Development of transition-metal-catalyzed
cycloaddition reactions leading to
polycarbocyclic systems*

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Abstract: We present a compilation of methodologies developed in our laboratories to assemble polycyclic structures containing small- and medium-sized cycles, relying on the use of transition-metal-catalyzed (TMC) cycloadditions. First, we discuss the use of alkylidene-cyclopropanes (ACPs) as 3C-atom partners, in particular in their Pd-catalyzed (3 + 2) cycloadditions with alkynes, alkenes, and allenes, reactions that lead to cyclopentane-containing polycyclic products in excellent yields. Then, we present the expansion of this chemistry to a (4 + 3) annulation with conjugated dienes, and to inter- and intramolecular (3 + 2 + 2) cycloadditions using external alkenes as additional 2C-π-systems. These reactions allow the preparation of different types of polycyclic structures containing cycloheptene rings, the topology of the products depending on the use of Pd or Ni catalysts. Finally, we include our more recent discoveries on the development of (4 + 3) and (4 + 2) intramolecular cycloadditions of allenes and dienes, promoted by Pt and Au catalysts, and discuss mechanistic insights supported by experimental and density functional theory (DFT) calculations. An enantioselective version of the (4 + 2) cycloaddition with phosphoramidite Au(I) catalysts is also presented.

Keywords: alkylidene-cyclopropanes; allenes; cycloaddition; polycycles; transition metals.

INTRODUCTION

Despite the enormous development of organic synthesis during the recent decades, the preparation of biomedical relevant natural products featuring relatively complex polycyclic skeletons is inefficient and requires a high number of steps. This represents an important drawback if one wants to obtain reasonable amounts of this type of products in a reasonable period of time. In order to progress in this direction and streamline the process of building complex polycyclic molecules, it is critical to invent new types of synthetic technologies that allow the assembly of these compounds from readily available starting materials, in few steps, using safe and inexpensive reagents, preferably catalysts, and producing a minimal amount of waste [1].

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Along these lines, one of the most interesting types of transformations concerns cycloaddition reactions because by allowing the assembly of cycles with simultaneous formation of at least two bonds they usually convey an interesting increase of structural and stereochemical complexity in a single step.

In this context, we have been working recently on the development of new types of cycloaddition reactions, mainly focusing on those involving transition-metal-catalyzed (TMC) processes. Cycloaddition reactions catalyzed by transition-metal catalysts have experienced a progressive growth in the last three decades, allowing the execution of transformations that are otherwise forbidden or extremely difficult. In many cases, it is even possible to perform these reactions in an asymmetric fashion by using chiral ligands [2].

Most of the TMC cycloaddition processes leading to carbocycles involve a reaction between different types of two carbon- and/or four carbon-atom unsaturated systems (e.g., alkynes, alkenes, allenes, or 1,3-dienes), thus leading to cyclic structures with an even number of carbons (basically 4, 6, and 8-membered rings). TMC cycloaddition reactions leading to 5, 7, or 9-membered carbocycles have lagged behind, although a variety of elegant approaches have also been developed during the last few decades [3].

A few years ago, we initiated a project aimed at the development of new TMC cycloaddition strategies that could allow the annulations of 3C-atom components and therefore lead to the formation of relevant polycyclic systems embedding odd-numbered cycles. In this review, we collect our results on the use of alkylidenecyclopropanes (ACPs) and allenes as 3C-atom precursors in several types of TMC cycloadditions involving Pd, Ni, Pt, or Au catalysts (Scheme 1). In the case of Au catalysis, we also demonstrated that changing the ligand at Au allows us to select whether the allene participates as a 3C-atom component in a (4 + 3) cycloaddition to a conjugated diene, or as a 2C-atom partner in a related (4 + 2) process.

TMC CYCLOADDITION REACTIONS OF ALKYLIDENECYCLOPROPANES

In the 1970s and 1980s, Noyori and Binger reported that methylene- and alkylidenecyclopropanes can participate in intermolecular (3 + 2) cycloaddition reactions with alkenes or alkynes when treated with specific Ni or Pd catalysts [4]. Some years later, Lautens, Motherwell, and Nakamura demonstrated that the annulation can also be carried out in an intramolecular way, although the reported examples usually involve very specific substrates whose synthesis is not particularly straightforward [2].

In view of these precedents, we envisaged the possibility of developing alternative TMC intramolecular (3 + 2) cycloadditions that could allow a more straight entry to bicycles featuring a 5-membered carbocycle. In particular, we decided to study the cycloaddition performance of ACPs like 2, substrates that could be easily assembled by means of a Pd-catalyzed allylic alkylation between an appropriate nucleophile and the readily available tosyl cyclopropyl derivative 1 [5]. Mechanistically, we hypothesized that the reaction of substrates like 2 with a Pd(0) catalyst could proceed through an initial insertion of Pd(0) on the distal bond of the cyclopropane ring to give intermediate I, followed by migratory insertion into the alkyne to provide a palladacyclohexane intermediate II. A subsequent reductive elimination would regenerate the Pd(0) catalyst and provide the bicyclic cycloaddition product 3 (Scheme 2).
According to this strategy, in 2003 we reported the first TMC intramolecular (3 + 2) cycloaddition between ACPs and alkynes, using a palladium catalyst generated in situ from a mixture of Pd$_2$(dba)$_3$ (6 %) and P(OiPr)$_3$ (20 %). The reactions were carried out in refluxing dioxane, and allowed the construction of a variety of interesting bicyclo[3.3.0]octenes in an efficient manner (65–96 % yield, Scheme 3, eq. 1) [6]. The scope of the cycloaddition turned out to be quite broad, tolerating a variety of different substituents at the alkyne unit [7].

Importantly, we later found that using a bulky phosphite ligand such as $\text{L}_1$, instead of P(OiPr)$_3$, it is possible to perform this reaction with reduced catalyst loadings (even as low as 0.5 mol % of Pd) [8]. Moreover, given that the preparation of the precursors and the cycloaddition are both Pd-catalyzed reactions, we tried to combine both processes in a one-pot tandem sequence, using the temperature to control the reactivity. Treatment of the carbanion 6 with tosylate 1, in the presence of Pd$_2$(dba)$_3$ (3 mol %), dppe (1 mol %), and $\text{L}_1$ (8 mol %), leads to the expected coupling product after 1 h at room temperature. Now, simply increasing the temperature of the reaction mixture up to 101 °C promotes the cycloaddition process. The cycloadduct 7 was isolated in a 78 % overall yield (Scheme 3, eq. 2). Thus,
a significant increase in skeletal complexity can be achieved in a single step from readily available and inexpensive precursors, and using catalytic conditions.

This cycloaddition chemistry could also be successfully extended to alkenes (Scheme 4, eq. 1). Again, the best results were achieved by using the bulky phosphite L1 as the palladium ligand, which allows minimizing competing β-hydride elimination processes that might occur on some of the palladium intermediates generated in the reaction. Using this methodology, we could assemble a variety of bicyclic systems in good yields and with excellent diastereoselectivities (Scheme 4, eq. 1). It is noteworthy that the reaction proceeds well for a range of substituents on the alkene, including alkyl, phenyl, and ester groups. On the other hand, the nature of the connecting tether is not critical, so that oxygen-, nitrogen-, and carbon-based linkers are tolerated [9].

Allenes also participate in this cycloaddition chemistry. Indeed, these unsaturated systems turned out to be more reactive than alkenes, leading to shorter reaction times in their intramolecular cycloadditions to ACPs (Scheme 4, eq. 2). For example, allene 10, in the presence of 3 mol % of Pd_2(dba)_3 and 7.8 mol % of L1 rendered, after only 25 min, the cycloadducts 11a,b in an excellent 90 % yield, and with a diastereoisomeric ratio higher than 14 to 1 [10].

Taking into account that the mechanistic course of the cycloaddition reaction presumably involves the formation of a metallacyclic intermediate of type II, we envisaged that the presence of a diene in the cycloaddition precursor might allow for the synthesis of 7-membered carbocycles, by way of a π-allylic rearrangement of such intermediate (from II to III, Scheme 5), and a final reductive elimination. Accordingly, a new (4 + 3) cycloaddition process between a conjugated diene and an ACP would be available.

Scheme 4 (3 + 2) Cycloaddition of ACPs with alkenes or allenes.

Scheme 5 Mechanistic hypothesis of a (4 + 3) cycloaddition of ACPs and dienes.
Gratifyingly, we found that this (4 + 3) cycloaddition reaction could be accomplished with a Pd catalyst generated from Pd$_2$(dba)$_3$ and a phosphoramidite ligand such as L$_2$ [11]. Thus, stereochemically rich 5,7-fused bicyclic systems of type 13, with up to three new stereoogenic centers, could be obtained from readily accessible dienylidencyclopropanes (12). The process takes place with complete stereoselectivity and moderate to good yields (40–73 %) (Scheme 6, eq. 1). As in the case of the (3 + 2) process, the preparation of the precursor and the cycloaddition reaction can also be coupled so that the whole transformation can be carried out in a one-pot operation. Moreover, we were delighted to find that the chiral phosphoramidite ligand L$_2$ induces asymmetry in the cycloaddition so that, for instance, cycloadduct 15 was isolated in a 59 % yield and a notable 64 % enantiomeric excess (Scheme 6, eq. 2). Optimization of this result is being further pursued in our labs using other ligands with different steric characteristics. To the best of our knowledge, this work represented the first report on a TMC (4 + 3) intramolecular cycloaddition of ACPs and provided the first examples of an enantioselective variant [11].

![Scheme 6](image)

Scheme 6 (4 + 3) Cycloaddition of ACPs and dienes including an asymmetric example.

The successful development of these (4 + 3) cycloadditions led us to envision other assembly strategies to obtain related polycyclic systems, in particular those based on (3 + 2 + 2) annulations between ACPs and two independent 2C-unsaturated components, such as in 16 (Scheme 7, eq. 1). The implementation of this strategy in a fully intramolecular way could produce fused tricyclic skeletons containing 7-membered carbocycles. Enedyne 16 does indeed experience the reaction when treated with catalytic amounts of Pd$_2$(dba)$_3$ and L$_1$, at 90 °C, to give the desired tricyclic structure 17 in a moderate yield (52 %) [12]. The scope of this cycloaddition is, however, limited, since the reaction does not tolerate substitution at the alkyne terminus. Fortunately, the use of an alkene instead of the alkyne as third component, such as in 18 (Scheme 7, eq. 2), led to a more efficient cycloaddition process, allowing the assembly of the tricycle 20 in a completely diastereoselective manner. In some cases and depending on the type of connecting tether, competitive (3 + 2) cycloaddition products are also observed, but in general, moderate to good yields of the (3 + 2 + 2) cycloadducts are obtained. Moreover, the competitive (3 + 2) pathway could be further minimized by introducing an electron-withdrawing substituent at the alkene terminus as in 19 (Scheme 7, eq. 2), substrate that provides the tri-carbocyclic product 21, containing three new stereocenters, in good yield.

Finally, a tandem process leading to 20, based on coupling the sodium salt of the diester 22 and cyclopropyl tosylate 1 was also possible, without compromising the overall efficiency of the reaction.
The transformation represents a quite impressive increase in complexity in a single catalytic step, from simple starting materials [12].

We have also tested the intermolecular version of this (3 + 2 + 2) cycloaddition under Pd catalysis, using the alkene component as an external additive. Unfortunately, the desired multicomponent addition did not take place, and we mainly observed standard intramolecular (3 + 2) adducts. However, we were gratified to see that running this reaction in presence of Ni(COD)$_2$ instead of the Pd catalyst afforded products that incorporate the external alkene. Thus, when alkynylidene cyclopropanes like 23 are treated with a slight excess of an electron-deficient alkene in the presence of catalytic amounts of Ni(COD)$_2$, bicarbocycles 24, resulting from a (3 + 2 + 2) cycloaddition process, are obtained as major products (Scheme 8, eq. 1). Contrary to the previous Pd-catalyzed cycloaddition, in these cases the cyclopropane is cleaved through the proximal sp$^3$-sp$^2$ C–C bond, rather than at the distal sp$^3$-sp$^3$ position [13]. Minor amounts of intermolecular (3 + 2) cycloadducts (25) could be also observed in some cases, although the scope of the (3 + 2 + 2) reaction proved to be quite broad. The best yields and selectivities were observed with enynes featuring electron-withdrawing groups at the alkyne unit (e.g., 23, R = CO$_2$Et, CH$_2$OR).

**Scheme 7** (3 + 2 + 2) Cycloaddition ACPs with alkynes and alkenes.

**Scheme 8** Ni-catalyzed (3 + 2 + 2) cycloaddition of ACPs and proposed mechanistic pathway.
Mechanistic experiments carried out with deuterated substrates together with density functional theory (DFT) calculations strongly suggest that these cycloadducts arise from an initial insertion of the Ni catalyst into the proximal bond of the cyclopropane ring, generating a Ni(II) intermediate (IV) that evolves through consecutive carbometallation, alkene insertion, and reductive elimination, to afford the final (3 + 2 + 2) adduct 24 (Scheme 8, eq. 2).

ALLENES AS 3C-ATOM COMPONENTS IN TMC CYCLOADDITION REACTIONS

Having demonstrated that ACPs are efficient 3C-atom components in a wide variety of TMC [3 + N (+ M)] cycloaddition processes, we were interested in finding other 3C-atom alternatives that could participate in novel TMC cycloadditions. Allenes have been successfully used as two-carbon atom components (2C) in several types of TMC cycloaddition reactions; however, their use as three carbon-atom components (3C) in metal-catalyzed cycloadditions has remained elusive until recent years [14].

Based on some reports demonstrating the ability of Au⁺ and Pt⁺ catalysts to induce reactions of allenes through cationic intermediates [15], we investigated the possibility of using allenes as allyl cation surrogates, so that they could participate in concerted [4C(4π)-3C(2π)] cycloadditions with conjugated dienes, a type of process related to those previously reported between oxyallyl cations and dienes [16]. Gratifyingly, we found that PtCl₂ is an excellent catalyst for promoting this intramolecular (4 + 3) cycloaddition between acyclic 1,3-dienes and allenes (e.g., 26, Scheme 9) [17]. The reaction tolerates a range of substituents in the allene and diene units, providing a variety of bicyclo[5.3.0]decane systems in a completely diastereoselective manner. The diastereoselectivity can be explained in terms of a favored exo-like approach between the allyl cation and the diene in the (4 + 3) process (Scheme 9).

DFT calculations as well as experimental data agree with a mechanism based on the metal activation of the allene to afford a metal-allyl cation intermediate of type VII, followed by a concerted (4 + 3) cycloaddition reaction with the diene. The resulting metal carbene species (VIII) evolve through a 1,2-hydrogen shift, leading to 7-membered carbocycles and regenerating the catalyst (PtCl₂) (Scheme 10).
In some cases, such as in the cycloaddition of allenediene 28, two different hydrogen shifts become competitive, leading to a mixture of two regioisomeric (4 + 3) adducts (29a and 29b), which are isolated in a 7:3 ratio and 87% global yield (Scheme 11, eq. 1). Remarkably, the cycloaddition of allenediene 30, equipped with a cyclopentyl substituent at the distal position of the allene, provided a good yield of the 5-7-6-tricyclic system 31. The formation of this product can be explained in terms of a 1,2-alkyl migration instead of the 1,2-H shift (Scheme 11, eq. 2).

Preliminary experimental results as well as the DFT computational studies also suggested that electrophilic Au complexes could be even better catalysts for these reactions, so we directed our efforts toward the development of Au-catalyzed versions of the processes. Gratifyingly, we found that the use of a cationic AuI catalyst featuring a σ-donating N-heterocyclic carbene ligand [(IPr)AuCl/AgSbF$_6$] permitted these (4 + 3) cycloadditions at room temperature or even lower. Further, dienes like furans, which gave complex mixtures of products with PtCl$_2$, afforded the products cleanly, therefore increasing the scope and synthetic utility of the process (Scheme 12) [18].
These Pt- and Au-catalyzed cycloadditions represent the first use of allenes as three carbon-atom components in any type of (4 + 3) catalytic cycloaddition and can probably be ranked among the most practical and rapid alternatives to construct cycloheptane-containing bicycles [19].

Curiously, while checking the scope of the method we found that the cycloaddition of allene diene 30 with [(IPr)AuCl2AgSbF6] provided the (4 + 3) cycloadduct 31, together with the (4 + 2) cycloadduct 35 (Scheme 13, eq. 1). Intrigued by this result, we further analyzed this reactivity and found that the proportion of either cycloadduct (31 or 35) could be altered just by changing the electronic characteristics of the ligand at Au. Therefore, sigma donating N-heterocyclic carbene ligands (i.e., IPr) favored the formation of the (4 + 3) adduct 31, whereas a π-acceptor ligand at Au, such as the triarylphosphite L1, favored the (4 + 2) adduct 35 [20]. Thus, starting from the same precursor, an allenediene disubstituted at the allene terminus, such as 30 or 36, we could divergently accede either to the 7- or 6-membered adducts, depending on the choice of the catalyst (Scheme 13).

Several experimental data, as well as theoretical calculations, suggest that the observed (4 + 2) cycloadducts are indeed the result of a ring contraction (1,2-alkyl shift, Scheme 14, path b) in the initially formed (4 + 3) carbene intermediate VIII. Thus, the ligand at Au determines the fate of this carbene intermediate and hence the formation of formal (4 + 3) or (4 + 2) adducts (Scheme 14) [20,21].
Finally, chiral phosphoramidite Au complexes, electronically similar to the arylphosphite complexes, have been found to induce excellent enantioselectivities in these (4 + 2) cycloaddition reactions (Scheme 15). Thus, allenediene 39 was converted into cycloadduct 40 in a 92% yield and 92% of enantiomeric excess [20]. Similarly, related allenediene cycloadditions provided the corresponding adducts (41–43) in good yields and excellent enantioselectivities (91–97% ee) [22].

Scheme 14 Proposed mechanistic pathway based on DFT calculations.

Scheme 15 Asymmetric (4 + 2) cycloaddition with chiral phosphoramidite Au complexes.

In summary, our research efforts during the past few years in this area has led to the discovery of several novel metal-catalyzed cycloaddition reactions involving the use of either have ACPs or allenes as 3C cycloaddition partners. The cycloaddition of ACPs are promoted by late transition-metal complexes, mainly Pd and Ni derivatives, and likely proceed by mechanisms involving initial oxidative additions into the cyclopropane ring. Those of allenes are initiated by activation of the π-system by carbophilic Au or Pt complexes. In these cases, we could also demonstrate that allenes can divergently behave as 3C- or 2C-atom cycloaddition partners, depending on the nature of the catalysts employed. The research has opened new alternatives to the synthesis of cyclopentane, cyclohexane, and cyclo-
heptane derivatives with notable efficiency and stereocontrol. Through experimental and theoretical analysis we have also derived important mechanistic information to understand the processes.

Ongoing work is focused on discovering and inventing additional transformations, applying these strategies to shorten the access to biomedically relevant polycyclic molecules, and developing practical asymmetric alternatives.

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