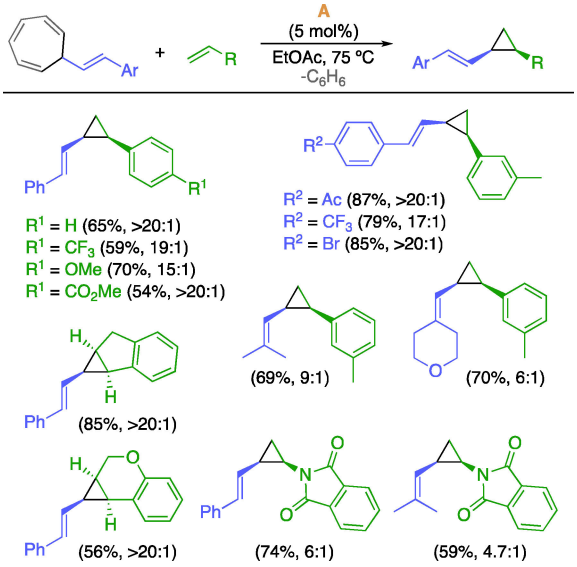


Scheme 19. Synthesis of 7-vinyl-1,3,5-cycloheptatrienes by Julia-Kocienski olefination.

Sulfone **39** can be prepared in multi-gram scale and stored indefinitely. Treatment of this reagent with LiHMDS followed by the addition of commercially available aldehydes or ketones allows the synthesis of a wide range of 7-vinyl and 7-styryl-1,3,5-cycloheptatrienes, which can be also employed to generate gold(I) carbenes by retro-Buchner reaction (Table 2).[55]

In the presence of 5 mol% of a cationic gold complex such as [(*t*BuXPhos)Au(MeCN)]SbF_6, these substrates undergo a retro-Buchner reaction at 75 °C releasing benzene and generating vinyl or styryl gold(I) carbenes that can cyclopropanate styrenes and other related activated alkenes, such as indenes, chromenes, or *N*-vinylphthalimides. This reaction generally proceeds efficiently and with good diastereocontrol, favoring the formation of the corresponding *cis*-vinylcyclopropanes (Table 2).[55]

Table 2. Representative scope of the vinyl cyclopropanation of styrenes and other related activated alkenes.



The mechanism of this transformation was studied both experimentally and computationally, giving rise to a consistent stereochemical model for the cyclopropanation, in which π–π stabilizing interactions lead to *cis* diastereoselectivity (Figure 1).

The reaction starts by the retro-Buchner reaction of the norcaradiene, which involves the cleavage of the two C–C bonds in complex **II**. The cleavage of the first C–C bond to give cationic $\mathbf{TS_{II\text{-}III}}$ is the rate-limiting step of the reaction. The cyclopropanation of styrene by carbene **V** proceeds through an asynchronous concerted mechanism, with an energy difference of 3.1 kcal·mol^{-1} favoring the *cis* cyclopropane over the *trans* product. This difference can be partially attributed to the electronic non-covalent π–π stabilizing interactions in the *cis*-$\mathbf{TS_{(VIa\text{-}VIIa)}}$ and its absence in the *trans*-$\mathbf{TS_{(VIa\text{-}VIIa)}}$.

5. Higher Cycloadditions of Gold(I) Carbenes *via* Retro-Buchner Reaction

5.1. Formal (4+1) Cycloaddition of Methylenecyclopropanes and Cyclobutenes with Aryl Gold(I) Carbenes

Apart from (2+1) cyclopropanations of alkenes, it was found that gold(I) carbenes generated by retro-Buchner reaction can engage in higher cycloadditions with different unsaturated partners.

In 2014, we reported that 7-aryl-1,3,5-cycloheptatrienes and methylenecyclopropanes[56] react under gold(I) catalysis to give arylcyclopentenes (Table 3).[57]

A range of aryl groups can be efficiently transferred in the carbene fragment using down to only 1 mol% of [(JohnPhos)Au(MeCN)]SbF_6 in up to 0.5 g scale. Not only aryl methylenecyclopropanes can be employed, but also alkyl methylenecyclo-

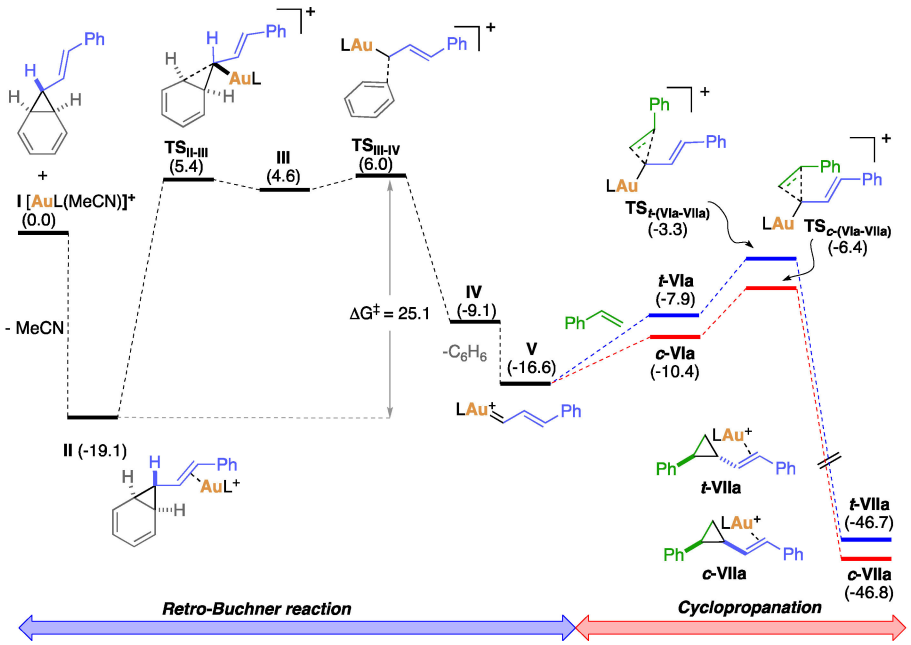
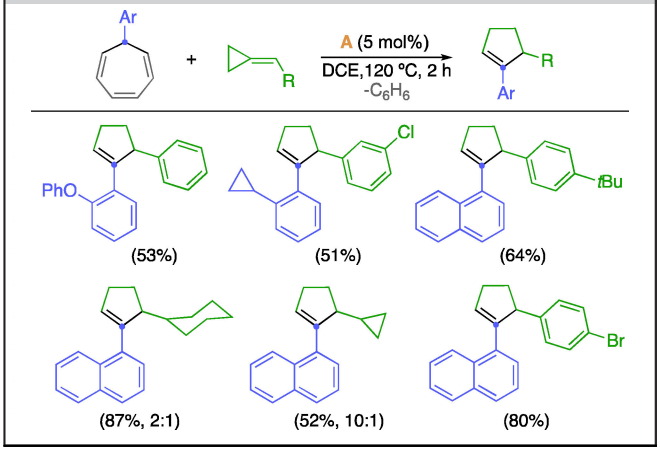
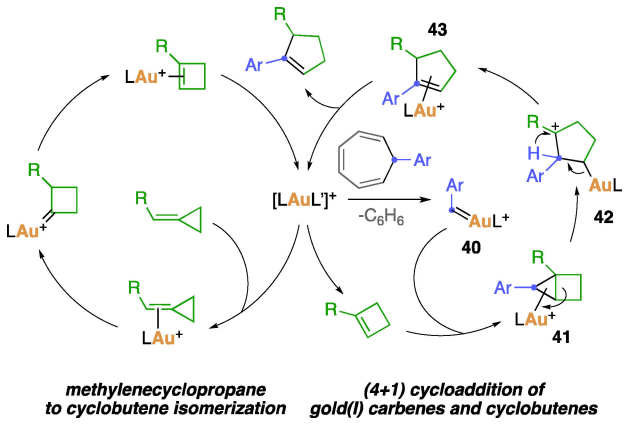


Figure 1. Calculated energies for the gold(I)-catalyzed retro-Buchner reaction and cyclopropanation. Energies in kcal·mol^{-1}. M06/6-31G(d)/M06/6-311+G(2d,p) (C, H, N, O, P) and SDD (Au) levels of theory, using JohnPhos as the phosphine ligand and SMD = dichloromethane for solvent effects. For specific details on the computational study, see the original publication.[55]

Table 3. Representative scope of the (4+1) cycloaddition of gold(I) carbenes with methylenecyclopropanes.





Scheme 20. Proposed mechanism for the formal (4+1) cycloaddition. $[LAuL']^+$ = gold complex **A**.

propanes were tolerated, although in these cases, mixtures of regioisomers ranging from 1.5:1 to 10:1 were obtained.[57]

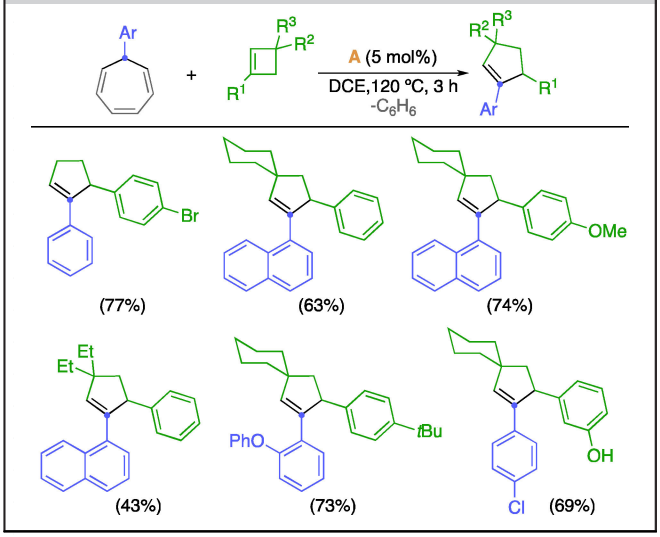
This formal (4+1) cycloaddition proceeds *via* triple gold(I) catalysis. The first steps involve a metal-catalyzed isomerization of methylenecyclopropanes to cyclobutenes, a ring-expansion process that had been reported before using Pt(II) or Pd(II)[58] (Scheme 20, left cycle).

The second part is the gold(I)-catalyzed retro-Buchner reaction to generate aryl gold(I) carbene **40**, which reacts with the cyclobutene to form bicyclo[2.1.0]pentane-gold(I) complex **41** (Scheme 20, right cycle). Opening of the cyclopropane leads to a cationic intermediate (**42**) that further evolves by 1,2-H shift to give the reaction product after deauration. The cyclopropanation of the cyclobutene probably follows a similar pathway to the one occurring in the gas phase for the cyclopropanation/retro-cyclopropanation of enol ethers with gold(I) carbenes reported by Chen and coworkers.[17] The mechanism of this triple gold(I)-catalyzed transformation was further investigated computationally by another group, obtaining results consistent with the experimental observations.[59]

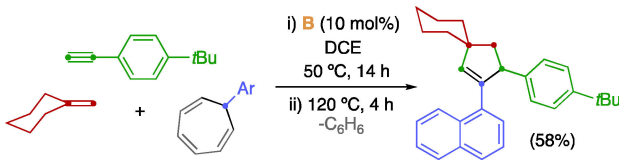
The hypothesis that cyclobutenes are indeed intermediates in this process was confirmed by the development of a similar methodology, under the same reaction conditions, but using cyclobutenes instead of methylenecyclopropanes (Table 4).[57]

Not only monosubstituted cyclobutenes could be employed, but also trisubstituted ones, allowing further expanding the scope of the (4+1) cycloaddition obtaining cyclopentenes with different substituents in good yields.

Table 4. Representative scope of the (4+1) cycloaddition of gold(I) carbenes with cyclobutenes.



Cyclobutenes can be prepared by a gold(I)-catalyzed [2+2] cycloaddition reaction of alkynes with alkenes.[60] By optimizing the reaction conditions, it was possible to combine both processes and develop a one-pot [2+2]–(4+1) sequence. This strategy allowed obtaining complex structures in a single reaction flask from very simple substrates: a cycloheptatriene, an alkyne, and an alkene, using 10 mol% of [(JohnPhos)Au(MeCN)]SbF_6 as the only catalyst (Scheme 21).[61]



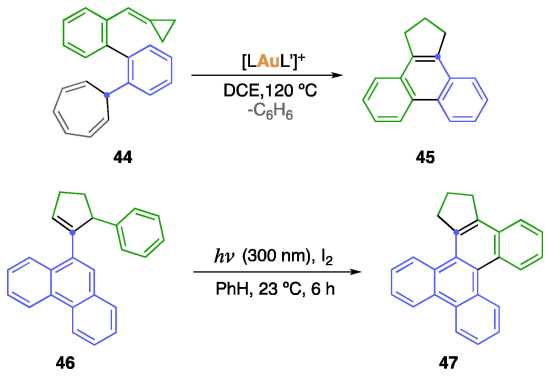
Scheme 21. One pot [2+2]–(4+1) sequential cycloadditions.

An intramolecular version of the (4+1) cycloaddition of an aryl gold(I) carbene with a methylenecyclopropane starting from substrate **44** was also developed, giving access to a polyarene fragment (**45**).[57] Furthermore, product **46** could be used to prepare a bigger polyarene fragment (**47**) *via* light induced cyclization (Scheme 22).[57]

5.2. Formal (3+2) Cycloaddition of Allenes with Aryl and Styryl Gold(I) Carbenes

Aryl gold(I) carbenes generated by retro-Buchner reaction can also engage in a formal (3+2) cycloaddition with allenes to give rise to indenes.[62] Indenes are important motifs present in many relevant natural products,[63] and are also used as building blocks for organic synthesis or organometallic chemistry.[64]

The reaction of 7-aryl-1,3,5-cycloheptrienes with 1,1-dialkylallenes at 120 °C in the presence of 5 mol% of [(JohnPhos)Au(MeCN)]SbF_6 gives rise to a very wide range of highly substituted indenes in moderate to good yields.[62] The reaction is general and tolerates substituents of different nature in the transferred aryl moiety, or even different aromatic units such as naphthalenes or phenanthrenes. Different alkyl substituents can be introduced by using different allene derivatives. Employing cyclic allenes is especially interesting since they afford spirocyclic indene structures difficult to access by other methods (Table 5).

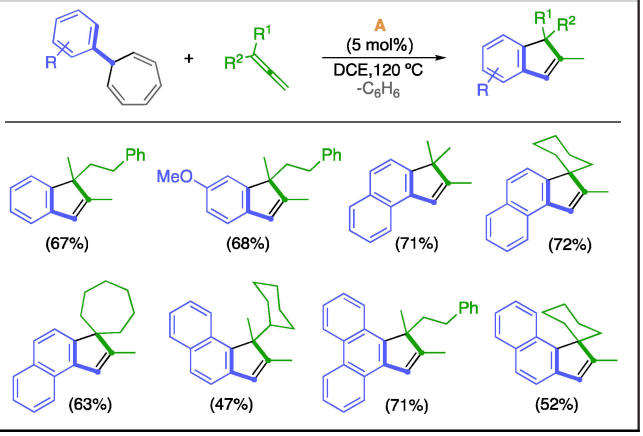


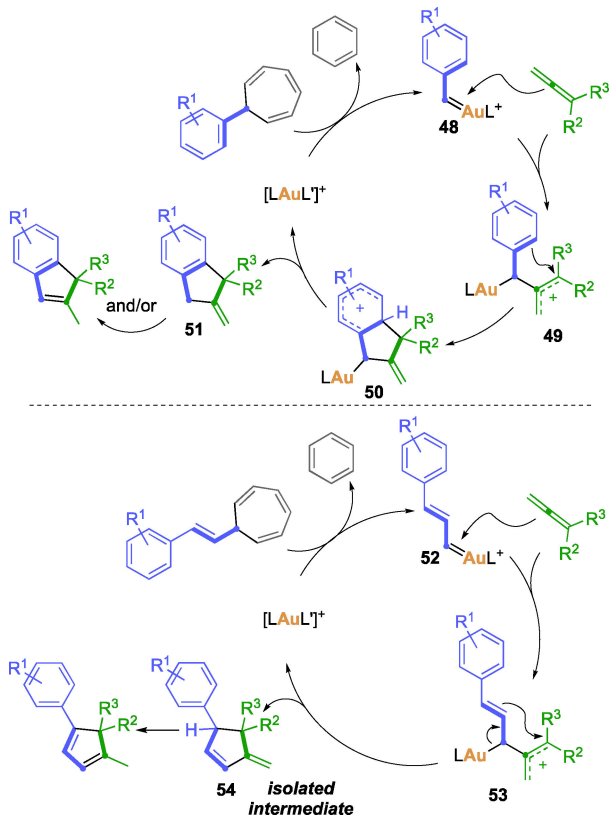
Scheme 22. Intramolecular (4+1) cycloaddition and preparation of polyarene fragments. [LAuL']$^+$ = [(IPr)Au(PhCN)]SbF_6 (5 mol%).

In a similar manner, 7-styryl-1,3,5-cycloheptatrienes reacted with allenes at 100 °C in the presence of 5 mol% of [(*t*BuXPhos)Au(MeCN)]SbF_6 through a formal (3+2) cycloaddition giving rise to highly substituted cyclopentadienes (Table 6).[62] Cyclopentadienes are relevant substrates, mainly as reactive diene components in the Diels–Alder reaction and as ligands in organometallic chemistry.[65] A range of highly substituted cyclopentadienes could be accessed, including both electron-poor and electron-rich aryl derivatives. As in the case of indenes, this methodology proves to be suitable for the synthesis of spirocyclic structures.

The proposed mechanism for these two transformations takes place in a very similar fashion.[62] In both cases, the first step is the gold(I)-catalyzed retro-Buchner reaction of the

Table 5. Selected examples of the (3+2) cycloaddition of aryl gold(I) carbenes with allenes to give indenes.





Scheme 23. Mechanistic proposal for the (3+2) cycloaddition of aryl or styryl gold(I) carbenes with allenes. [LAuL']$^+$ = **A** or **B** (5 mol%).

corresponding aryl or styryl cycloheptatriene to release carbenes **48** or **52**, respectively (Scheme 23). Each carbene undergoes electrophilic attack at the central carbon atom of the allenes to give allyl cationic species **49** and **53**. In the first case (for the indene synthesis, Scheme 23, upper cycle), intramolecular electrophilic aromatic substitution gives intermediate **50**, which can undergo rearomatization and protonolysis of the Au–C bond to form **51** which after isomerization gives the corresponding indene. Alternatively, protonation of the exocyclic double bond of **50** with concomitant deauration would directly furnish the indene.

In the case of the synthesis of cyclopentadienes (Scheme 23, bottom cycle), cyclization of **53** would give **54**, which is finally isomerized to the corresponding product. Using short reaction times, it is possible to isolate and characterize intermediates **54** by GC–MS and ^{1}H NMR, further confirming the proposed reaction pathway.

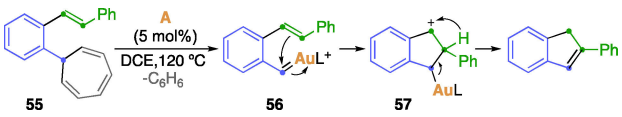
6. Intramolecular Reactivity of Gold(I) Carbenes and Further Transformations

6.1. Intramolecular Synthesis of Indenes and Fluorenes

Right after the discovery of the aryl-cyclopropanation through gold(I) carbenes *via* retro-Buchner reaction, our group developed a range of transformations involving intramolecular reactivity of different substrates, based mainly in Friedel–Crafts-type trapping of the carbene intermediates.[66] This led to two general methodologies to synthesize indenes and fluorenes, allowing access to a rich variety of structures that arise from different modifications of the starting substrates.

In the presence of 5 mol% of [(*t*BuXPhos)Au(MeCN)]SbF_6, substrates such as **55** undergo a retro-Buchner reaction, generating gold(I) carbenes **56** that can react intramolecularly with the alkenes to give carbocationic intermediates such as **57**, which further evolve *via* 1,2-H shift to form indenes (Scheme 24).

This transformation was shown to be suitable for the preparation of a variety of substituted indenes (Table 7).



Scheme 24. Proposed mechanism for the formation of indenes *via* retro-Bucher reaction.

Table 6. Selected examples of the (3+2) cycloaddition of styryl gold(I) carbenes with allenes to give cyclopentadienes.

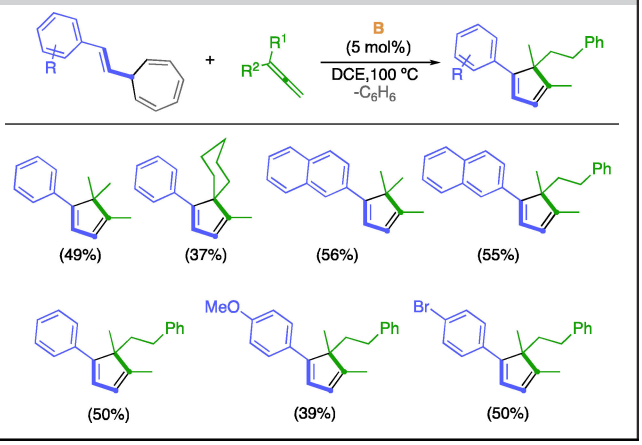
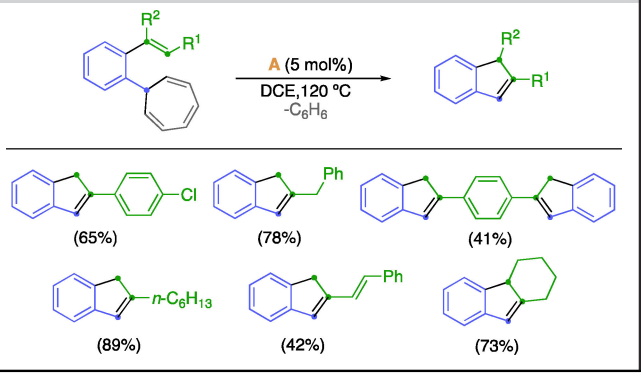
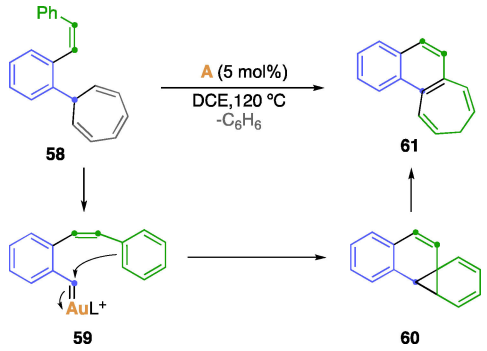


Table 7. Selected examples of the intramolecular synthesis of indenes.

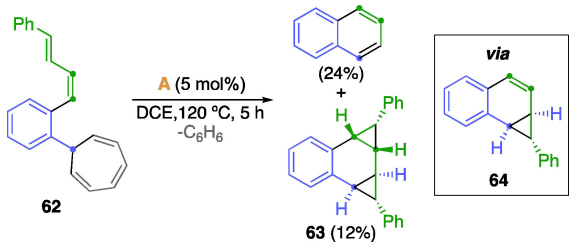


In contrast, when a *cis* stilbene was employed as starting substrate (**58**) under the same reaction conditions, we observed an intramolecular Buchner ring expansion.[66] Presumably, as a result of the proximity of the phenyl ring to the gold carbene in intermediate **59**, an intramolecular Buchner reaction occurs followed, giving **60**, which undergoes a disrotatory norcaradiene-to-cycloheptatriene opening and a 1,5-H shift, furnishing cycloheptatriene **61** (Scheme 25).



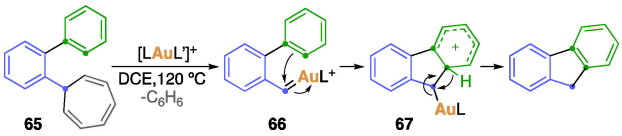
Scheme 25. Intramolecular retro-Buchner–Buchner reaction sequence.

Following this approach, it was possible to shed more light into the mechanism of the gold(I)-catalyzed synthesis of naphtalenes *via* annulation–fragmentation of phenyl-linked 1,6-enynes, that was previously discussed in Scheme 11.[19] Thus, when diene **62** was heated to 120 °C in the presence of 5 mol% of [(JohnPhos)Au(MeCN)]SbF_6 catalyst, it was possible to observe the formation of both naphthalene and biscyclopropane **63**.[66] This can be rationalized by a retro-Buchner reaction, followed by an intramolecular cyclopropanation of the distal double bond of the diene, giving tricyclic intermediate **64**. This compound can further evolve through retro-cyclopropanation releasing naphthalene and generating a free gold(I) carbene [LAu=CHPh]$^+$ that can cyclopropanate another unit of **64** assembling biscyclopropane **63** (Scheme 26).



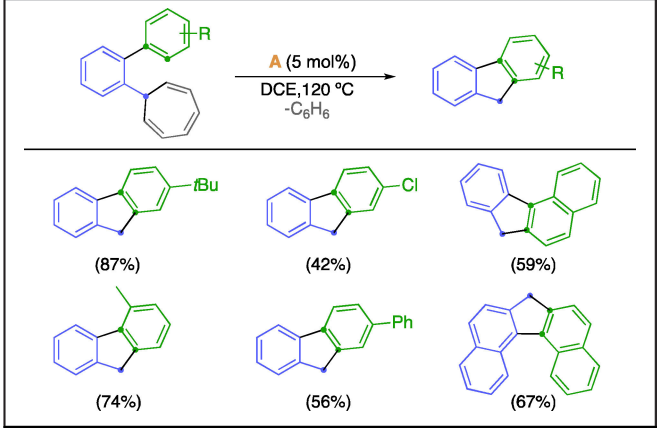
Scheme 26. Intramolecular retro-Buchner–Buchner reaction sequence.

When instead of a stilbene, a biphenyl unit is linked to a cycloheptatriene (**65**), under gold(I) catalysis, the resulting carbene is trapped by the second aromatic ring furnishing a fluorene (Scheme 27[66] Both computational work and experimental evidence support that the trapping occurs *via* a Friedel–Crafts-type reaction of gold(I) carbene **66** to give



Scheme 27. Proposed mechanism for the formation of fluorenes. [LAu-L']$^+$ = **A** (5 mol%).

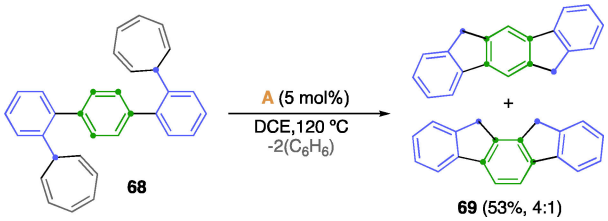
Table 8. Selected examples of the intramolecular synthesis of fluorenes.



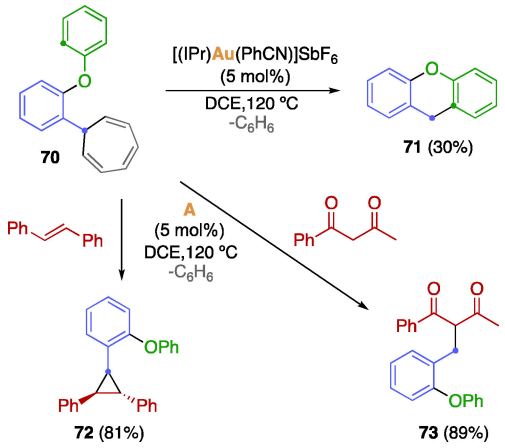
Wheland intermediate **67**. This cationic intermediate further evolves through a 1,2-H shift to form a fluorene. Some examples of the scope are highlighted in Table 8. Both electron-rich and electron-poor carbene fragments could be delivered intramolecularly. Interestingly, starting from 2-binaphthylcycloheptatriene, it was possible to obtain 7*H*-dibenzo[*c*,*g*]fluorene in 67% yield,[66] in the shortest route reported so far.[67]

Furthermore, as depicted in Scheme 28, this methodology could be extended to a double annulation, preparing interesting structures,[66] such as indeno[1,2-*b*]fluorene (**69**) as a 4:1 mixture with indeno[2,1-*a*]fluorene in 53% isolated yield from **68**.[68]

Generally, aryl carbenes generated by pyrolysis of aryl diazomethanes undergo formal insertion into the adjacent ortho position of the XC_6H_5 ring when X=CH_2 or NH, whereas substrates with X=O or S lead to a Buchner ring expansion. In our case, substrate **70** gave 9*H*-xanthene (**71**).[66] This is the product of formal insertion of the gold(I) carbene into the ortho position of the phenyl group. The resulting carbenes could also be trapped intermolecularly with high yields using *trans*-



Scheme 28. Double annulation *via* retro-Buchner reaction.



Scheme 29. Reactivity of *o*-cycloheptatrienyl phenoxybenzene.

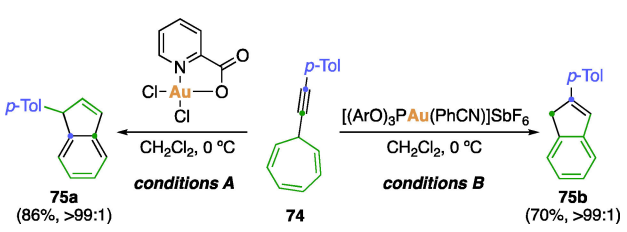
stilbene to give cyclopropanes such as **72** or with a 1,3-diketone giving **73** (Scheme 29).

6.2. Gold(I)-Catalyzed Isomerization of 7-Alkynyl Cycloheptatrienes: Generation of Barbaralyl Cations

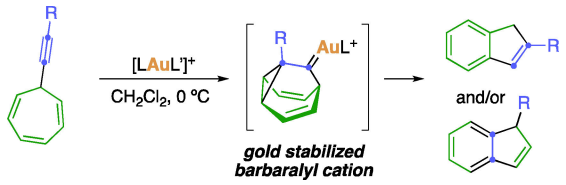
In contrast to aryl or vinyl/styryl derivatives, 7-alkynyl-1,3,5-cycloheptatrienes (**74**) undergo cycloisomerization reactions at low temperature under gold(I) or gold(III) catalysis leading to indenes through the generation of stabilized barbaralyl cations.[69] This is another way of generating gold carbenes in solution from cycloheptatrienes that does not involve a fragmentation process.

The ratio of regioisomers **75 a**/**75 b** (Scheme 30) is sensitive to the gold catalyst employed. Gold trichloride, cationic phosphine-gold(I), and N-heterocyclic carbene-gold(I) complexes led to mixtures of products. However, the pyridine carboxylate Au(III) complex employed in conditions A (Scheme 30) gave preferentially 1-aryl-1*H*-indenes such as **75 a**. On the other hand, using a phosphite gold(I) complex (Scheme 30, conditions B) led exclusively to 2-aryl-1*H*-indenes like **75 b**.

This catalyst-controlled regioselectivity allowed to obtain a wide range of 1- and 2-aryl substituted 1*H*-indenes just by using the appropriate gold catalysts for each case. The formation of 1-substituted indenes involves a remarkable transformation in which the alkyne carbon atoms end up at the bridge of the indene. Supported by DFT calculations, we hypothesized that the intermediacy of a barbaralyl species, generated by an initial 1,6-enyne cyclization, could be responsible for the observed reactivity (Scheme 31).[69a]



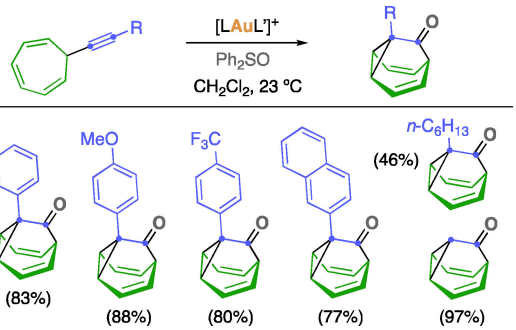
Scheme 30. Gold(III)- or gold(I)-catalyzed isomerization of 7-alkynyl-1,3,5-cycloheptatrienes to indenes.



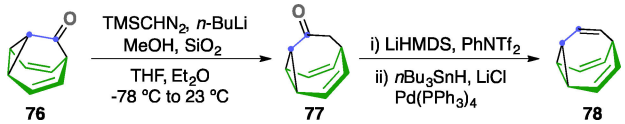
Scheme 31. Gold-catalyzed isomerization of 7-alkynyl-1,3,5-cycloheptatrienes to indenes through a barbaralyl cation intermediate.

To prove our hypothesis, the trapping by oxidation of the gold stabilized barbaralyl cation was studied. In the presence of gold(I) cationic complexes (bearing phosphine or NHC ligands), under oxidative conditions, these 7-alkynyl-1,3,5-cycloheptatrienes can be cycloisomerized and trapped as barbaralones,[70] interesting fluxional molecules that have been central to the understanding of the phenomena of valence tautomerism.[71] This discovery led to a straightforward synthesis of 1-substituted barbaralones from alkynes and commercially available tropylium tetrafluoroborate (Table 9).

Table 9. Selected examples of the gold(I)-catalyzed oxidative synthesis of barbaralones. [LAuL']$^+$ = [(IPr)Au(MeCN)]SbF$_6$.



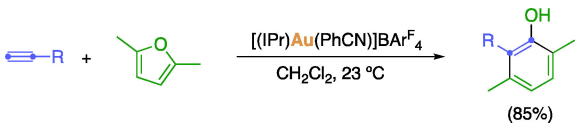
The development of this methodology also allowed to accomplish a very short total synthesis of bullvalene **78** (another related fluxional compound) in five steps from commercially available starting materials and 10% overall yield (Scheme 32).[70]



Scheme 32. Synthesis of bullvalone (**77**) and bullvalene (**78**).

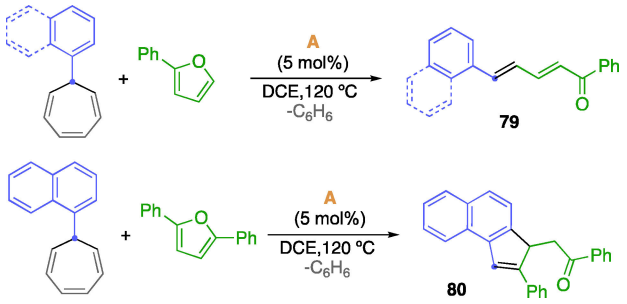
6.3. Ring Opening of Furans with Gold(I) Carbenes Generated by Retro-Buchner Reaction

The reactivity of gold(I) carbene intermediates with furans has been well studied.[72] It has been shown that under homogeneous gold(I) catalysis, alkynes can react with furans to give rise to phenols, both intramolecularly[72,73] or intermolecularly (Scheme 33).[74]

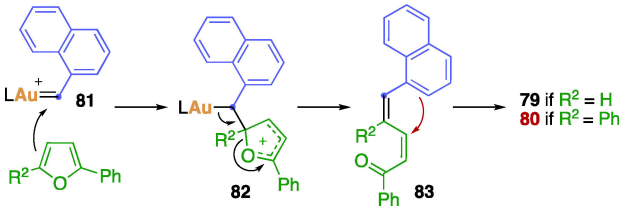


Scheme 33. Gold(I)-catalyzed intramolecular reaction of alkynes with furans.

We discovered that the electrophilic addition of gold(I) carbenes to furans followed by ring opening results in the formation of cyclopentenones, polyenes or polycyclic compounds.[75] These gold(I) carbenes were generated by reactions of propargyl carboxylates or 1,6-enynes, but also from 7-aryl-1,3,5-cycloheptatrienes *via* retro-Buchner reaction. When a 2-substituted furan reacts with an aryl gold(I) carbene, an α,β,γ,δ-unsaturated ketone (**79**) was formed, whereas if the furan is 2,5-disubstituted, indene (**80**) is formed instead (Scheme 34).



Scheme 34. Opening of furans with gold(I) carbenes *via* retro-Buchner reaction.



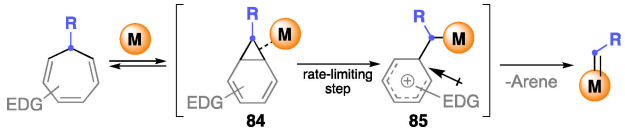
Scheme 35. Proposed mechanism for the opening of furans with gold(I) carbenes.

Mechanistically, the reaction of the 7-aryl-1,3,5-cycloheptatriene with a cationic gold(I) catalyst generates aryl gold(I) carbene **81** (Scheme 35).[75] The corresponding furan reacts with the gold carbene to give rise to cationic intermediate **82**, which further evolves *via* ring opening, furnishing diene **83**. If the furan was monosubstituted, **83** undergoes *Z* to *E* isomerization to give ketone **79**. Alternatively, if a 2,5-disusbtituted furan was used, diene **83** can cyclize by a Michael-type ring closing to afford **80**.

7. Second Generation of Cycloheptatrienes

7.1. The Room Temperature Gold(I)-Catalyzed Retro-Buchner Reaction

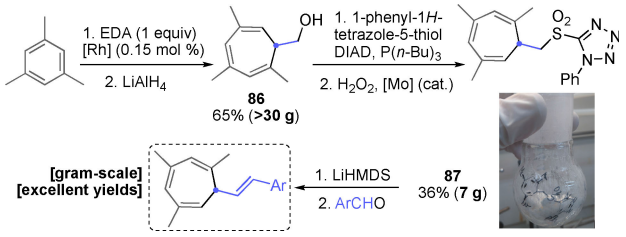
Despite the variety of reactivities that have been explored with this chemistry, the gold(I)-catalyzed retro-Buchner reaction was still limited by requiring temperatures in the range of 75–120 °C for the decarbenation process. This complicates the development of stereoselective transformations, and makes the methodologies involving a retro-Buchner reaction less attractive for its application in the functionalization of complex molecules. A solution to this problem came through the design of a new generation of more reactive cycloheptatrienes that can undergo a retro-cyclopropanation at room temperature under gold(I) catalysis. Previous computational work revealed that the rate-limiting step of the decarbenation of 7-styryl-1,3,5-cycloheptatrienes was the cleavage of the first C–C of the corresponding norcaradiene giving a Wheland-type cationic intermediate (see Figure 1).[55] This led to the hypothesis that introducing electron donating groups on the cycloheptatriene ring would lower the energy barrier for the decarbenation process (Scheme 36).[76]



Scheme 36. Working hypothesis for the design of a new generation of more reactive cycloheptatrienes.

This theoretical model was backed up by different experimental findings that were already mentioned in the introduction. For example, Scheme 7 shows how a hexamethylnorcardiene can undergo a rhodium-promoted retro-Buchner reaction to release hexamethylbenzene, although the authors claimed that lower methylated substrates (in effect, bearing less number of electron donating groups) did not undergo this transformation.[36] Furthermore, in the synthesis of naphthalenes *via* annulation–fragmentation shown in Schemes 10 and 11, intermediate **23**, which undergoes an analogous gold(I)-catalyzed decarbenation at room temperature, can be considered as an electron-rich norcaradiene derivative. Based on this reasoning, the synthetic route for the synthesis of 7-styryl-1,3,5-cycloheptatrienes *via* Julia-Kocienski olefination was adapted for the preparation of a new generation of more reactive 7-styryl-1,3,5-trimethyl-1,3,5-cycloheptatrienes. Second-generation Julia-Kocienski reagent **87** can be obtained as a stable and easy-to-handle white solid in multi-gram scale by a sequence involving

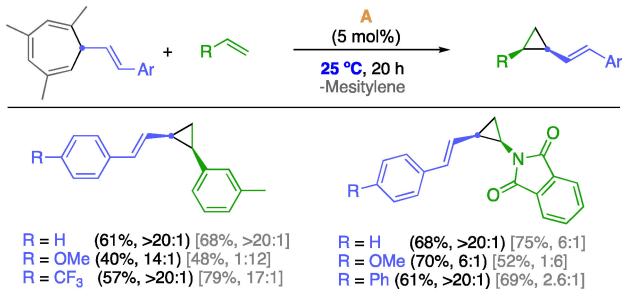
a Rh(II)-catalyzed ring expansion of mesitylene with ethyl diazoacetate (EDA), reduction of the ester, Mitsunobu reaction with 1-phenyl-1*H*-tetrazole-5-thiol, and oxidation (Scheme 37).[76]



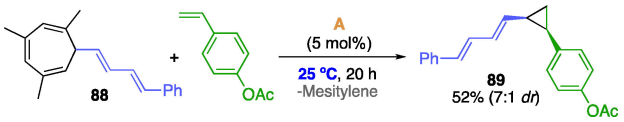
Scheme 37. Synthesis and reactivity of second-generation Julia-Kocienski reagent **87**.

This strategy was used to prepare a broad range of trimethylated 7-styryl cycloheptatrienes, that undergo the retro-Buchner–cyclopropanation sequence at room temperature under gold(I) catalysis.[76] The cyclopropanation of styrenes and other activated olefins takes place in good yields, comparable to those obtained at high temperature with the first generation of cycloheptatrienes (Table 10).[55]

Table 10. Selected examples of the cyclopropanation at room temperature. Yield (*cis*/*trans* ratio) at 25 °C between parenthesis, and yield (*cis*/*trans* ratio) at 75 °C with the first generation of cycloheptatrienes between brackets.



Improved diastereoselectivities were obtained, especially with challenging alkenes such as *N*-vinylphthalimide. Moreover, when very electron-rich cycloheptatrienes were employed, it was possible to obtain selectively the *cis* product at 25 °C, while at high temperatures (75 °C), the *trans* one is obtained due to a *cis* to *trans* isomerization of vinylcyclopropanes promoted by gold that occurs especially fast for these substrates.[55] This methodology was also applied for the late-stage functionalization of several biologically relevant complex products. Furthermore, in a similar fashion, a (*E*,*E*)-dienyl gold(I) carbene could be generated from **88** and trapped with *p*-acetylstyrene giving diene **89** (Scheme 38).[76]

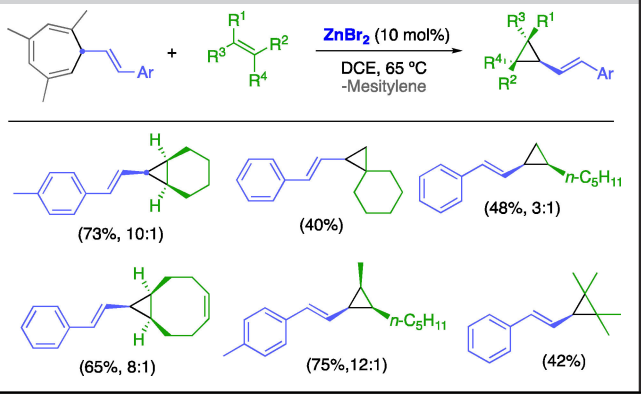


Scheme 38. Cyclopropanation with a vinylogous styryl gold(I) carbene.

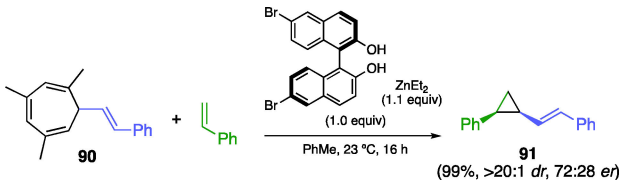
7.1. The Zinc(II)-Catalyzed Retro-Buchner Reaction

Besides allowing to overcome the requirement of high temperatures to perform the retro-Buchner reaction, this new generation of cycloheptatrienes solved other limitations of the process. Remarkably, we discovered that these more reactive cycloheptatrienes can undergo a decarbenation in the presence of zinc(II) halides, using simple and cheap $ZnBr_2$ as catalyst for both the retro-Buchner and the cyclopropanation reaction.[76] This finding not only allowed swapping the expensive gold complex for a zinc halide, but also expanding the scope of the transformation to the cyclopropanation of simple unactivated alkenes, for which the gold(I)-catalyzed version of the reaction generally gives poor yields (Table 11).

Table 11. Representative examples of the zinc(II)-catalyzed cyclopropanation of simple unactivated alkenes.



In addition, it was also found that 1 equiv. of the chiral Lewis acid that is formed *in situ* by the addition of $ZnEt_2$ to enantiomerically pure (*R*)-6,6-dibromo-BINOL can also cleanly promote the retro-Buchner reaction of cycloheptatriene **90** at room temperature. With this system, it was possible to cyclopropanate styrene obtaining **91** in quantitative yield, with excellent diastereoselectivity and in a 72:28 ratio of enantiomers. This is the only example reported to date of an enantioselective transformation involving the trapping of a metal carbene generated *via* retro-Buchner reaction (Scheme 39).[76]



Scheme 39. Enantioselective cyclopropanation promoted by a BINOL–Zn(II) complex.

8. The Retro-Buchner Reaction in Total Synthesis

8.1. Towards the Cycloaurenones and the Dysiherbols

As a part of our program to apply new synthetic methodologies in the synthesis of natural or biologically relevant products.[3d,77] we designed the first approach for the assembly of the carbon skeleton of the cycloaurenones and the dysiherbols.[62] Cycloaurenones A–C are three natural products that display a *cis*-decalin in their carbon skeleton, whereas dysiherbols A–C show a *trans*-fused decalin (Figure 2).[78]

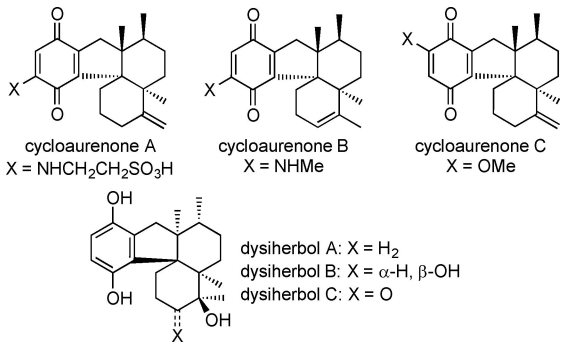
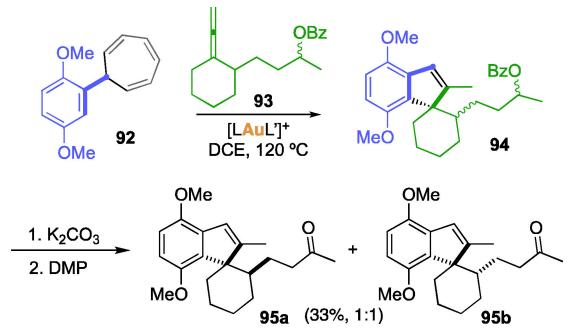


Figure 2. Cycloaurenones A–C and dysiherbols A–C.

These compounds are biogenetically related to other natural products isolated from sponges,[79] displaying antimicrobial, anti-HIV, anti-inflammatory, anti-proliferative, and anti-secretory activities, which have attracted the interest of synthetic chemists.[80] However, no total synthesis of any of the cycloaurenones or dysiherbols has been reported so far.

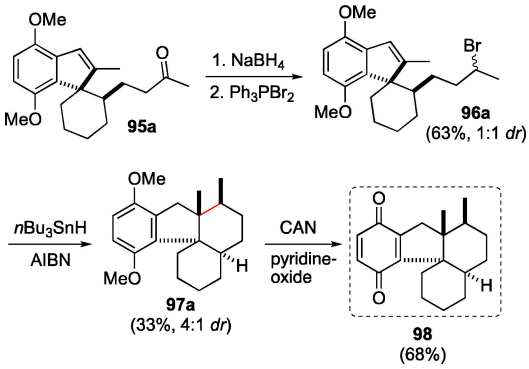
Our approach commenced by the key (3+2) cycloaddition of an aryl gold(I) carbene (generated by retro-Buchner reaction of cycloheptatriene **92**) with allene **93**, based on our previously developed methodology (see Table 5), giving spirocyclic intermediate **94** with 5 mol% of [(IPr)Au(PhCN)]SbF_6.[62] Deprotection and oxidation gave a mixture of ketones **95a** and **95b** in 33% yield over the three steps and in a 1:1 ratio (Scheme 40).

Each one of the two diastereoisomers **95a** and **95b** can be separated and used to assembly the skeletons of the cycloaurenones or the dysiherbols, respectively. Reduction of ketone **95a** and subsequent treatment with Ph_3PBr_2 gave bromide **96a**. Treatment of **96a** with nBu_3SnH in the presence of AIBN triggers a radical cyclization giving 33% of tetracyclic product

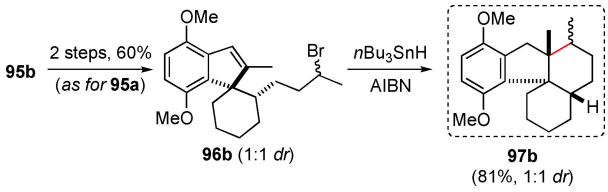


Scheme 40. Synthesis of spirocyclic ketone intermediates. $[LAuL']^+ = [(IPr)Au(PhCN)]SbF_6$ (5 mol%).

97a. Finally, oxidative deprotection of the methoxy groups with cerium ammonium nitrate and 2,6-pyridinedicarboxylic acid *N*-oxide gave quinone **98**, which presents the carbon skeleton of the cycloaurenones (Scheme 41).[62]



Scheme 41. Assembly of the cycloaurenones carbon skeleton (**98**).

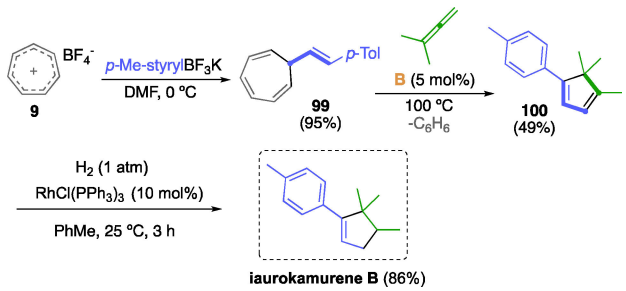


Scheme 42. Assembly of the dysiherbols carbon skeleton (**97b**).

Following the same synthetic strategy, the tetracyclic carbon skeleton of the dysiherbols (**97b**) was obtained in three steps from intermediate **95b** (Scheme 42).[62]

8.2. Total Synthesis of Laurokamurene B

Laurokamurene B, isolated from the red algae *Laurencia okamurae*, is a member of a small family of natural sesquiterpenes which display antifungal and cytotoxic activity.[81] Several synthetic approaches towards laurokamurene B have been reported, but the routes are relatively long considering the low



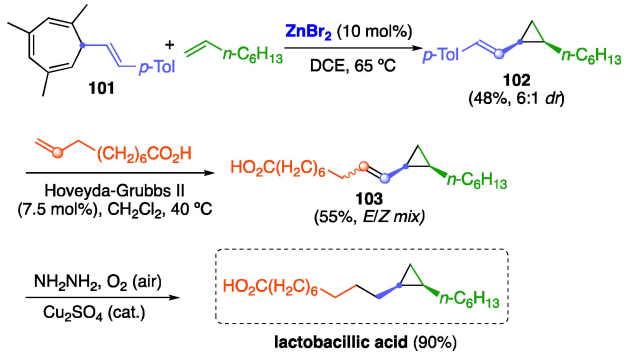
Scheme 43. Total synthesis of laurokamurene B.

structural complexity of this natural product.[82] Our approach was based on a (3+2) cycloaddition between a styryl gold(I) carbene and an allene (Scheme 43).[62] The reaction of potassium *p*-methylstyryltrifluoroborate with tropylium tetrafluoroborate (**9**) gives cycloheptatriene **99** in almost quantitative yield. A formal (3+2) cycloaddition between 3-methylbuta-1,2-diene and the styryl gold(I) carbene generated *via* retro-Buchner reaction from **99** gave rise to cyclopentadiene **100**, which was selectively hydrogenated using Wilkinson's catalyst to provide laurokamurene B in 86% yield. This synthesis of laurokamurene B requires just three steps from commercially available starting materials and proceeds in 39% overall yield.

8.3. Synthesis of Cyclopropane-Containing Fatty Acids

Lactobacillic acid is one of the several cyclopropane-containing fatty acids that have been isolated from natural sources,[83] and have attracted the interest of many synthetic organic chemists.[84] After overcoming the reactivity issues related to low efficiencies on the cyclopropanation of unactivated alkenes *via* retro-Buchner reaction by the use of zinc(II) halides, an straightforward route for the total synthesis of lactobacillic acid was accomplished (Scheme 44).[76]

The zinc(II)-catalyzed retro-Buchner reaction of second-generation cycloheptatriene **101** allowed the diastereoselective cyclopropanation of 1-octene, assembling the *cis*-cyclopropane core of lactobacillic acid (**102**). A cross-metathesis between **102** and 9-decenoic acid afforded **103** as an *E*/*Z* mixture, which after



Scheme 44. Total synthesis of lactobacillic acid.

subsequent reduction of the double bond with diimide, gave lactobacillic acid in 90% yield. This represents a very versatile route, since it could potentially be used to obtain a variety of both natural or non-natural cyclopropane-containing fatty acids just by tuning the number or carbon atoms in the aliphatic chains of the two terminal alkenes.[76]

9. Summary and Outlook

Progress in synthetic organic chemistry relies on the discovery of more efficient new reactions that allow transforming simple substrates into highly complex molecules. Over the past years, homogeneous gold(I) catalysis proved to be a powerful tool for accomplishing such task, by the development of efficient methodologies that proceed through the generation of highly reactive carbenes under catalytic conditions. Nevertheless, the generation of metal carbenes in a general and controlled manner is still an ongoing challenge, for which metal-catalyzed retro-cyclopropanation (decarbenation) reactions, such as the gold(I)-catalyzed retro-Buchner reaction of cycloheptatriene derivatives, proved to be a powerful alternative. This chemistry represents a convenient access to aryl or styryl gold(I) carbenes, that can be trapped efficiently by alkenes, affording cyclopropanes with a broad range of different substituents. Higher intermolecular cycloadditions or intramolecular reactivity of these intermediates allow to access complex and relevant scaffolds such as indenes, fluorenes, cyclopentenes, or cyclopentadienes in a general fashion. The usefulness of these transformations was proved by its application in total synthesis of natural products, one of the high-end applications of organic synthesis. Using more reactive cycloheptatrienes, these reactions can even be carried out at room temperature, and the feasibility of generating carbenes, not only with gold, but also with zinc was also recently been demonstrated. This finding opens a door for the generation of other metal carbenes *via* retro-Buchner reaction as an alternative to the traditional methods based on metal-promoted decomposition of diazo compounds.

Acknowledgements

We thank Agencia Estatal de Investigación (AEI)/FEDER, UE (CTQ2016-75960-P and FPI Fellowship to C.G.M.), Severo Ochoa Excellence Acreditation 2014–2018 (SEV-2013-0319 and FPI Predoctoral Fellowship to M.M.), the European Research Council (Advanced Grant No. 321066), the AGAUR (2017 SGR 1257) and CERCA Program / Generalitat de Catalunya for financial support.

Conflict of Interest

The authors declare no conflict of interest.

Keywords: gold catalysis · retro-Buchner reaction · cyclopropanation · cycloadditions · total synthesis

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Manuscript received: July 24, 2018
Accepted Article published: September 1, 2018
Version of record online: October 5, 2018