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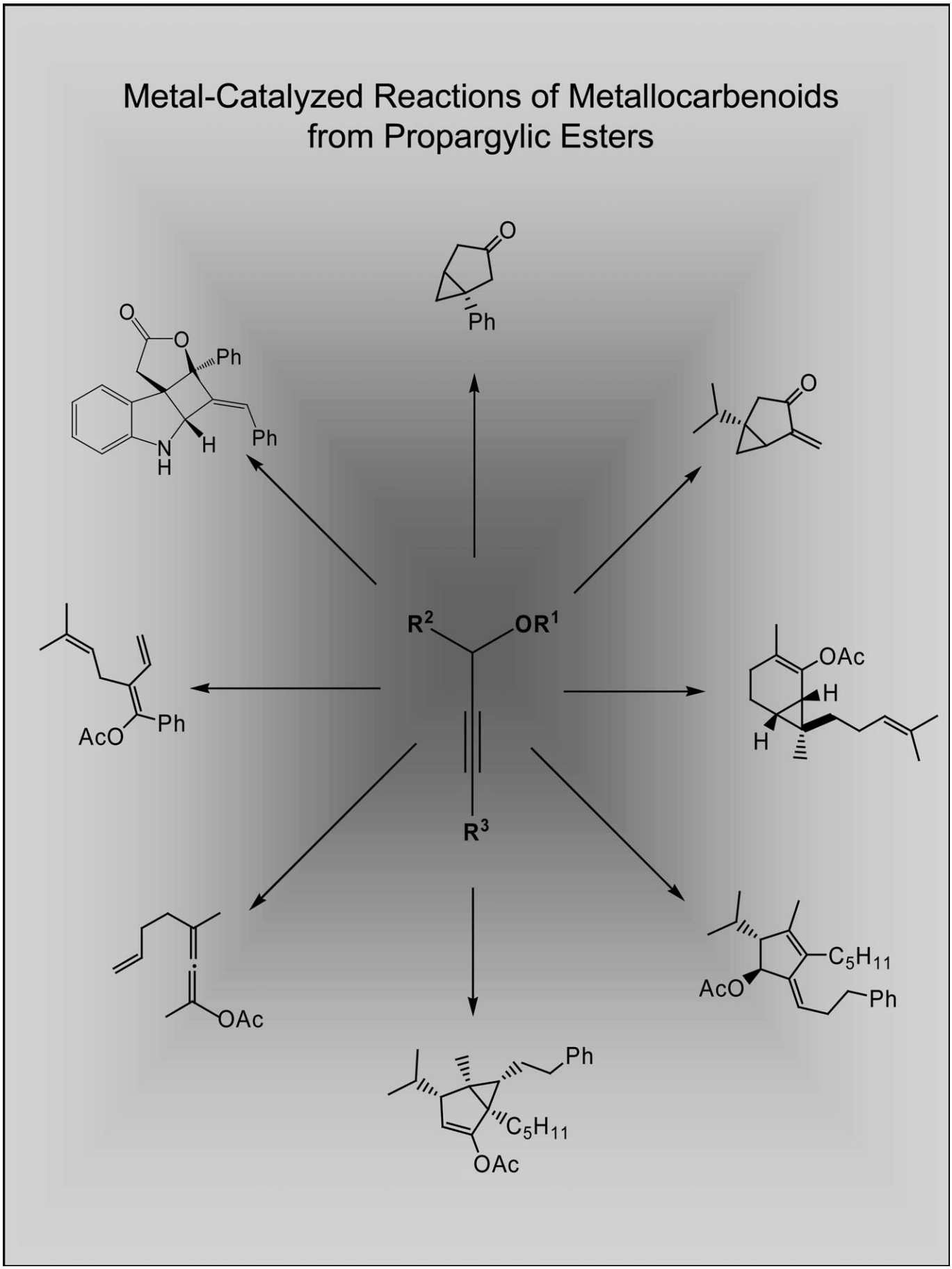
# Metal-Catalyzed Reactions of Metallocarbenoids from Propargylic Esters



# Recent Developments in the Metal-Catalyzed Reactions of Metallocarbenoids from Propargylic Esters

**José Marco-Contelles*[a] and Elena Soriano*[b]**

**Abstract:** The transition-metal-catalyzed intramolecular cycloisomerization of propargylic carboxylates provides functionalized bicyclo[*n*.1.0]enol esters in a very diastereoselective manner and, depending on the structure, with partial or complete transfer of chirality from enantiomerically pure precursors. The subsequent methanolysis gives bicyclo[*n*.1.0] ketones, hence resulting in a very efficient two-step protocol for the syntheses of α,β-unsaturated cyclopropyl ketones, key intermediates for the preparation of natural products. The results from mechanistic computational studies suggest that they probably proceed through cyclopropyl metallocarbenoids, formed by *endo*-cyclopropanation, that undergo a 1,2-acyl migration. Finally, the potential of the intermolecular reaction and the related pentannulation of propargylic esters bearing pendant aromatic rings are also discussed.

**Keywords:** carbenoids · enynes · natural products · Rautenstrauch cyclopropanation · transition metals

[a] Prof. Dr. J. Marco-Contelles
Laboratorio de Radicales Libres
Instituto de Química Orgánica General (CSIC)
c/Juan de la Cierva, 3, 28006 Madrid (Spain)
Fax (+34) 91-564-48-53
E-mail: iqoc21@iqog.csic.es

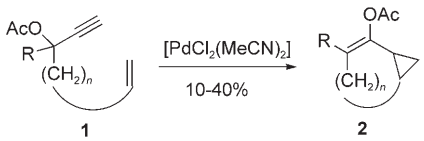
[b] Dr. E. Soriano
Laboratorio de Resonancia Magnética
Instituto de Investigaciones Biomédicas (CSIC)
c/Arturo Duperier, 4, 28029-Madrid, Spain
Fax (+34) 91-585-45-87
E-mail: esoriano@iib.uam.es

## Introduction

In the last decade, transition-metal-catalyzed cycloisomerization reactions of enynes have been extensively investigated for the synthesis of a number carbo- or heterocyclic ring systems.[1] In this context, the diverse and rich reactivity of the readily available propargylic esters has continued to attract the interest of different research groups.[2] In this account we will summarize the most significant recent reported transformations of propargylic carboxylates, including the cycloisomerization reaction of esters of 3-hydroxylated *n*-en-1-ynes, the intermolecular reaction of tertiary propargylic esters with alkenes, and the pentannulation reaction of propargylic esters bearing different aromatic rings. Some applications of these processes to the synthesis of natural products will be discussed. In addition, we will present a mechanism based on a DFT analysis, showing that the enantioselective outcome of these processes can be predicted and rationalized via metallocarbenoid species as reactive intermediates.[3]

## The Intramolecular Process: Synthesis of Bicyclo[*n*.1.0]enol Esters (the "Rautenstrauch Cyclopropanation")

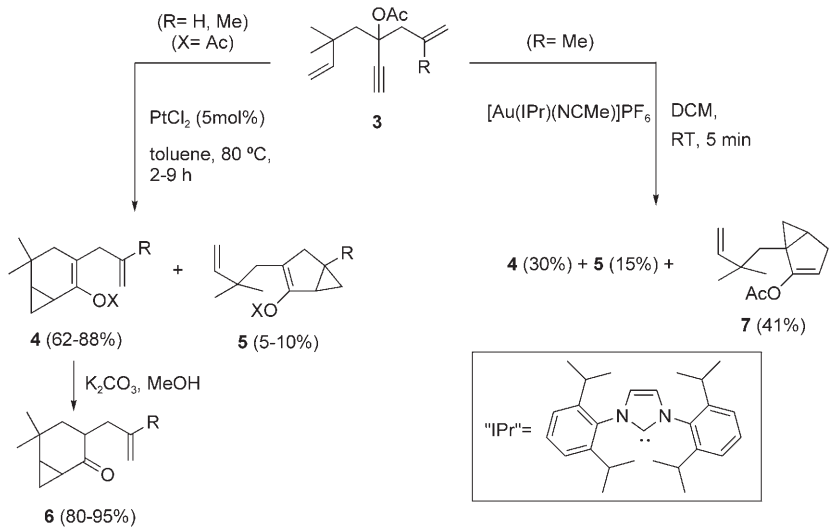
Most of the recent contributions to this subject are based on a preliminary communication by Rautenstrauch in 1984 reporting the $[PdCl_2(MeCN)_2]$-catalyzed cycloisomerization reaction of unsaturated propargylic acetates (**1**; $n=2$ and 3; R = alkyl) leading to bicyclic derivatives (**2**) in poor yields (10–40%), without further structural or experimental details (Scheme 1).[4]




Scheme 1. The Rautenstrauch cyclopropanation.[4]

Very surprisingly, this transition-metal-catalyzed rearrangement of a propargylic ester, that we propose to name the Rautenstrauch cyclopropanation, and its possible large synthetic potential, remained neglected for a long time. It was only very recently, in the course of a collaboration with Malacria's group when we rediscovered this reaction, reported in 2002, in the course of the $PtCl_2$-mediated transformation of some 4-ethynyl-octa-1,7-dien-4-carboxylates (**3**), which provided mixtures of compounds **4** and **5**, major product (**4**) being obtained in better and synthetically useful chemical yields (Scheme 2).[6] Note that the structure of the precursor **3** allowed not only the preferred Rautenstrauch cyclopropanation of the 6-hepten-1-yn-3-carboxylate, but the simultaneous and first example of a similar reaction on a 5-hexen-1-yn-3-carboxylate yielding bicyclo[3.1.0]hexenol acetate (**5**).[6] As reported, the Rautenstrauch cyclopropanation was still possible by shortening and/or by elongation of the tether connecting the double bond and the propargylic center, allowing the synthesis of a series of bicyclo-[*n*.1.0]enol carboxylates, a fact that has resulted, for instance, in a new method for the synthesis of simple, or fused, cyclooctane derivatives.[6] In addition, a very mild method was at hand for the synthesis of enol acetates, the methanolysis of which led to the corresponding bicyclo-[*n*.1.0]ketones (**6**) in excellent yields (Scheme 2) in a two-step protocol,[6] which can be regarded as an equivalent of the cycloisomerization of α-diazocarbonyl compounds[7] with evident advantages.

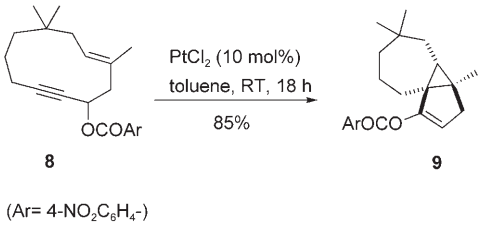



Scheme 2. The Rautenstrauch cyclopropanation rediscovered.[6]

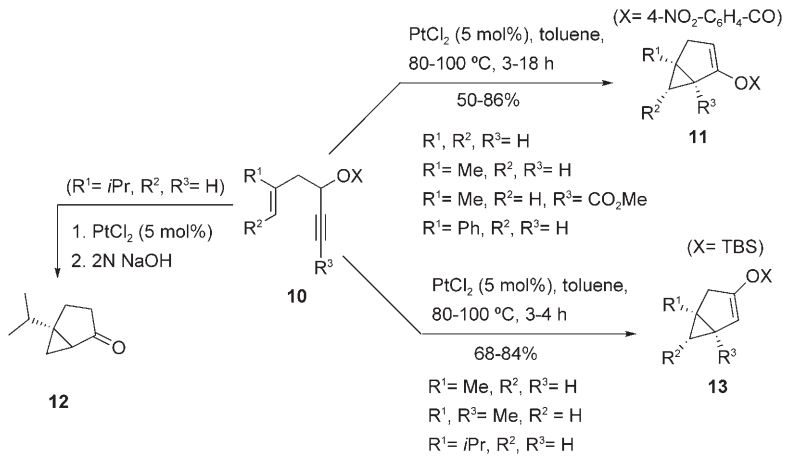
After our preliminary communication[6] a plethora of manuscripts has been published showing the scope and generality of this cyclopropanation method. Very recently, for instance, Nolan has reported that the use of *N*-heterocyclic carbene (NHC) as ligands in the gold(I)-catalyzed cycloisomerization of the same precursor **3** affords, in addition to compounds of type **4** and **5**, a new carbocyclic product **7** in variable yields depending on the catalytic system {in the best case, 41% using $[Au(IPr)(NCMe)]PF_6$}[8] (Scheme 2). This report shows how subtle modifications on the catalytic system can affect the course of these cycloisomerization reactions.

Similarly, Malacria's group has described the $PtCl_2$-catalyzed transannular cycloisomerization of 1,5-enynes, showing the power of this methodology for the stereocontrolled access to tricyclic derivatives (Scheme 3).[9]

In a very interesting work, the same group has also re-investigated the previously observed $PtCl_2$-catalyzed cycloisomerization of a 1,5-enyne embedded in precursor **3** (Scheme 2), by extending it to more simple and diverse secondary 5-en-1-yn-3-ol systems (**10**).[10] As shown in Scheme 4, the expected hexabicyclo-[3.1.0]enol-4-nitrobenzoates (**11**) were obtained in good yields using precursors substituted at the double bond and/or at the acetylenic moiety. A mechanism has been proposed and a practical application to the synthesis of sabina ketone (**12**) has been reported.[10] However, a more relevant finding described in this paper was the $PtCl_2$ cycloisomerization reaction of related free alcohols or *tert*-butyldimethylsilyl ethers (OTBS); under the same experimental conditions the silyloxy enol ethers **13** were obtained in good yield from compounds **10** (Scheme 4). Note that in this case a 1,2-hydrogen shift leaves the silyloxy moiety at the same position, while in the carboxylate-containing precursors the migrating group was the acyloxy moiety affording the rearranged enol ester. Again, a subtle change on the type of protecting group allowed the authors to favor the migration of one of the possible functional groups, and consequently, the preparation of different bicyclo[3.1.0]hexane ketones from readily available unsaturated propargylic derivatives.[10,11]

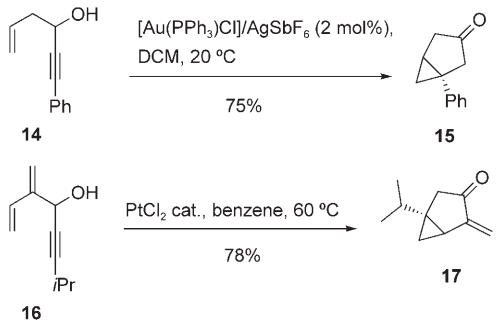



Scheme 3. $PtCl_2$-catalyzed transannular cycloisomerization of 1,5-enynes.[9]




Scheme 4. $PtCl_2$-catalyzed cycloisomerization of 5-en-1-yn-3-ol systems.[10]

In an independent work, Fürstner and co-workers have reported that the Rautenstrauch cyclopropanation of an acetylated hydroxylated 1,5-enyne can be promoted by using AuCl as catalyst,[12] and have also analyzed in depth the metal-catalyzed cycloisomerization of hydroxylated enynes [see for instance the case of compound **14** affording ketone **15** (Scheme 5)], including the stereochemical implications.

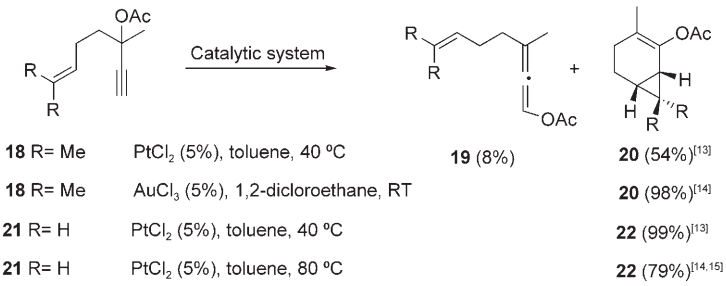



Scheme 5. Metal-catalyzed cycloisomerization of hydroxylated enynes.[12]

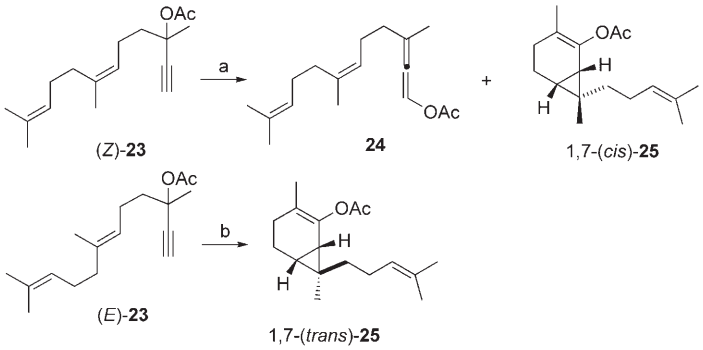
Finally, the synthesis of natural sabinone (**17**) has been described from a suitable precursor **16** (Scheme 5).[12]

In the meantime our group has explored different aspects of the Rautenstrauch cyclopropanation.[13] New 1,6-enyne derivatives were prepared, simplifying the structure of our former precursors **3** (Scheme 2), including a methyl substituent at the quaternary propargylic center, fixing in two methylene carbons the tether connecting the unsaturated double bond with the quaternary center, moving the *gem*-dimethyl groups to the terminal carbon of the alkene moiety, and incorporating different acyloxy groups (acetyloxy, benzoyloxy, tricholoroacetyloxy, 3,4,5-trimethoxybenzoyloxy, carbonate) to operate in the rearrangement process.[13] Not unexpectedly, in the usual experimental conditions, and from all these derivatives, compound **18** gave the best results, affording a mixture of the not previously detected allene-type of compounds **19**, and the expected Rautenstrauch product (**20**) in moderate yield (Scheme 6); very interestingly, compound **21** lacking the methyl groups at the terminal olefinic bond, afforded the enol acetate **22** in almost quantitative chemical yield (Scheme 6).

In an independent work, Fürstner and Hannen have also prepared the same compounds (**18**, **21**) and submitted to transition-metal-catalyzed cycloisomerization, confirming our own results, but improving significantly the chemical yields, since $AuCl_3$ worked much efficiently than $PtCl_2$, affording clean reaction mixtures, free from the allene secondary products.[14,15] Starting from commercial nerylacetone, compound (*Z*)-**23** (Scheme 7) has been synthesized and submitted to cyclization giving allene **24** and enol ester 1,7-*cis*-**25**, in higher yield when using $AuCl_3$[14] rather than $PtCl_2$ as catalyst.[13] Similar results were obtained from precursor (*E*)-**23**, prepared from geranylace-




Scheme 6. Metal-catalyzed cycloisomerization of new propargylic acetates.[13–15]



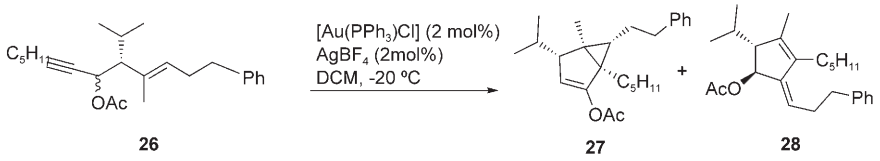

Scheme 7. Reagents: a: $PtCl_2$ (5%), toluene, 40 °C, 32 h [**24** (10%) + 1,7-(*cis*)-**25** (49%)][13] a: $AuCl_3$ (5 mol%), 1,2-dichloroethane [1,7-(*cis*)-**25** (87%)][15] b: $AuCl_3$ (5 mol%), 1,2-dichloroethane [1,7-(*trans*)-**25** (95%)][15]

tone, furnishing compounds with the opposite stereochemistry at the double bond in the allene derivative and at the cyclopropyl ring in the enol ester (Scheme 7).[13,15] These results clearly confirmed that transition-metal-promoted cycloisomerization process of trisubstituted alkenes is possible and proceeds stereospecifically translating the configuration of the reacting alkene into the stereochemistry of the forming cyclopropane, the *Z* isomer affording the *cis* isomer, while the *E* isomer leads to the corresponding *trans* derivative.

Finally, note that compounds **20** and **25** have the skeleton of carane-type of terpenoids, and that the methodology appears as a simple and efficient entry to this family of natural products.[13] Fürstner and Hannen successfully converted intermediate **20** into 2-carene, and compound **25** into sesquicarene.[15]

Gagosz has also reported on the gold(I)-catalyzed isomerization of 3-hydroxylated 1,5-enynes showing that different reaction pathways can be involved in these transformations depending on substitution pattern and the relative stereochemical arrangement of substituents.[16a] As an example, it has been described that acetate **26**, submitted to cyclization as a mixture of *syn*:*anti* (6:1) isomers, afforded compounds **27** and **28** in 10% and 74% yields, respectively (Scheme 8);




Scheme 8. Cycloisomerization of compound **26**.[16]

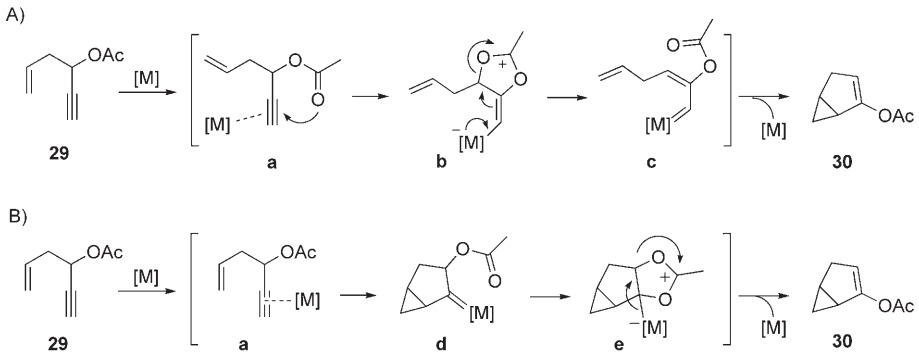
product **27** is the normal Rautenstrauch adduct, but **28** corresponds to a new mode of skeletal reorganization.[16]

In view of the evident interest of these results, the mechanism of this rearrangement has been immediately addressed. Accordingly, a simple proposal was advanced,[6] and widely accepted.[8–10,13–15,17] As shown in Scheme 9A, the acetate in a typical product (**29**) might be able to participate in the rearrangement by attacking the polarized metal–alkyne complex initially formed; then, the resulting metallocarbene is trapped by the terminal alkene giving a product **30** in which the acetyloxy group has migrated.

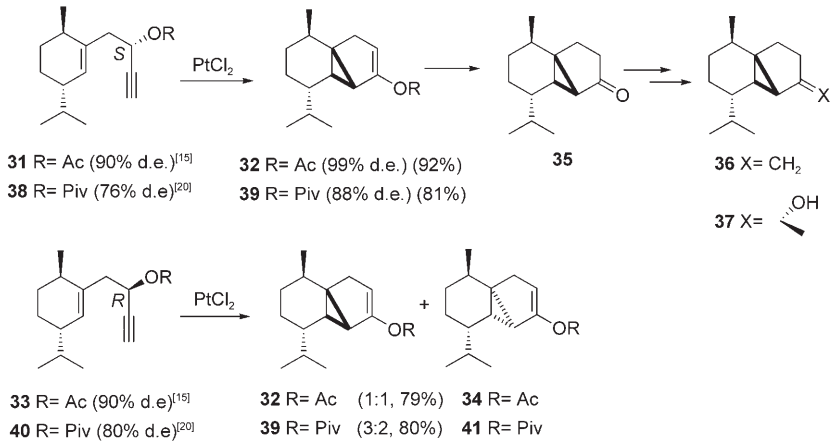
However, computational analyses carried out by us on 1,5- and 1,6-enynes, have revealed that an alternative path involving the inverse sequence of steps should be possible and energetically favored.[18] As shown in Scheme 9B, the activation of the triple bond by the metal complex triggers the intramolecular nucleophilic attack of the double bond by an *endo*-pathway, leading to a cyclopropylmetallocarbenoid (**d**). The formation of this key intermediate has also been proposed, and now is widely accepted in other $Pt^{II}$-mediated cycloisomerizations of enynes.[3,19] A subsequent stepwise 1,2-migration of the propargylic ester affords the bicyclic[*n*.1.0] derivatives. The computed energy values reveal that the step **a**→**b** (Scheme 9) takes place with an activation energy 2 kcal mol$^{-1}$ higher than **a**→**d** (Scheme 9B). In addition, the remainder energy profile for the first reaction path (Scheme 9A) shows values up to 20 kcal mol$^{-1}$ above those calculated for the alternative mechanism.

To validate or refute our proposal, it was necessary to prepare enantiomerically pure unsaturated propargylic carboxylates and then submit them to cyclization. This analysis has been recently reported. If the cyclopropanation step proceeds before the 1,2-acyloxy group migration, the stereochemical outcome should be clearly dependent on the absolute configuration of the stereocenter being destroyed. Although the most evident and simple substrate cases, such as enantiomerically pure precursors of type **29** (Scheme 9) still remain to be investigated, complex enantiomerically pure compounds have been synthesized and transformed by Fürstner[15] and Fehr.[20]

In a project directed to the synthesis of (−)-α-cubebene (**36**) and (−)-cubebol (**37**) (Scheme 10), Fürstner and Hannen prepared compounds (*S*)-**31** and (*R*)-**33** from (*R*)-(−)-carvone.[15] While acetate (*S*)-**31** afforded diastereomerically pure enol acetate **32** in a clean cycloisomerization catalyzed by $PtCl_2$ (2 mol%), in toluene, at 80 °C, under the same experimental conditions, (*R*)-**33** gave a mixture of compounds **32** and **34** in a 1:1 ratio, in 79% yield; compound **34** was shown to be the epimer of acetate **32** at the new formed stereocenters. Enol acetate **32** was submitted to methanolysis to give ketone **35** that after standard transformations provided natural cubebanes **36** and **37** (Scheme 10).[15]




Scheme 9. A) Original mechanism for the Rautenstrauch cyclopropanation,[6] and B) alternative mechanism according to DFT calculations.[18]



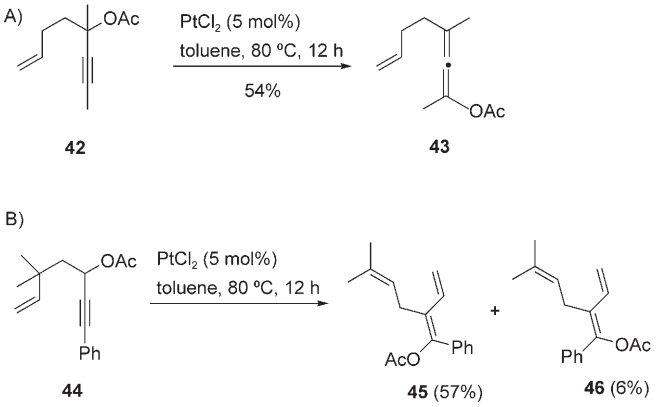

Scheme 10. Rautenstrauch cyclopropanation of enantiomerically pure propargylic carboxylates.[15,20]

Fehr has also described the synthesis of (−)-cubebol (**37**) from a related enol carboxylate **39** prepared by following a similar synthetic approach, by $PtCl_2$-promoted cycloisomerization of enantiomerically pivalate (*S*)-**38** (Scheme 10).[20] He also observed that a diastereomerically enriched mixture of epimer (*R*)-**40** gave in addition to the previously isolated pivalate **39**, a new enol pivalate **41** that resulted to be its epimer at the new stereocenter. Fehr has also proved that inexpensive $[Cu(CH_3CN)_4]BF_4$ efficiently catalyzes all these cycloisomerizations.[20]

These results support our mechanistic proposal, and unequivocally confirm that the chirality at the propargylic center determines the stereochemical outcome of the Rautenstrauch cyclopropanation, and that this reaction precedes the rearrangement event.[21] Hence, the transfer of chiral information cannot be justified by a planarized, achiral, vinyl carbene intermediate **c** (Scheme 9A), but should result from a C–C bond-forming process that takes place before the cleavage of the stereogenic C–O bond.[22] Accordingly, the mechanistic proposal in Scheme 9A must be dismissed and reconsidered in future developments.

Finally, note that the most significant limitation for the intramolecular Rautenstrauch cyclopropanation concerns the substitution at the terminal acetylene carbon in hept-6-en-1-yne derivatives. As shown, allene **43** is formed through transition-metal-catalyzed 1,3-migration of the acetate group in precursor (**42**)[13,15] (Scheme 11A), whereas compound **44** affords open-chain trienes **45** and **46**, as a result of a further isomerization of the allene structure, which undergoes a 3,3-rearrangement.[23]

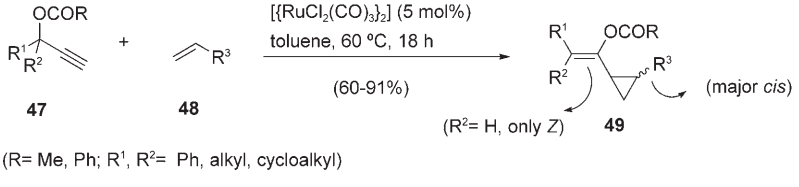
However, in a very recent and interesting communication, Buzas and Gagosz[16b] have shown that the gold(I)-catalyzed cycloisomerization of 5-en-2-yn-1-yl acetates provides an efficient entry to acetoxy bicyclo[3.1.0]hexenes, which can be converted into 2-cycloalken-1-ones.




Scheme 11. Unsuccessful Rautenstrauch cyclopropanation processes. A) Allene synthesis by $PtCl_2$-catalyzed rearrangement of enyne acetates.[15] B) Tandem $PtCl_2$-catalyzed thermal 3,3-rearrangement of enyne acetates.[23]

## The Intermolecular Process: The Reaction of Tertiary Propargylic Acetates with Alkenes

Soon after our publication,[6] Ohe and Uemura published the intermolecular version of the Rautenstrauch cyclopropanation reaction.[24] This is a valuable transformation that allows the synthesis of vinyl cyclopropanes (**49**) from propargylic carboxylates (**47**) and alkenes (**48**; Scheme 12). A complete analysis of the reaction has been reported.[24b] Under the best experimental conditions using $[\{RuCl_2(CO)_3\}_2]$ as catalytic system, only tertiary, or secondary ($R^1$ = Ph, $R^2$ = H) propargylic carboxylates (**47**) and mono- or *gem*-disubstituted alkenes ($R^3$ = alkyl, phenyl, *O*-*t*-Bu, OAc, etc.; **48**; Scheme 12) proved to be suitable precursors in a reaction that is highly stereoselective affording only *Z*-**49** isomers at the double bond and major *cis* (from 3:1 to 9:1) isomers at the cyclopropane ring. Unsuccessful reactions have been observed for primary, secondary alkyl-substituted, and *gem*-diphenyl-substituted propargylic carboxylates.[24]




Scheme 12. Intermolecular Rautenstrauch Ru-catalyzed cyclopropanation of alkenes and propargylic carboxylates.[24]

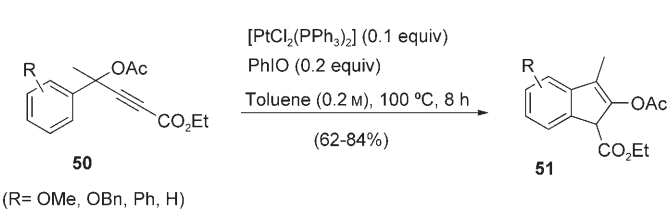
Further insights into this reaction have been provided by Toste and co-workers.[25] They have observed that, in contrast to the intramolecular Rautenstrauch cyclopropanation, no intermolecular transfer of chirality was detected in the [AuCl($PPh_3$)]-catalyzed reaction of an enantiomerically pure propargylic acetate with styrene, a fact that seems consistent with the formation of a vinyl gold(I)–carbene species as an intermediate. Remarkably, these authors have also developed a successful enantioselective gold(I)-catalyzed cyclopropanation of alkenes from propargylic esters by using chiral ligands such as (*R*)-DTBM-SEGPHOS-gold(I) (up to 70% *ee* was observed; DTBM-SEGPHOS = [(4,4′-bi-1,3-benzodioxole)-5,5′-diyl-bis(di(3,5-di-*tert*-4-methoxyphenyl)-phosphane)]).[25] Unfortunately, a deep mechanistic analysis to account for these apparently contradictory experimental facts between intra- and intermolecular version of this process has not be performed so far.

Tenaglia and Marc have extended this reaction to alkenes that remained unreacted under the Uemura's conditions,[24] including strained norbornenes, norbornadienes, and benzonorbornadienes, with success, the Ru complexes [RuCp-$(MeCN)_3$]$PF_6$ and [RuClCp-$(PPh_3)_2$] being the most efficient catalysts.[26]

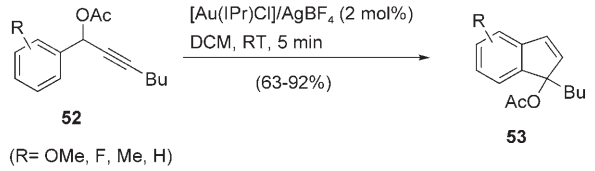
## Pentannulation Reactions on Aromatic Ring Systems

Pentannulation on aromatic or heterocyclic ring systems has emerged as a potent and useful tool in organic synthesis.[27] Very recently, propargylic esters have been investigated with success as suitable precursors in order to accomplish this task. For instance, Sarpong has reported that differently substituted propargylic acetates (**50**), easily available from acetophenone, on refluxing in toluene in the presence of [$PtCl_2$-$(PPh_3)_2$] as catalyst, gave the complex and highly functionalized indene derivatives **51** in good yields (Scheme 13).[28]

Nolan has reported that related secondary propargylic acetates **52**, when using NHC complexed with gold(I) salts, afford indenes **53** (Scheme 14), most probably involving a mechanism starting by the transition-metal electrophilic activation of the alkyne, followed by two successive 1,2-migrations (or a single 1,3-migration) of the acetate group, which after further activation by the [$Au^+$] fragment would lead to the final hydroarylation product.[29]

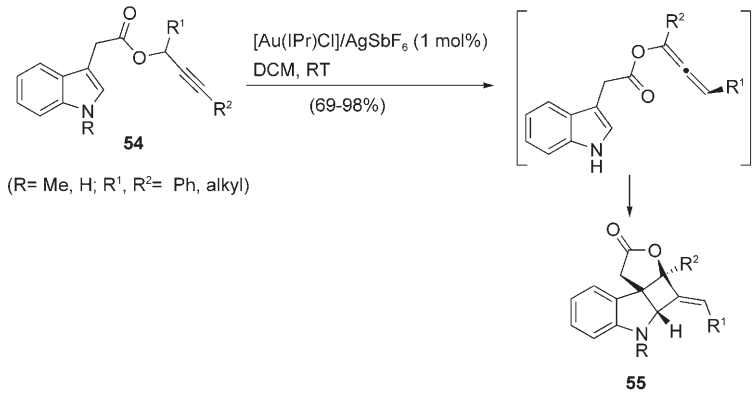



Scheme 13. Pentannulation reaction on propargylic acetates.[28]




Scheme 14. Pentannulation reaction on secondary propargylic acetates.[29]

Finally, Zhang has recently described an interesting issue for the transition-metal-catalyzed cycloisomerization of propargylic carboxylates, reporting the case in which the unsaturated moiety remains attached to the carboxylic ester group; in the synthesized precursors the double bond is now located in a β-substituted indol ring.[30] As shown in Scheme 15, the isomerization of secondary esters **54** to the highly functionalized 2,3-indoline-fused cyclobutanes **55** was efficiently catalyzed by [AuCl($PPh_3$)] with $AgSbF_6$ as additive, in dichloromethane as solvent, at room temperature.[30] The final product **55** is the result of a tandem Au-catalyzed 3,3-rearrangement to give an allene intermediate followed by a transition-metal-mediated [2+2]cycloaddition.[30]




Scheme 15. Tandem Au-catalyzed 3,3-rearrangement plus [2+2] cycloaddition of secondary propargylic esters.[30]

## Conclusion

The results summarized in this Concept highlight the strong synthetic potential and scope of late transition-metal-catalyzed reactions for fully atom economical and complex carbon–carbon bond-forming reactions. The Rautenstrauch cyclopropanation of readily available chiral or racemic propargylic carboxylates is thus a very useful reaction for the synthesis of complex bicyclo[*n*.1.0] enol carboxylates in high chemical yields; it proceeds under mild reaction conditions with high stereoselectivity and transfer of chirality, and is quite general from the structure–reactivity point of view.

The basic methanolysis of the resulting compounds provides bicyclo[*n*.1.0]ketones, valuable building blocks for the preparation of a variety of natural products. As a result, a more convenient and efficient synthetic strategy has been described that avoids the use of α-diazocarbonyl compounds for the same purpose. A reaction mechanism has been advanced and confirmed by experimental evidence, which supports the involvement of metallocarbenes as key species formed through a cyclopropanation event that precedes the 1,2-acyloxy migration. The intermolecular Rautenstrauch cyclopropanation has been also covered, showing that this reaction works very efficiently for the synthesis of new type of vinyl cyclopropyl derivatives. Finally, recent developments in the related pentannulation reaction of propargylic esters has also been included.

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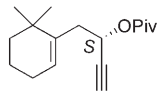
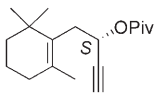


I



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