



Coinage metal-catalyzed carbo- and heterocyclizations involving alkenyl carbene intermediates as C3 synthons



Enol López, Olaya Bernardo, Luis A. López*

Departamento de Química Orgánica e Inorgánica, Instituto Universitario de Química Organometálica "Enrique Moles" and Centro de Innovación en Química Avanzada (ORFEO-CINQA), Universidad de Oviedo, c/Julián Clavería 8, 33006 Oviedo, Spain

ARTICLE INFO

Article history:

Received 5 July 2022

Revised 6 September 2022

Accepted 12 September 2022

Available online 16 September 2022

Keywords:

Coinage metals

Alkenyl carbenes

Three-carbon synthons

Carbocyclization

Heterocyclization

ABSTRACT

Over recent years, coinage metal alkenyl carbene intermediates have attracted significant attention as three-carbon synthons. Catalytically generated from a variety of readily available precursors, these intermediates can engage in a wide number of carbo- and heterocyclizations providing efficient routes to carbo- and heterocycles otherwise difficult to achieve. In this Review, we aim to highlight the most relevant advances in this exciting topic.

© 2022 The Author(s). Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Contents

Introduction	1
Common precursors for the catalytic generation of alkenyl carbene intermediates	2
(3 + n) carbocycloaddition reactions of alkenyl carbene intermediates	3
Synthesis of four-membered carbocyclic compounds via formal (3 + 1) cycloaddition reaction	3
Synthesis of five-membered carbocyclic compounds via formal (3 + 2) cycloaddition reaction	3
Synthesis of seven-membered carbocyclic compounds via formal (4 + 3) cycloaddition reaction	6
(3 + n) heterocycloaddition reactions of alkenyl carbene intermediates	6
Synthesis of four-membered heterocyclic compounds via formal (3 + 1) cycloaddition reaction	6
Synthesis of five-membered heterocyclic compounds via formal (3 + 2) cycloaddition reaction	6
Synthesis of six-membered heterocyclic compounds through formal (3 + 3) cycloaddition reactions	8
Synthesis of seven-membered heterocyclic compounds through formal (4 + 3) cycloaddition reactions	9
Summary and outlook	9
Declaration of Competing Interest	9
Acknowledgements	9
References	9

Introduction

The 1,3-dipolar cycloaddition reaction is arguably one of the most powerful methodologies for the construction of five-membered heterocyclic compounds [1]. Many 1,3-dipoles and dipo-

* Corresponding author.

E-mail address: lalg@uniovi.es (L.A. López).

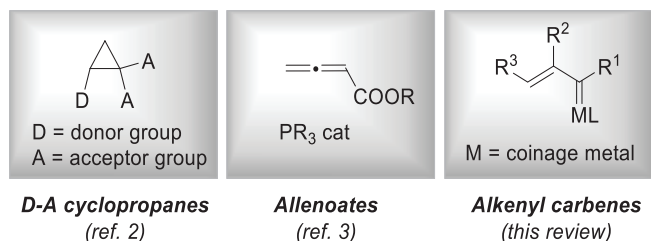
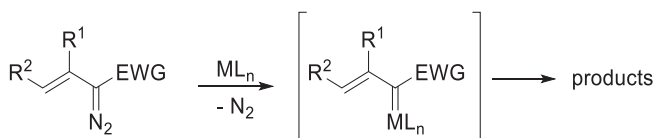


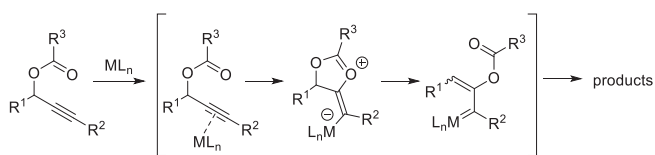
Fig. 1. Common three-carbon synthons.



Scheme 1. Stabilized vinyl diazo compounds as precursors for the generation of coinage metal vinyl carbene intermediates.

larophiles have been successfully developed allowing the synthesis of structurally diverse heterocyclic systems. The all-carbon version of this cycloaddition reaction would represent a convenient access to five membered carbocycles, common structural motifs found in a plethora of natural product and bioactive compounds. Unfortunately, this reaction remains highly challenging and a very few systems have been identified as suitable all-carbon 1,3-dipoles (Figure 1). In this regard, activated cyclopropanes, particularly those featuring donor and acceptor groups (the so called donor-acceptor (DA) cyclopropanes), because of the presence of a highly polarized bond, can engage in several Bronsted and Lewis acid catalyzed formal (3 + 2) cycloadditions affording functionalized five-membered carbo- and heterocycles [2]. On the other hand, the phosphine-catalyzed (3 + 2) cycloaddition reaction of allenyl esters has also recently emerged as a convenient methodology for the efficient and selective preparation of a wide range of carbo- and heterocycles, in which the allene derivative serves as a three-carbon synthon [3]. In the last few years, coinage-metal catalyzed transformations with generation of alkenyl carbene intermediates have evolved into a powerful synthetic tool. The purpose of this review is to showcase these recent contributions. Our discussion will focus almost exclusively on cyclizations in which the carbene intermediate serves as a three-carbon synthon. Consequently, processes such as cyclopropanations or isomerization, although extremely useful, will not be covered.

This Review first briefly discusses the most common precursors for the generation of alkenyl carbene intermediates. The reactivity of these intermediates will be discussed in the two remaining parts. First, we will focus on those synthetic procedures yielding carbocyclic compounds. Finally, a selection of synthetic procedures for the synthesis of heterocyclic compounds will be discussed.



Scheme 2. Coinage metal vinyl carbene intermediates from propargyl esters via [1,2]-acyloxy shift.

Common precursors for the catalytic generation of alkenyl carbene intermediates

Several precursors have demonstrated their suitability for the catalytic generation of alkenyl carbene intermediates in processes catalyzed by coinage metals [4].

Very likely, stabilized diazo compounds are the most popular precursors for the generation of carbene intermediates [5]. Those diazo compounds with a vinyl group attached to the diazo function, the so-called stabilized vinyl diazo compounds (Scheme 1), have been intensively investigated and have emerged as very fruitful reagents in transition metal catalyzed transformations. Most of these transformations are supposed to proceed by means of metal vinyl carbene intermediates. Rhodium catalysts are by far the most widely used ones in transformations of vinyl diazo compounds. However, coinage metals (particularly, gold) have recently evolved into useful catalysts for diazo compound decomposition. These studies demonstrated that coinage metal-based catalysts are in most cases complementary to the rhodium catalysts [6].

Because of the hazardous nature associated with some diazo compounds, attempts have been made to replace diazo compounds with safer and more stable carbene precursors. In this regard, important advances have been achieved by using *N*-sulfonylhydrazones [7]. In particular, vinyl-*N*-sulfonylhydrazones in the presence of transition metal catalysts have provided new synthetic opportunities based on the generation of vinyl carbene intermediates.

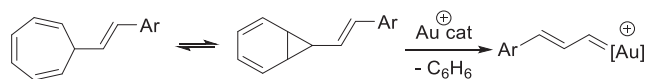
Propargyl esters and related propargylic derivatives are also common precursors for the generation of alkenyl carbene intermediates [8]. The metal-catalyzed transformations of these unsaturated substrates have been extensively investigated in the last two decades. This process would involve initial coordination of the C–C triple bond to the carbophilic catalyst. Then, 5-*exo*-dig cyclization and subsequent ring opening would generate carbene intermediates in a process involving a formal [1,2]-acyloxy shift (Scheme 2). The generated intermediate would evolve to the final products by diverse inter- or intramolecular processes. Based on this chemical behavior, a wealth of synthetic applications have been developed. Among coinage metals, gold complexes have been the most widely used catalysts in these transformations. This rearrangement is usually observed for terminal alkynes ($R^2 = H$) or alkynes featuring an ester group ($R^2 = COOR$). In some cases (mainly when $R^2 =$ alkyl or aryl), a competitive pathway leading to metal allene complexes via 6-*endo*-dig cyclization and subsequent ring opening was also reported. This alternative evolution has also found many synthetic applications [9].

While less popular, cyclopropene derivatives have been also reported to serve as suitable precursors for the catalytic generation of metal vinyl carbene intermediates [10]. This process would involve initial coordination and subsequent ring opening of the cyclopropene with generation of a reactive carbene intermediate that is trapped in situ by suitable reagents (Scheme 3).

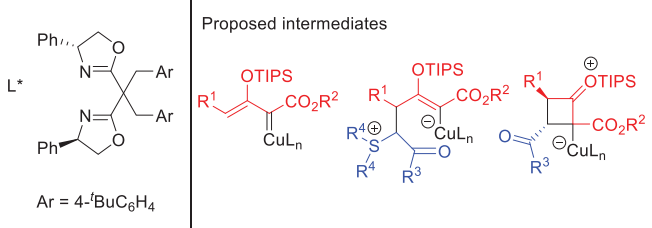
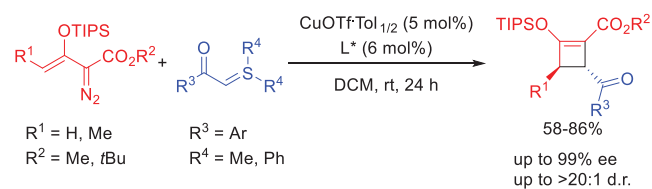
In a completely different approach, the group of Echavarren has reported the generation of alkenyl gold-carbene intermediates from 7 alkenyl 1,3,5-cycloheptatrienes through a *retro*-Buchner



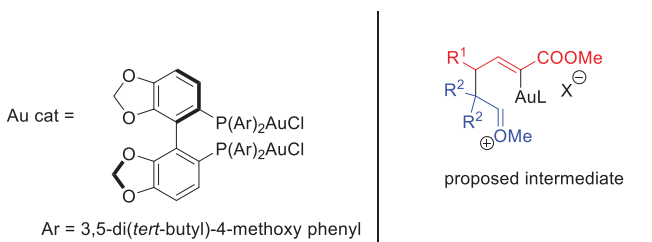
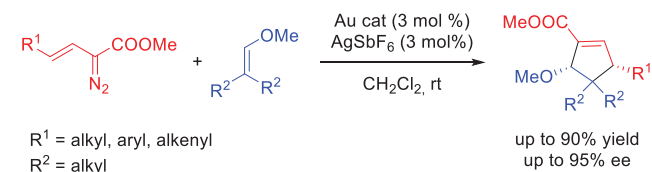
Scheme 3. Coinage metal vinyl carbene intermediates from cyclopropenes.



Scheme 4. Alkenyl gold(I) carbenes by *retro*-Buchner reaction from 7 alkenyl 1,3,5-cycloheptatrienes.

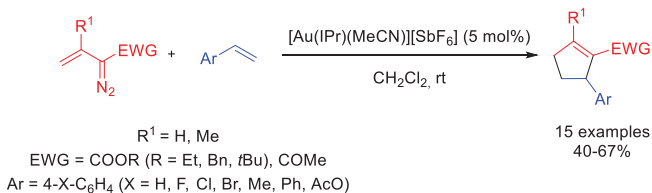


Scheme 5. Copper(I)-catalyzed (3 + 1) cycloaddition of sulfur ylides and metalloenolcarbenes.

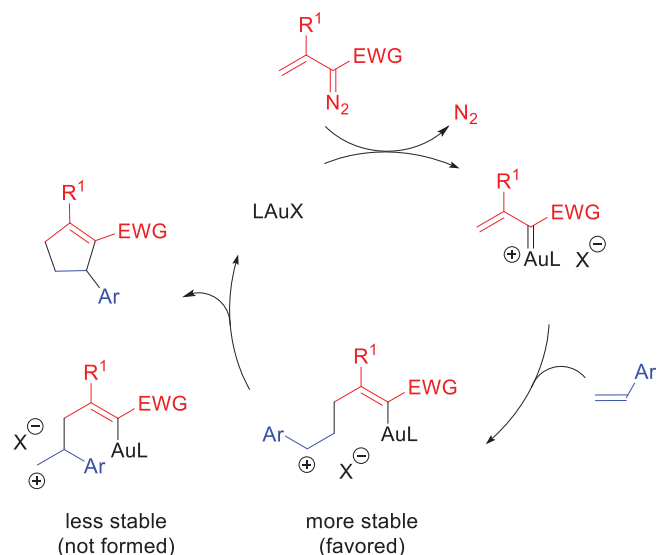


Scheme 6. Enantioselective gold(I)-catalyzed (3 + 2) cycloaddition reaction of vinylidiazocompounds and enol ethers.

reaction (Scheme 4) [11]. The so generated reactive intermediates can be trapped by alkenes affording vinylcyclopropanes in a highly selective way [12].



Scheme 7. Gold(I)-catalyzed (3 + 2) cycloaddition reaction of vinylidiazocompounds and styrene derivatives.



Scheme 8. Proposed mechanism for the gold(I)-catalyzed (3 + 2) cycloaddition reaction of vinylidiazocompounds and styrene derivatives.

(3 + *n*) carbocycloaddition reactions of alkenyl carbene intermediates

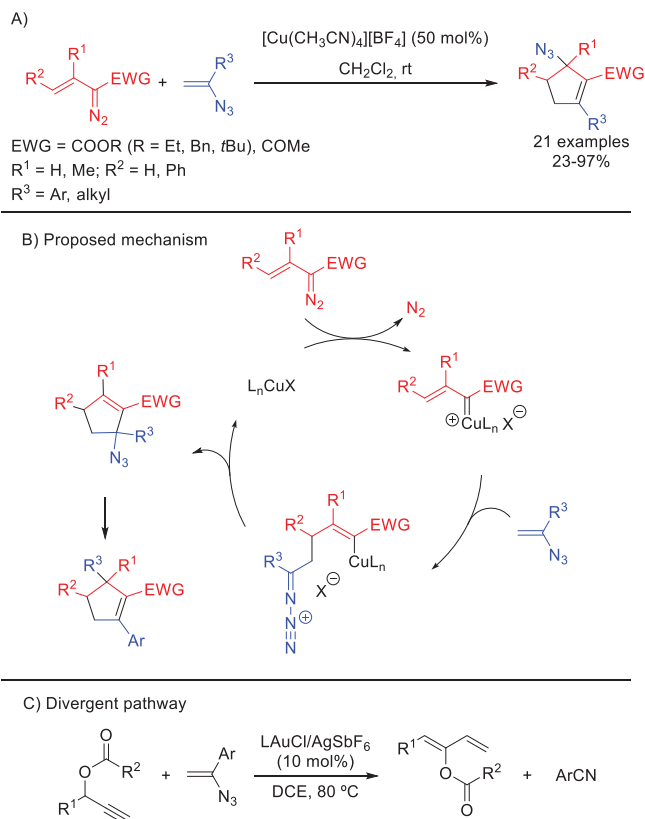
Synthesis of four-membered carbocyclic compounds via formal (3 + 1) cycloaddition reaction

In 2017, Doyle and co-workers reported the synthesis highly functionalized cyclobutene derivatives through copper-catalyzed (3 + 1) cycloaddition reaction of triisopropylsilyl-substituted enoldiazoacetates with nucleophilic sulfur ylides (Scheme 5) [13–14]. Good yields and high enantio- and diastereoselectivities (up to 99% ee and > 20:1 d.r.) were achieved with a chiral copper(I) triflate/double sidearmed bisoxazoline complex catalyst. This transformation is proposed to proceed through generation of a copper-enolcarbene intermediate. Then, nucleophilic addition of the sulfur ylide onto the electrophilic vinyllogous position of the metal carbene would generate a vinylcopper intermediate, which would evolve to the final functionalized cyclobutene by displacement of the R₂S leaving group.

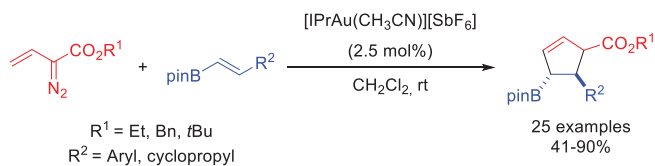
Synthesis of five-membered carbocyclic compounds via formal (3 + 2) cycloaddition reaction

The reaction of several unsaturated substrates such as alkenes, alkynes and allenes with alkenyl carbene intermediates, generated *in situ* from suitable precursors, has recently evolved into a powerful method for the regioselective synthesis of five-membered carbocyclic compounds.

A major breakthrough in this field was reported by Davies and coworkers, who developed the enantioselective gold(I)-catalyzed (3 + 2) cycloaddition of vinylidiazooacetates and enol ethers (Scheme 6) [15]. In this way, highly functionalized cyclopentene derivatives were obtained in good yields and enantioselectivities when (*R*)-DTBMSegphos(AuCl)₂ was used as the catalyst. This gold-catalyzed transformation is proposed to proceed by initial generation of a gold carbene intermediate. Vinyllogous attack of the vinyl ether would generate a zwitterionic intermediate which could directly evolve to the final cyclopentene derivative. An alternative pathway involving (4 + 2) cycloaddition between the gold carbene intermediate and the enol ether with generation of a metallocyclohexene could not be completely ruled out. Interestingly,

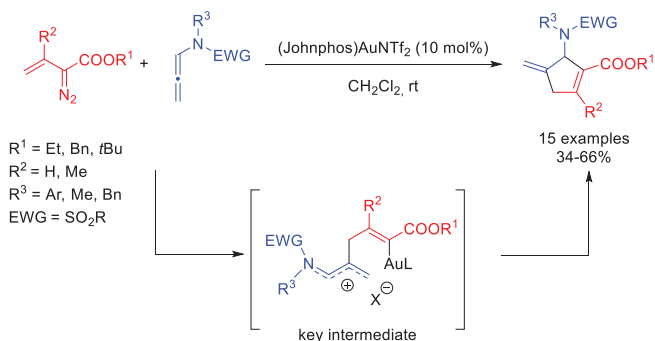


Scheme 9. A) Copper(I)-promoted (3 + 2) cycloaddition/allylic azide rearrangement of stabilized vinyl diazo compounds and vinylazide derivatives. B) Proposed mechanism. C) Divergent outcome in the gold-catalyzed reaction of propargyl esters and vinylazides.



Scheme 10. Gold-catalyzed (3 + 2) cycloaddition of vinyl diazo compounds and pinacol alkenylboronates.

this outcome stands in marked contrast with that previously reported by the same group for the rhodium-catalyzed reaction [16].



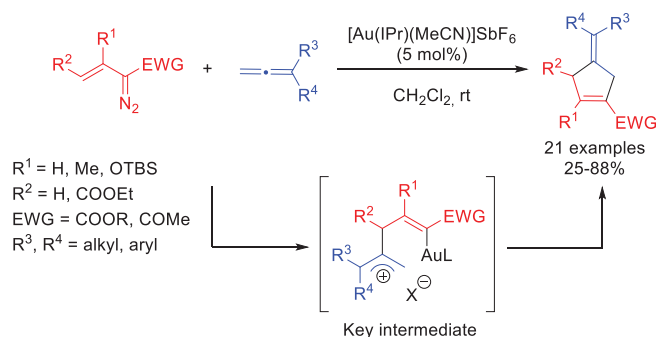
Scheme 11. Gold(I)-catalyzed (3 + 2) cycloaddition reaction of vinyl diazo compounds and allenamides.

Based on previous research on gold-catalyzed reactions of stabilized vinyl diazo compounds and non-activated alkenes [17], our group reported the synthesis of functionalized cyclopentene derivatives by formal (3 + 2) cycloaddition of alkenyl gold-carbene intermediates with styrenes (Scheme 7) [18]. Cyclopropane derivatives resulting from a competitive (2 + 1) cyclization were formed as minor side-products (5–15 %).

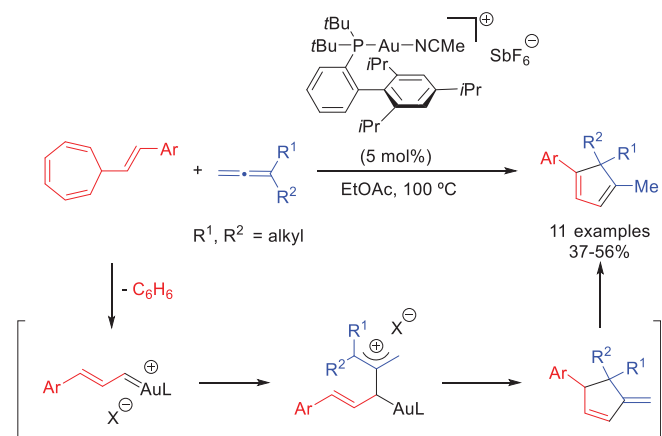
A mechanistic proposal for the formation of the cyclopentene derivatives is depicted in Scheme 8. Initial decomposition of the vinyl diazo compound would generate a gold carbene intermediate. On the basis of previous results, this intermediate would display a high electrophilic character at the vinylogous position. Consequently, it would be involved in a stepwise (3 + 2) cycloaddition reaction initiated by attack of the styrene derivative to the vinylogous position with formation of a cationic intermediate. A final cyclization step would provide the final products. In this regard, the observed regiochemical outcome would rely on the formation of the most stable benzylic carbocationic intermediate.

A related (3 + 2)-cycloaddition has been reported in the copper-promoted reaction of vinyl diazo compounds and vinylazides (Scheme 9, A). Specifically, functionalized cyclopentene derivatives were obtained through a formal (3 + 2) cycloaddition/allylic azide rearrangement sequence [19]. This process demonstrated a good scope in the azide component. Notably, the azide function is preserved in the final cyclopentene derivatives, thus providing interesting synthetic opportunities. The proposed mechanism for this transformation (Scheme 9, B) would rely on initial reaction of the vinyl diazo compound with the copper(I) complex to generate a copper(I) alkenylcarbene intermediate. Then, the vinylazide would attack to the vinylogous position of the carbenic species. Subsequent cyclization and allylic rearrangement of the azide function would account for the formation of the final products. The formation of a highly stable alkene would be the driving force for the rearrangement of the azide. Notably, these results contrasted with those previously reported by Liu and coworkers in the reaction of vinylazides with gold alkenylcarbene intermediates generated from propargyl esters, which provided diene derivatives (Scheme 9, C) [20].

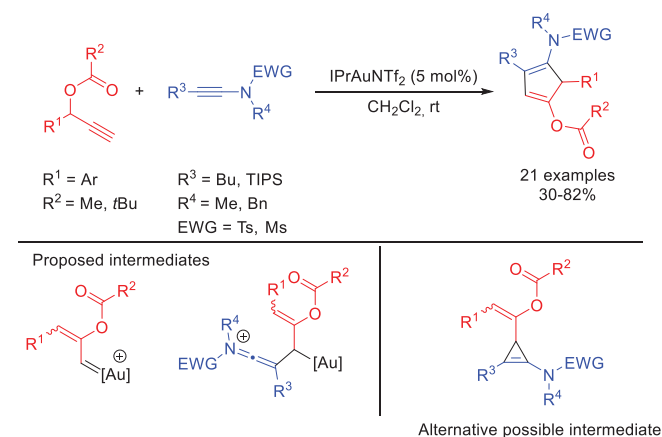
More recently, we also reported the gold-catalyzed reaction of vinyl diazo compounds and alkenylboronates to give cyclopentenyl boronic esters (Scheme 10) [21]. This formal (3 + 2) cycloaddition reaction proceeds in good yields with complete regio- and stereoselectivity. As in the previous examples, a stepwise mechanism with initial generation of an electrophilic gold carbene intermediate would account for the formation of the formal (3 + 2) cycloadducts. Through well-established procedures for the derivatization of the boronate moiety, the (3 + 2) cycloadducts available by this protocol could be transformed efficiently into a range of functionalized cyclopentene derivatives.



Scheme 12. Gold(I)-catalyzed (3 + 2) cycloaddition of vinyl diazo compounds and allenes.



Scheme 13. Gold(I)-catalyzed synthesis of cyclopentadienes from styrylcycloheptatrienes and allenes.



Scheme 14. Gold(I)-catalyzed reaction of propargyl esters and ynamides.

Gold-catalyzed transformations of vinylidiazocompounds with more elaborated unsaturated systems have also been reported. For instance, some gold(I)-catalyzed formal (3 + 2) cycloaddition reactions between alkenyl gold carbene intermediates and allenes have been developed. In 2016, our group reported the reaction of allenamide derivatives with vinylidiazocompounds to afford five-membered carbocycles regioselectively (Scheme 11) [22]. A relevant feature of this cycloaddition reaction is the participation of the proximal C=C bond of the allenamide, a very unusual regioselectivity pattern in gold-catalyzed cyclizations of allenamides [23].

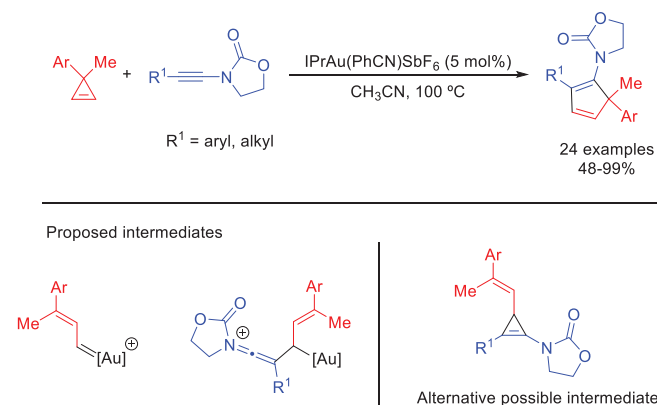
This transformation is proposed to proceed through initial decomposition of the diazo component and subsequent attack of central carbon of the allenamide to the electrophilic vinylogous position of the generated alkenyl carbene intermediate. Subsequent cyclization would deliver the final cycloadducts. Very likely, the preferential activation of the diazo partner with generation of a gold carbene intermediate would account for this divergent regiochemical outcome.

Soon after, we extended this reactivity to electronically unbiased allenes. Specifically, we found that reaction of non-activated allene derivatives with alkenyldiazo compounds in presence of 5 mol% of [IPrAu(MeCN)][SbF₆] provided alkylidenecyclopentene derivatives (Scheme 12) [24]. As in the reaction of allenamides, a stepwise mechanism involving initial activation of the diazo compound with generation of a gold carbene intermediate has been proposed. Nucleophilic attack of the central carbon of the allene to the vinylogous position of the carbene intermediate would generate an allyl cation, that would evolve to the final product through a cyclization reaction. It is worth to note that this process represented the first intermolecular gold-catalyzed cycloaddition involving non-activated allene derivatives.

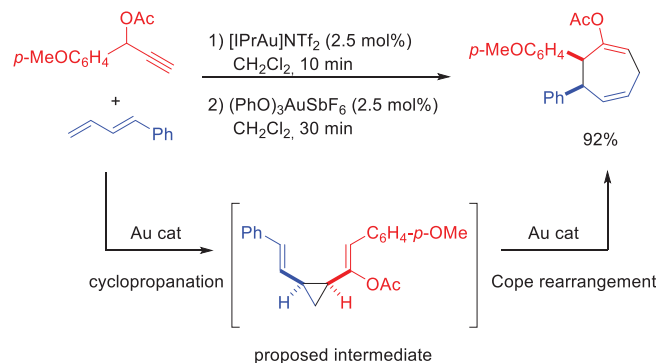
In 2017, Echavarren and coworkers reported that styryl gold(I) carbenes, generated from 7-styryl-1,3,5-cycloheptatrienes, react with allenes to give cyclopentadiene derivatives arising from a formal (3 + 2) cycloaddition reaction in moderate yields (Scheme 13) [25]. As stated before, the reaction would involve initial gold(I)-promoted *retro*-Buchner reaction of 7-styryl-1,3,5-cycloheptatrienes to release benzene and generate a styryl gold(I) carbene. Subsequent attack of the central carbon of the allene component to the carbene carbon atom would generate an allyl cation intermediate. Cyclization and isomerization would deliver the final cyclopentadiene derivative.

The intermolecular trapping of coinage metal vinyl carbene intermediates by alkynes remains challenging. In 2013, Hashmi and co-workers reported the regioselective synthesis of functionalized cyclopentadienes by gold-catalyzed cyclization of ynamides and propargyl esters (Scheme 14) [26]. This formal (3 + 2) cycloaddition reaction would involve initial generation of a gold carbene intermediate through 1,2 acyloxy shift. This intermediate would evolve to the final products through a stepwise pathway consisting of initial attack of the nucleophilic carbon atom of the ynamide to the electrophilic one of the carbene intermediate and final ring closure of the resulting intermediate. An alternative pathway involving cyclopropanation of the ynamide, ring opening of the resulting cyclopropene and final cyclization could also operate.

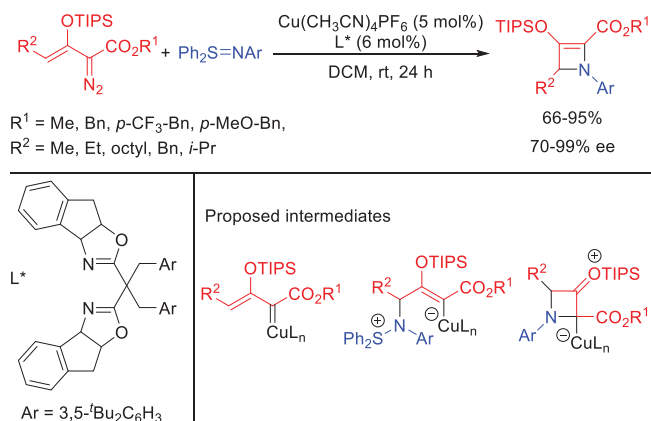
In a related transformation, Chen, Huang and coworkers reported the gold-catalyzed reaction of cyclopropenes and ynamides in 2017 [27]. In this transformation, cyclopentadiene deriva-



Scheme 15. Gold(I)-catalyzed reaction of cyclopropenes and ynamides.

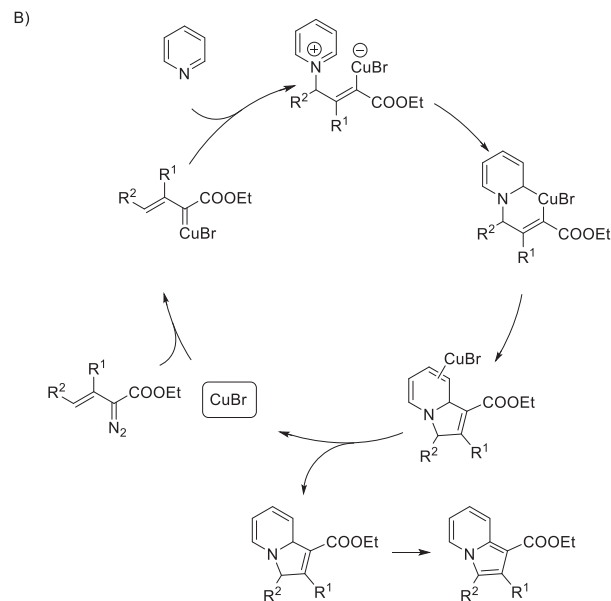
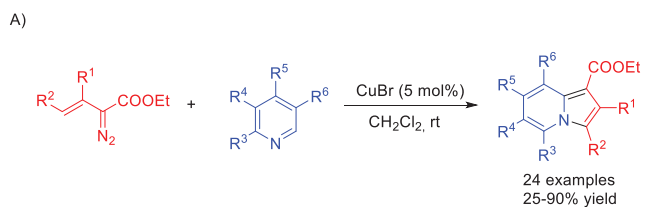


Scheme 16. Gold(I)-catalyzed cycloheptanulation reaction.



Scheme 17. Copper(I)-catalyzed (3 + 1) cycloaddition of imido-ylide and metallo-enolcarbenes.

tives arising from a formal regioselective (3 + 2) cycloaddition were formed in excellent yields (Scheme 15). This reaction would proceed by initial activation of the cyclopropene with generation of a gold carbene intermediate. Nucleophilic attack of the ynamide to the carbene species followed by cyclization would account for the formation of the final products. As in the previous example, the authors cannot discard an alternative pathway involving initial cyclopropanation of the ynamide.



Scheme 18. A) Copper(I)-catalyzed (3 + 2) cycloaddition of stabilized alkenyldiazo compounds and pyridines. B) Proposed pathway.

Synthesis of seven-membered carbocyclic compounds via formal (4 + 3) cycloaddition reaction

The synthesis of seven-membered carbocyclic compounds from coinage metal alkenyl carbene intermediates remains clearly underdeveloped. In 2011, Nevado and coworkers reported the highly stereoselective synthesis of *cis*-2,3-disubstituted cycloheptenyl acetates through gold-catalyzed reaction of propargyl acetates and 1,4-dienes [28]. A representative example is depicted in Scheme 16. This cycloheptannulation reaction is proposed to proceed through a sequence comprising cyclopropanation and subsequent Cope rearrangement. Based on this transformation, a stereocontrolled approach to the Frondosins A and B scaffolds was also reported.

(3 + n) heterocycloaddition reactions of alkenyl carbene intermediates

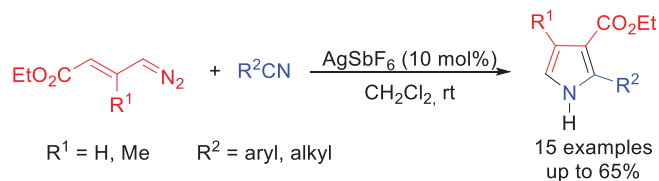
Synthesis of four-membered heterocyclic compounds via formal (3 + 1) cycloaddition reaction

To the best of our knowledge, there is only a contribution on the synthesis of four-membered heterocyclic compounds through formal (3 + 1) cycloaddition involving alkenyl carbene intermediates [29]. In 2019, Doyle and coworkers reported the enantioselective synthesis of tetrasubstituted azetidine 2-carboxylates through copper(I)-catalyzed (3 + 1) cycloaddition of silyl-protected γ -substituted enoldiazoacetates and *N*-arylsulfilimines (Scheme 17) [30]. The 2-azetidine products were obtained in high yields and with good to excellent enantioselectivity when using a copper(I)-sabox catalyst. This transformation would proceed by initial generation of a *Z*-metallo-enolcarbene intermediate followed by nucleophilic addition of the imido-sulfur ylide onto the electrophilic vinylogous carbon of the carbene intermediate. Subsequent cyclization by displacement of the diphenyl sulfide group and copper elimination would account for the formation of the final products. Moreover, the (3 + 1) cycloadducts were stereoselectively transformed into relevant azetidine-2-carboxylates by Pd-catalyzed hydrogenation.

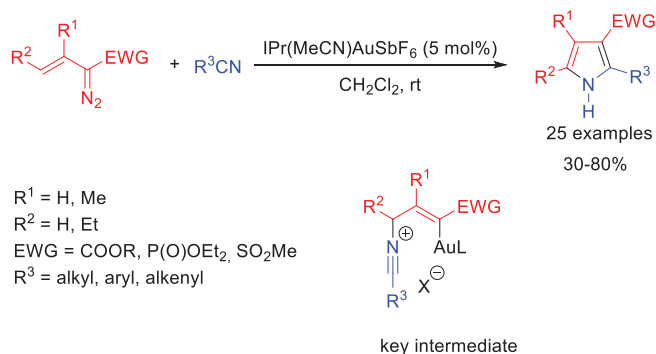
Synthesis of five-membered heterocyclic compounds via formal (3 + 2) cycloaddition reaction

A number of relevant nitrogen heterocycles has been prepared by (3 + 2) cycloaddition reaction of the corresponding precursor of the alkenyl carbene intermediate with the appropriate unsaturated nitrogen-containing substrates.

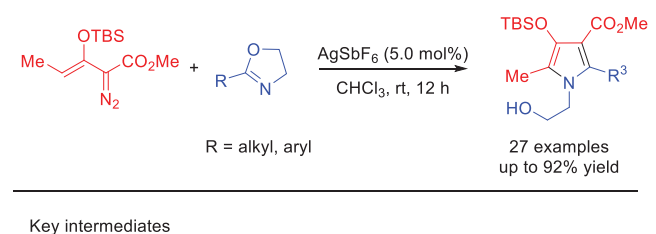
Inspired by an elegant contribution by Doyle and coworkers reporting the copper(II)-catalyzed synthesis of dihydropyrrole derivatives through formal (3 + 2) cycloaddition reaction of α,β -unsaturated imines with vinyldiazoacetates [31], our group investigated the reactivity of vinyldiazo compounds toward pyridines [32]. This study resulted in the copper(I)-catalyzed regioselective synthesis of functionalized indolizines resulting from a formal (3 + 2) cycloaddition reaction (Scheme 18, A). An extremely wide scope of pyridine derivatives successfully undergoes this cycloadd-



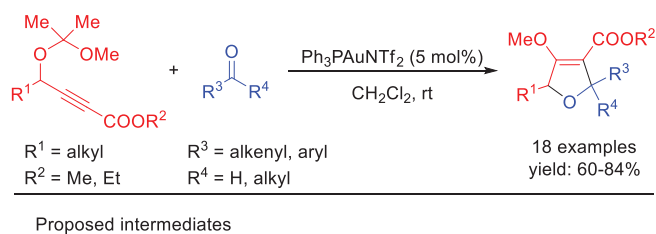
Scheme 19. Silver(I)-catalyzed cycloaddition of vinylogous diazoesters and nitriles.



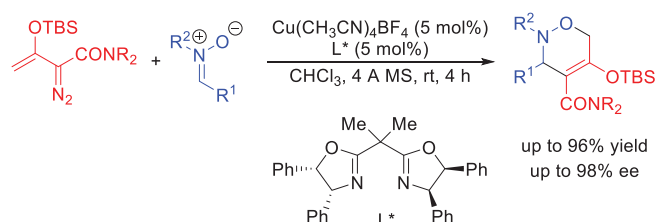
Scheme 20. Gold(I)-catalyzed cycloaddition of stabilized diazo compounds and nitriles.



Scheme 21. Synthesis of functionalized pyrrole derivatives by Ag(I)-catalyzed reaction of enoldiazoacetates and imino ethers.



Scheme 22. Gold(I)-catalyzed (3 + 2) approach to functionalized 2,5-dihydrofurans.



Scheme 23. Copper(I)-catalyzed (3 + 3) cycloaddition reaction of enoldiazoacetates with nitrones.

dition including those featuring functional groups such as nitro, halogen, vinyl, cyano, ester, acetyl, aldehyde in different positions of the pyridine ring. Besides simple pyridine derivatives, benzo-fused pyridines such as quinoline, isoquinoline or phenanthridine were also suitable substrates for this reaction. From a mechanistic point of view, this reaction is believed to proceed through a copper (I) alkenylcarbene intermediate which would evolve to the final product through a sequence involving vinylogous attack of the pyridine component/cyclization/reductive elimination/oxidative aromatization (Scheme 18, B). A computational study would support this mechanistic picture [33].

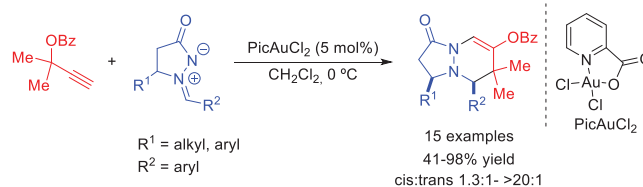
In 2013, the group of Lou and our group concurrently reported the regioselective synthesis of pyrrole derivatives *via* metal-catalyzed (3 + 2) cycloaddition of diazo compounds and nitriles [34–35].

Thus, Lou and coworkers demonstrated that AgSbF₆ is an effective catalyst in the reaction of vinylogous diazoesters and nitriles providing di- and trisubstituted pyrrole derivatives in moderate yields (Scheme 19) [34]. A silver carbene intermediate has been proposed as key intermediate in this (3 + 2) cycloaddition reaction. A sequential nucleophilic attack of the nitrile to the carbenic position and subsequent cyclization would account for the observed regioselectivity.

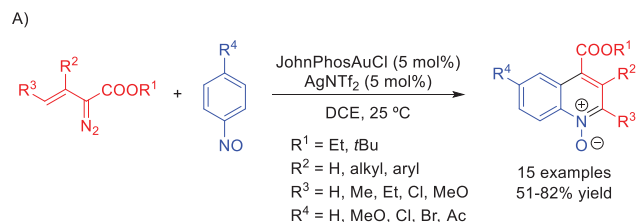
Independently, our group reported the regioselective synthesis of functionalized pyrrole derivatives *via* gold(I)-catalyzed formal (3 + 2) cycloaddition of stabilized vinyl diazo derivatives and nitriles (Scheme 20) [35]. This cyclization reaction demonstrated a broad scope with respect to both components. This transformation would involve initial reaction of the vinyl diazo compound with the gold complex with generation of a gold alkenyl carbenoid intermediate. Then, regioselective nucleophilic attack of the nitrile to the vinylogous position would afford a vinyl gold intermediate, which by cyclization and tautomerism would produce the final pyrroles.

In 2021, Doyle and co-workers developed a synthesis of highly functionalized pyrroles through Ag(I)-catalyzed reaction of enol diazoacetates and imino ethers (Scheme 21) [36]. Once again, the formation of the pyrrole derivatives would involve initial formation of a metalloenolcarbene with substantial electrophilic character at the vinylogous position. Nucleophilic attack of the imine nitrogen, followed by intramolecular cyclization and C–O bond cleavage would account for the formation of the final product.

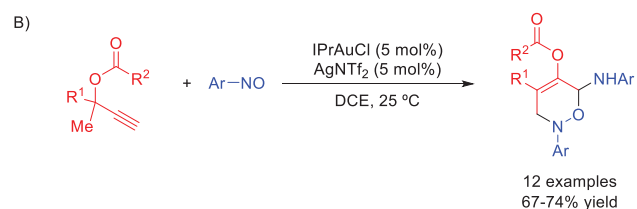
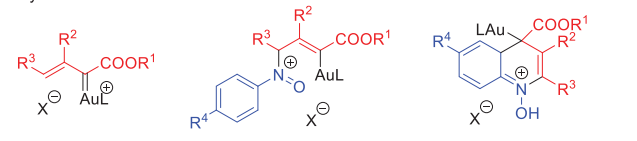
As compared with nitrogen heterocycles, the formation of five-membered oxygen heterocycles by (3 + 2) cycloaddition reactions involving alkenylcarbene intermediates remains much less explored. In this regard, the group of Zhang reported the gold(I)-catalyzed reaction of propargyl substrates featuring an acetal function and a terminal carboxylate group with aldehydes and ketones to give functionalized 2,5-dihydrofuran derivatives (Scheme 22) [37]. This process relies on initial migration/fragmentation of the acetal moiety with formation of a reactive alkenyl gold intermediate, which would participate in a stepwise (3 + 2) cycloaddition with the carbonyl component.



Scheme 24. Gold-catalyzed (3 + 3)-cycloaddition of azomethine imines with propargyl esters.



Key intermediates



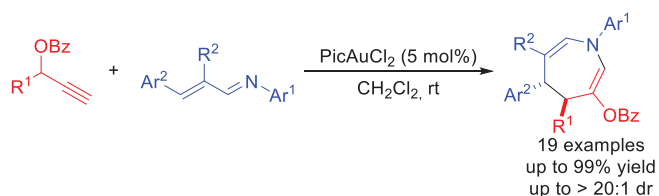
Scheme 25. A) Gold-catalyzed (3 + 3)-cycloaddition of nitrosobenzenes with alkenyldiazo compounds generated from alkenyldiazo compounds. B) Gold-catalyzed (4 + 2)-cycloaddition of nitrosobenzenes with alkenyldiazo compounds generated from propargyl esters.

Synthesis of six-membered heterocyclic compounds through formal (3 + 3) cycloaddition reactions.

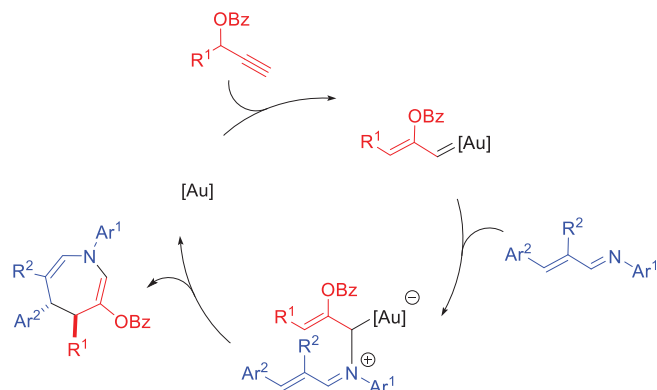
Doyle and coworkers developed a number of efficient and selective (3 + 3) cycloaddition reactions of enoldiazo compounds [38]. For example, they reported the copper-catalyzed cycloaddition of enoldiazoacetamides with nitrones (Scheme 23) [39]. In this transformation, copper catalysts outperformed those based on rhodium, previously used in transformations of enoldiazoacetates. Excellent yields and enantioselectivities were achieved by using copper(I) tetrafluoroborate/bisoxazoline complex as catalyst. Mechanistically, this transformation is suggested to proceed through a cyclopropene as key intermediate, which would serve as the effective carbene precursor. A control experiment would support this mechanistic assumption. Notably, the copper catalyst has a crucial role on the final outcome since copper(I) triflate afforded open-chain products arising from a Mannich reaction.

Subsequently, the same group extended this reactivity to enoldiazosulfones [40]. Once again, copper complexes were the catalysts of choice to obtain the corresponding (3 + 3) cycloadducts in high yields and excellent enantiocontrol.

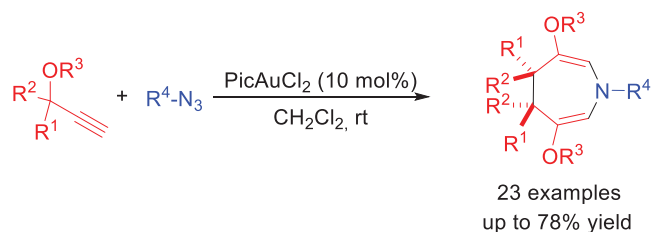
In 2009, Toste and coworkers reported the gold-catalyzed (3 + 3)-cycloaddition of azomethine imines with propargyl esters (Scheme 24) [41]. A gold(III) picolinic acid complex (PicAuCl₂) served as suitable catalyst for this transformation. This reaction is proposed to proceed by initial gold-promoted 1,2-rearrangement



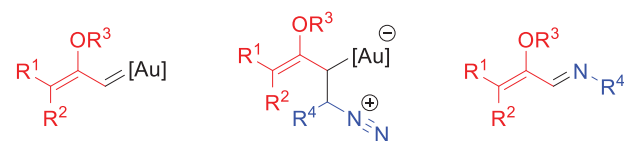
Scheme 26. Synthesis of azepines by gold(III)-catalyzed formal (4 + 3)-cycloaddition.



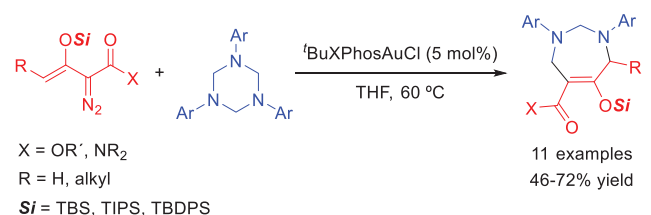
Scheme 27. Mechanism for the gold(III)-catalyzed formal (4 + 3)-cycloaddition.



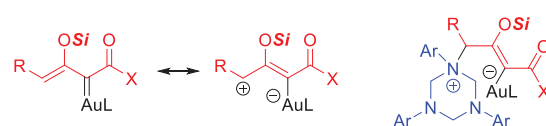
Proposed intermediates



Scheme 28. Gold(III)-catalyzed reaction of propargyl esters and azides.



Postulated intermediates



Scheme 29. Gold(III)-catalyzed formal (4 + 3) cycloaddition of enol diazo compounds and hexahydro-1,3,5-triazines.

of the propargyl ester with generation of a gold-carbenoid intermediate which would evolve to the final products by a stepwise (3 + 3) cycloaddition involving initial nucleophilic attack of the nitrogen of the azomethine imine component to the carbenic atom followed by stereoselective ring closing.

On the other hand, Liu and coworkers obtained quinolone oxides resulting from a formal (3 + 3) cycloaddition in the gold-catalyzed reaction of nitrosobenzenes and alkenyldiazo esters (Scheme 25, A) [42]. A catalytic system comprising JohnPhosAuCl and AgNTf₂ (5 mol% each) proved optimal for this transformation. Regarding the substrate scope both electron-deficient and -rich

nitrosobenzenes were compatible with this protocol affording the corresponding products in good yields. This formal (3 + 3) cycloaddition reaction would involve: 1) initial decomposition of the diazo component with generation of a gold carbenoid intermediate, 2) attack of the nitroso function to the vinylogous position of the organometallic intermediate, and 3) 6- π electrocycloaddition followed by final aromatization. This study represented the first gold-catalyzed transformation of an alkenyl diazo compound involving a gold carbene intermediate and anticipated the enhanced vinylogous reactivity of this type of intermediates, a common feature of most of the subsequently developed synthetic applications based on alkenyl gold carbenoids generated from diazo compounds.

Interestingly, in the same study the authors reported a divergent pathway when using propargyl esters as the gold carbene precursors. In that case, oxazine derivatives resulting from a formal (4 + 2) cycloaddition were formed (Scheme 25, B).

Synthesis of seven-membered heterocyclic compounds through formal (4 + 3) cycloaddition reactions.

A few examples of synthesis of seven-membered heterocyclic compounds in processes involving coinage metal alkenyl carbene intermediates have been reported so far. In 2008, Toste et al reported the gold-catalyzed formal (4 + 3)-cycloaddition of α,β -unsaturated imines and propargyl esters to form azepine derivatives (Scheme 26) [43]. A gold(III) picolinic acid catalyst (PicAuCl₂) proved to be the catalyst of choice for this transformation. Notably, the reaction with secondary benzylic propargylic esters proceeded with complete *trans*-selectivity.

This reaction is proposed to proceed by initial gold-promoted 1,2-rearrangement of the propargyl ester with generation of a gold-carbenoid intermediate which would evolve to the final products by a stepwise (4 + 3) cycloaddition involving nucleophilic attack of the imine nitrogen with formation of an allylgold intermediate that would undergo intramolecular nucleophilic addition (Scheme 27).

A closely related transformation was developed by Chen, Hu and co-workers. Thus, the gold-catalyzed reaction of two equivalents of propargyl ester with an alkyl azide provided functionalized 4,5-dihydro-1*H*-azepine derivatives (Scheme 28) [44]. The gold-carbenoid intermediate generated from initial 1,2-rearrangement of the propargyl ester is proposed to play a dual role in this transformation. First, its trapping by the azide would generate a vinylic imine intermediate. Once formed, the vinyl imine intermediate would undergo a formal (4 + 3) cycloaddition with a second equivalent of vinyl gold carbenoid to provide the final products.

In 2016, Sun and co-workers reported the synthesis of seven-membered heterocycles through gold-catalyzed reaction of enol diazocompounds with hexahydro-1,3,5-triazines (Scheme 29) [45]. This formal (4 + 3) cycloaddition reaction was compatible with enol diazoacetates with different substitution pattern. Enol diazoacetamides were also suitable substrates for this cycloaddition reaction. A gold carbene intermediate resulting from initial decomposition of the diazo compound has been proposed as key intermediate in this transformation. Subsequent nucleophilic addition of the triazine to the vinylogous position followed by cyclization would account for the formation of the final products.

Summary and outlook

In this Review, we have summarized some relevant coinage metal-catalyzed carbo- and heterocyclizations involving alkenyl carbene intermediates as C3 synthons. In the last decade, this field has become extremely active providing a number of efficient

approaches to valuable carbo- and heterocyclic compounds. Most of these transformations exhibit exquisite levels of selectivity. Notably, in most cases, coinage metal catalysts display a divergent performance, thus nicely complementing those methodologies based on other metal catalysts. In spite of these relevant recent contributions, a critical analysis of the current state of the art provided in this Review allows the identification of some areas in which there is yet room for improvement and further experimental effort would be required. For example, the field has been clearly dominated by gold catalysts and the development of silver and, particularly, copper-based catalysts would be advantageous in terms of sustainability. The search for new and easily available precursors for the generation of these reactive intermediates would be very helpful. Moreover, with a few notable exceptions, enantioselective approaches remain clearly underdeveloped. Finally, efforts aimed at a better understanding of the mechanistic pathways would be extremely positive. We are fully convinced that these intermediates will continue to play an important role in organic synthesis and catalysis.

Data availability

No data was used for the research described in the article.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

Financial support of our research in this field from Ministerio de Ciencia e Innovación, Agencia Estatal de Investigación (AEI) and Fondo Europeo de Desarrollo Regional (FEDER) (Grant PID2019107469RB-I00) is gratefully acknowledged. E. L. thanks the Principado de Asturias for a predoctoral grant (Severo Ochoa Program).

References

- [1] For a recent review on the synthetic impact of 1,3-dipolar cycloadditions, see: M. Breugst, H.-U. Reissig *Angew. Chem. Int. Ed.* 59 (2020) 12293–12307.
- [2] [a] B.L. Pagenkopf, N. Vemula, *Eur. J. Org. Chem.* (2017) 2561–2567, For representative reviews on the chemistry of donor-acceptor cyclopropanes, see:; [b] M.A. Kerr, *Isr. J. Chem.* 56 (2016) 476–487; [c] H.K. Grover, M.R. Emmett, M.A. Kerr, *Org. Biomol. Chem.* 13 (2015) 655–671; [d] T.F. Schneider, J. Kaschel, D.B. Werz, *Angew. Chem. Int. Ed.* 53 (2014) 5504–5523; [e] M.A. Cavitt, L.H. Phun, S. France, *Chem. Soc. Rev.* 43 (2014) 804–818; [f] F. de Nanteuil, F. De Simone, R. Frei, F. Benfatti, E. Serrano, *J. Waser, Chem. Commun.* 50 (2014) 10912–10928; [g] H.-U. Reissig, R. Zimmer, *Chem. Rev.* 103 (2003) 1151–1196.
- [3] For a review on the phosphine-catalyzed (3+2) cycloadditions of activated allenes with electrophiles, see: Wei, Y.; Shi, M. *Org. Chem. Front.* 2017, 4, 1876–1890.
- [4] For a general review on recent methodologies for the generation of metal carbene intermediates, see: M. Jia, S. Ma *Angew. Chem. Int. Ed.* 55 (2016) 9134–9166.
- [5] [a] M. Regitz, G. Maas, *Diazo Compounds: Properties and Synthesis*, Academic Press, London, 1986, pp. 65–198, For general reviews on the reactivity of stabilized diazo compounds, see:; [b] A. Padwa, M.D. Weingarten, *Chem. Rev.* 96 (1996) 223; [c] M.P. Doyle, M.A. McKervey, T. Ye, *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*, Wiley, New York, 1998; [d] H.M.L. Davies, R.E.J. Beckwith, *Chem. Rev.* 103 (2003) 2861; [e] Z. Zhang, J. Wang, *Tetrahedron* 64 (2008) 6577.
- [6] E. López, S. González-Pelayo, L.A. López, *Chem. Rec.* 17 (2017) 312–325.
- [7] Selected reviews on the use of *N*-sulfonylhydrazones as diazo precursors: a) Liu, Z.; Sivaguru, P.; Zononi, G.; Bi, X. *Acc. Chem. Res.* 2022, 55, 1763–1781; b) Xia, Y.; Wang, J. *J. Am. Chem. Soc.* 2020, 142, 10592–10605; c) Xiao, Q.; Zhang,

- Y.; Wang, J. *Acc. Chem. Res.* **2013**, *46*, 236–247; d) Barluenga, J.; Valdés, C. *Angew. Chem. Int. Ed.* **2011**, *50*, 7486–7500.
- [8] Selected reviews on metal-catalyzed rearrangements of propargyl esters: a) Shiroodi, R. K.; Gervorgian, V. *Chem. Soc. Rev.* **2013**, *42*, 4991–5001; b) Marion, N.; Nolan, S. P. *Angew. Chem. Int. Ed.* **2007**, *46*, 2750–2752; c) Fürstner, A.; Davies, P. W. *Angew. Chem. Int. Ed.* **2007**, *46*, 3410–3449.
- [9] Review: Wang, S., Zhang, G., Zhang, L. *Synlett* 2010 692 706.
- [10] For a recent review on the synthetic utility of cyclopropenes, see: R. Vicente *Chem. Rev.* **121** (2021) 162–226.
- [11] C.R. Solorio-Alvarado, Y. Wang, A.M. Echavarren, *J. Am. Chem. Soc.* **133** (2011) 11952–11955.
- [12] B. Herlé, P.M. Holstein, A.M. Echavarren, *ACS Catal.* **7** (2017) 3668–3675.
- [13] Y. Deng, L.A. Massey, P.Y. Zavalij, M.P. Doyle, *Angew. Chem. Int. Ed.* **56** (2017) 7479–7483.
- [14] For a related synthesis of cyclobutenes by copper (I)-catalyzed formal (3+1) cycloaddition of vinyl diazo and simple diazo compounds, see: Barluenga, J.; Riesgo, L.; López, L. A.; Rubio, E.; Tomás, M. *Angew. Chem. Int. Ed.* **2009**, *48*, 7569–7572. For a recent asymmetric version of this transformation, see: Xu, Y.; Wang, Z.; Sun, J. *Org. Lett.* **2021**, *23*, 7613–7617.
- [15] J.F. Briones, H.M.L. Davies, *J. Am. Chem. Soc.* **135** (2013) 13314–13317.
- [16] The rhodium-catalyzed process resulted in the formation of acyclic products resulting from a combined C-H insertion/Cope rearrangement: Lian, Y.; Davies, H. M. L. *J. Am. Chem. Soc.* **2011**, *133*, 11940–11943.
- [17] J. Barluenga, G. Lonzi, M. Tomás, L.A. López, *Chem. Eur. J.* **19** (2013) 1573–1576.
- [18] E. López, G. Lonzi, L.A. López, *Synthesis* **49** (2017) 4461–4468.
- [19] E. López, L.A. López, *Angew. Chem. Int. Ed.* **56** (2017) 5121–5124.
- [20] S.B. Wagh, R.-S. Liu, *Chem. Commun.* **51** (2015) 15462–15464.
- [21] K. Yamamoto, E. López, P. Barrio, J. Borge, L.A. López, *Chem. Eur. J.* **26** (2020) 6999–7003.
- [22] E. López, J. González, L.A. López, *Adv. Synth. Catal.* **358** (2016) 1428–1432.
- [23] Gold-catalyzed cyclizations of allenamides are highly regioselective, the distal C=C being solely involved. For an exception, see: Wang, Y.; Zhang, P.; Qian, D. Zhang, J. *Angew. Chem. Int. Ed.* **2015**, *54*, 14849–14852.
- [24] E. López, G. Lonzi, J. González, L.A. López, *Chem. Commun.* **52** (2016) 9398–9401.
- [25] X. Yin, M. Mato, A.M. Echavarren, *Angew. Chem. Int. Ed.* **56** (2017) 14591–14595.
- [26] Rettenmeier, E.; Schuster, A. M.; Rudolph, M. Rominger, F.; Gade, C. A.; Hashmi, A. S. K. *Angew. Chem. Int. Ed.* **2013**, *52*, 5880–5884.
- [27] X. Cheng, L. Zhu, M. Lin, J. Chen, X. Huang, *Chem. Commun.* **53** (2017) 3745–3748.
- [28] D. Garayalde, K. Krüger, C. Nevado, *Angew. Chem. Int. Ed.* **50** (2011) 911–915.
- [29] In 2012, our group reported the synthesis of substituted 2-azetines by copper (I)-catalyzed (3+1) cycloaddition of vinyl diazoacetates and iminoiodinanes (Barluenga, J.; Riesgo, L.; Lonzi, G.; Tomás, M.; López, L. A. *Chem. Eur. J.* **2012**, *18*, 9221–9224). However, this transformation does not involve alkenyl carbene intermediates and is proposed to proceed through an aziridination/ring expansion sequence.
- [30] K.O. Marichev, K. Wang, K. Dong, N. Greco, L.A. Massey, Y. Deng, H. Arman, M.P. Doyle, *Angew. Chem. Int. Ed.* **58** (2019) 16188–16192.
- [31] M.P. Doyle, M. Yang, W. Hu, L.S. Gronenberg, *J. Am. Chem. Soc.* **125** (2003) 4692–4693.
- [32] J. Barluenga, G. Lonzi, L. Riesgo, L.A. López, M. Tomás, *J. Am. Chem. Soc.* **132** (2010) 13200–13202.
- [33] For a mechanistic study of this transformation, see: L.A. López, J. González *Org. Biomol. Chem.* **17** (2019) 646–654.
- [34] R.J. Billedeau, K.R. Klein, Y. Lou, *Org. Lett.* **15** (2013) 1421–1423.
- [35] G. Lonzi, L.A. López, *Adv. Synth. Catal.* **355** (2013) 1948–1954.
- [36] K. Dong, A. Humeidi, W. Griffith, H. Arman, X. Xu, M.P. Doyle, *Angew. Chem. Int. Ed.* **60** (2021) 13394–13400.
- [37] G. Zhang, L. Zhang, *J. Am. Chem. Soc.* **130** (2008) 12598–12599.
- [38] For a review on cycloaddition reactions of enoldiazo reagents, Q.-Q. Cheng, Y. Deng, M. Lankelma, M.P. Doyle *Chem. Soc. Rev.* **46** (2017) 5425–5443.
- [39] Q.-Q. Cheng, J. Yedoyan, H. Arman, M.P. Doyle, *J. Am. Chem. Soc.* **138** (2016) 44–47.
- [40] F.G. Adly, K.O. Marichev, J.A. Jensen, H. Arman, M.P. Doyle, *Org. Lett.* **21** (2019) 40–44.
- [41] N.D. Shapiro, Y. Shi, F.D. Toste, *J. Am. Chem. Soc.* **131** (2009) 11654–11655.
- [42] V.V. Pagar, A.M. Jadhav, R.-S. Liu, *J. Am. Chem. Soc.* **133** (2011) 20728–20731.
- [43] N.D. Shapiro, F.D. Toste, *J. Am. Chem. Soc.* **130** (2008) 9244–9245.
- [44] H. Liu, X. Li, Z. Chen, W.-X. Hu, *J. Org. Chem.* **77** (2012) 5184–5190.
- [45] C. Zhu, G. Xu, J. Sun, *Angew. Chem. Int. Ed.* **55** (2016) 11867–11871.