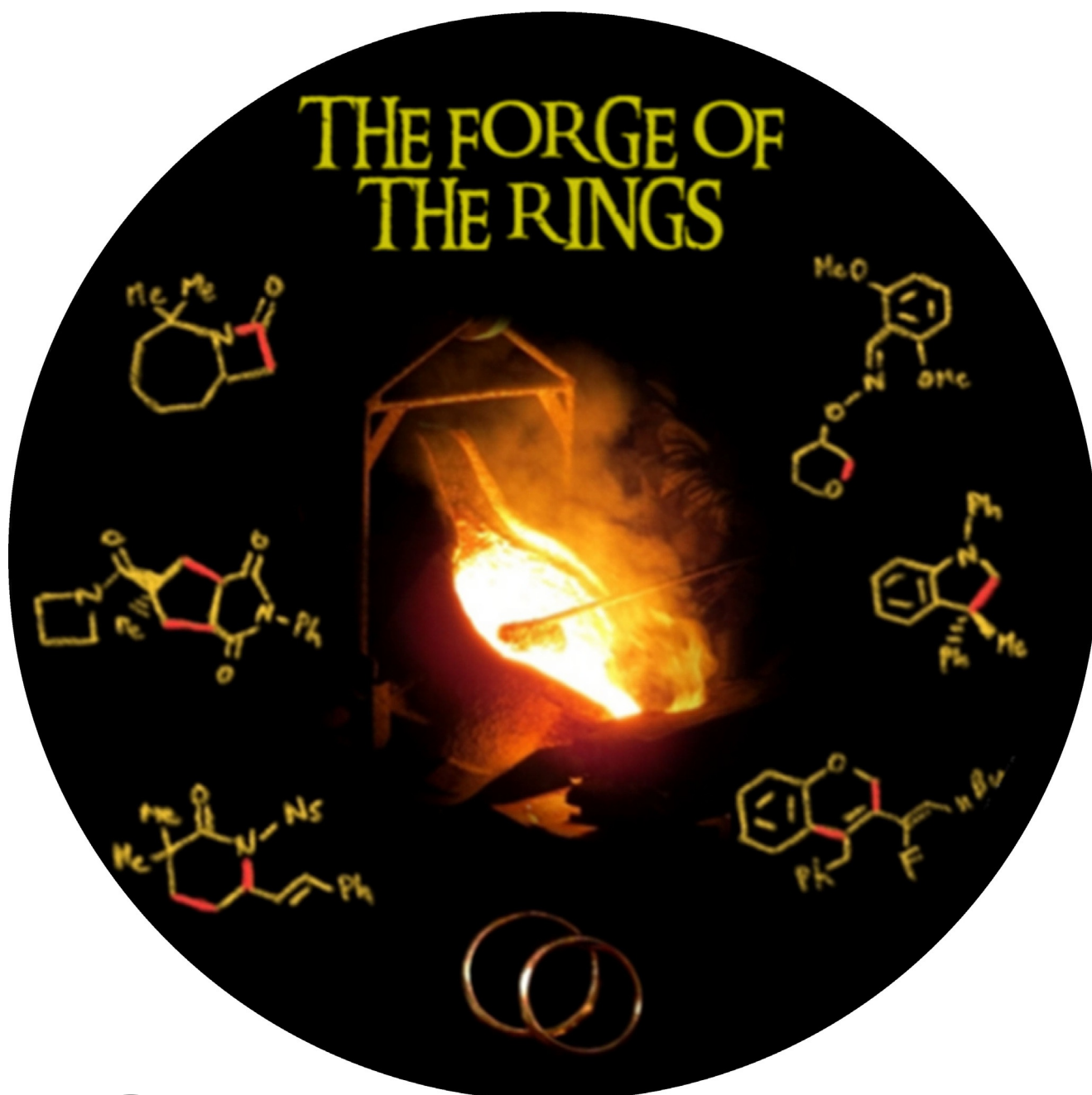


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Transition-Metal-Catalyzed Annulations Involving the Activation of C(sp³)-H Bonds

Marc Font, Moisés Gulías,* and José Luis Mascareñas****Angewandte**
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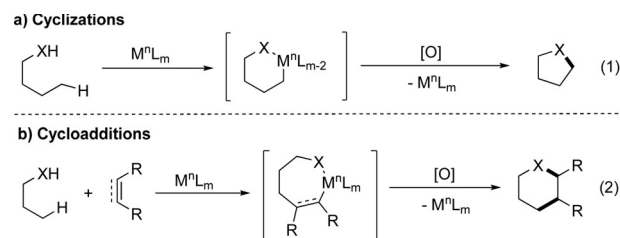
The selective functionalization of $C(sp^3)$ –H bonds using transition-metal catalysis is among the more attractive transformations of modern synthetic chemistry. In addition to its inherent atom economy, such reactions open unconventional retrosynthetic pathways that can streamline synthetic processes. However, the activation of intrinsically inert $C(sp^3)$ –H bonds, and the selection among very similar C–H bonds, represent highly challenging goals. In recent years there has been notable progress tackling these issues, especially with regard to the development of intermolecular reactions entailing the formation of C–C and C–heteroatom bonds. Conversely, the assembly of cyclic products from simple acyclic precursors using metal-catalyzed $C(sp^3)$ –H bond activations has been less explored. Only recently has the number of reports on such annulations started to grow. Herein we give an overview of some of the more relevant advances in this exciting topic.

1. Introduction

Synthetic technologies relying on C–H activation processes are among the most powerful tools in modern organic chemistry, in part because they allow a rapid and atom-economical increase in molecular complexity from simple, unfunctionalized precursors.^[1–5] The most effective approaches to perform C–H activation/functionalization reactions rely on the use of transition-metal catalysts, which in many cases promote C–H bond cleavage by concerted metalation-deprotonation (CMD) or oxidative addition processes.^[4,5]

Most of the metal-catalyzed C–H functionalizations so far described involve the activation of $C(sp^2)$ –H bonds. These reactions include oxidations, cross-couplings, cyclizations, and formal cycloadditions, among others.^[3,6–10] Noticeably, analogous reactions involving the cleavage of $C(sp^3)$ –H bonds are much less common and more challenging. This is in part due to the lower acidity of $C(sp^3)$ –H bonds and the formation of less stable carbon–metal bonds.^[11,12]

Nonetheless, in the last decade there has been an increasing number of reports dealing with the intermolecular functionalization of $C(alkyl)$ –H bonds.^[13–17] Remarkably, similar reactions enabling annulation processes—both cyclizations and cycloadditions, which are very attractive from a constructive standpoint—are much scarcer,^[18,19] and only recently have they started to increase.



Scheme 1. Mechanistic outline of a) transition-metal-catalyzed cyclizations and b) formal cycloadditions involving the activation of $C(sp^3)$ –H bonds.

This Minireview aims to highlight significant advances in the development of annulation reactions based on the activation and cleavage of $C(sp^3)$ –H bonds. We do not intend to be comprehensive, and thus we will only consider the most relevant approaches entailing cyclizations and formal cycloadditions that proceed through metalacyclic intermediates, such as those outlined in Scheme 1. Annulations involving the generation of carbenoid^[20,21] and nitrenoid^[22] intermediates, or additions to π -allyl intermediates resulting from the activation of C–H bonds,^[23] will not be discussed. Most of the schemes included in this Minireview follow a common format: the general reaction highlighting (in bold) the bonds formed in the process, some key mechanistic intermediates (shown

in parentheses), and a few selected products made using the method.

2. Transition-Metal-Catalyzed Cyclizations Promoted by the Activation of $C(sp^3)$ –H Bonds

2.1. Lactonizations and Lactamizations

Among the first examples of transition-metal-catalyzed $C(sp^3)$ –H functionalizations, acetoxylation reactions occupy a central role. In 2004, the Sanford group reported the direct acetoxylation of $C(alkyl)$ –H bonds in substrates bearing oxime or pyridine directing groups, by using $Pd(OAc)_2$ as a catalyst and $PhI(OAc)_2$ as an oxidant and acetyl source.^[24] Since this report, the number of methods for the direct conversion of hydrocarbon precursors into valuable acetylated products has grown significantly.^[15,17]

Related intramolecular processes were first reported in 1991 by Kao and Sen, who observed the formation of small amounts of β - and γ -lactones upon reacting aliphatic carbox-

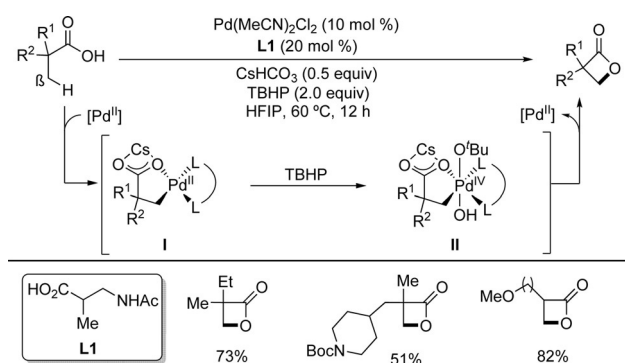
[*] Dr. M. Font, Prof. M. Gulías, Prof. J. L. Mascareñas
Centro Singular de Investigación en Química Biolóxica e Materiais Moleculares (CIQUS)
Departamento de Química Orgánica
Universidade de Santiago de Compostela
15782, Santiago de Compostela (Spain)
E-mail: marc.font@usc.es
moises.gulias@usc.es
joseluis.mascarenas@usc.es

The ORCID identification number for one of the authors of this article can be found under: <https://doi.org/10.1002/anie.202112848>.

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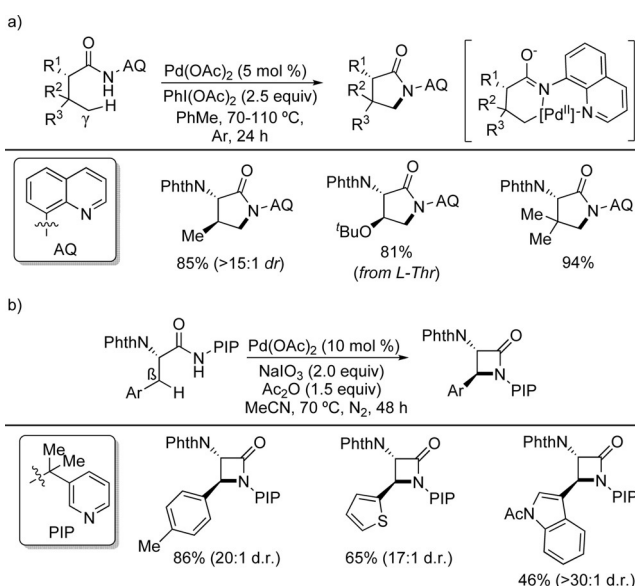
lylic acids with sub-stoichiometric amounts of K_2PtCl_4 and K_2PtCl_6 .^[25] Despite this early observation, progress in the lactonization of carboxylic acids enabled by $C(sp^3)-H$ activations has been very slow, and essentially limited to *ortho*-methylbenzoic acids^[26–28] or precursors equipped with a bidentate directing group.^[29]

Selective β -lactonization processes remained elusive until very recently, when Zhuang and Yu developed an effective strategy for promoting this reaction from alkyl carboxylic acids that relies on Pd^{II}/Pd^{IV} catalytic cycles (Scheme 2).^[30] The use of β -amino acid ligand **L1**, which chelates the metal



Scheme 2. Pd^{II} -catalyzed β -lactonization of alkyl carboxylic acids.

into a six-membered cycle with a large bite angle, seems to be key to facilitate the $C-H$ activation, as well as to trigger the reductive elimination in the ensuing alkyl- Pd^{IV} intermediate (**II**, Scheme 2). The authors also demonstrated that the resulting β -lactones represent versatile platforms for the selective installation of diverse functionalities at the β position of the carboxylic acid. Later on, the same research



Scheme 3. a) Pd^{II} -catalyzed γ -lactamization of alkyl amides bearing 8-aminoquinoline (AQ) directing groups. b) Pd^{II} -catalyzed β -lactamization of alkyl amides bearing the 2-pyridylmethyl (PIP) directing group.



Marc Font studied chemistry at the University of Girona, where he was awarded his PhD in 2015 under the supervision of Prof. X. Ribas and Prof. M. Costas. His PhD studies included research at the University of California, Berkeley with Prof. J. F. Hartwig. Subsequently, he was awarded a Marie Curie postdoctoral fellowship for research with Prof. I. Larrosa at the University of Manchester, UK. In 2017, he joined the University of Santiago de Compostela, where he is currently Juan de la Cierva fellow. His research focuses on transition-metal-catalyzed $C-H$ functionalization reactions and their mechanisms.



Moisés Gullás obtained his PhD in 2006 at the University of Santiago de Compostela. In 2007–2009 he was a Marie-Curie postdoctoral fellow in the research group of Prof. M. J. Gaunt at the University of Cambridge, UK. In 2015, he received the Spanish Society of Chemistry Young Investigator Award and, in 2016, he became permanent professor at the University of Santiago de Compostela and principal investigator at the CIQUS. His current research focuses on metal-catalyzed $C-H$ functionalization and asymmetric synthesis.



José Luis Mascareñas completed his PhD at the University of Santiago in 1988. After postdoctoral work at Stanford University (USA) under the supervision of Prof. P. Wender (1989–1990), he moved to the University of Santiago (permanent professor: 1993 and full professor: 2005). He has been scientific director of CIQUS since 2014. In 2015 he received the gold medal of the Spanish Society of Chemistry, and in 2016 was appointed a member of the European Academy of Sciences. His research combines discovering novel methods based on metal catalysis and chemical biology to develop synthetic tools for biological intervention.

group reported the cyclization of aliphatic diacids into five- to seven-membered lactone rings.^[31]

Alkyl amides can also cyclize to form γ - or β -lactams, provided they are equipped with N,N -bidentate directing groups, which not only favor the $C-H$ activation but also stabilize high-valent Pd^{IV} intermediates.^[3,4,32] Chen and co-workers described in 2013 the γ -lactamization of secondary carboxamides containing 8-aminoquinoline (AQ) auxiliaries to give pyrrolidinones (Scheme 3a).

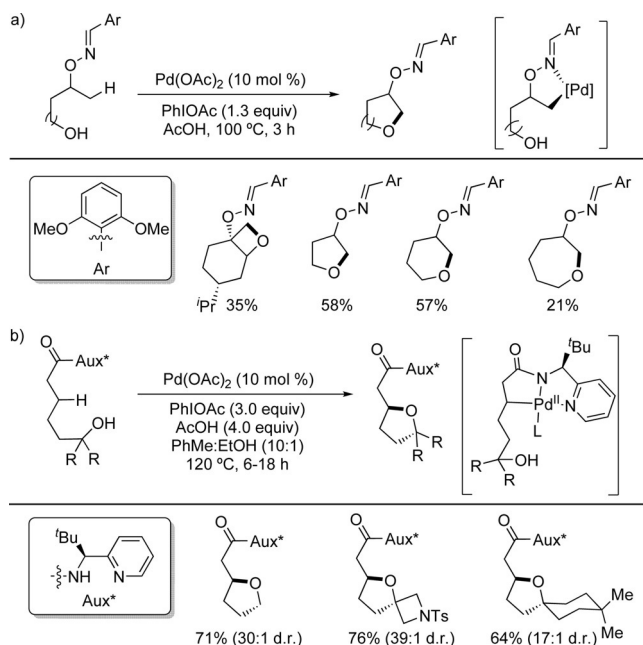
Mechanistically, it has been postulated that the reaction entails the formation of six-membered palladacycle intermediates, and involves Pd^{II}/Pd^{IV} redox cycles.^[33] In a related transformation, the Shi group demonstrated that 2-(pyridine-2-yl)isopropylamine (PIP) auxiliaries are particularly efficient at promoting the activation of benzylic methylene $C-H$ bonds in β -aryl alanines to afford β -lactams (Scheme 3b).^[34] The same group subsequently reported an updated version of the cyclization using 5-methoxyquinolin-8-amine auxiliaries, which are easier to remove than the PIP pendants.^[35]

Several additional examples of related lactamizations to build five- and six-membered lactams, also based on palladium catalysis, have been described.^[19,36–38] Interestingly, first-row transition-metal (Co, Ni, and Cu) catalysts can also catalyze the lactamization of amides equipped with bidentate directing groups. These reactions proceed through similar mechanistic pathways to those proposed for Pd.^[19]

Despite all these advances, there are still many challenges ahead, such as the development of lactamizations of substrates lacking auxiliary directing groups, the controlled formation of different ring sizes, and the implementation of enantioselective variants.

2.2. Oxa- and Azacyclizations

The formation of oxacycles by the direct oxacyclization of aliphatic alcohols has proven more challenging than the homologous lactonizations. This is mainly associated with the inability of hydroxy groups to work as directing groups in the C–H activation step. However, some strategies based on introducing designed directing groups in the substrates have been successfully implemented. In 2015, the Dong group reported a Pd-catalyzed synthesis of cyclic ethers from the corresponding aliphatic alcohols by using an oxime auxiliary (Scheme 4a).^[39] The authors proposed that, after the C–H activation of the terminal methyl group of the substrate, there is an oxidation of Pd to form an alkyl-Pd^{IV} intermediate, which undergoes an S_N2-type reductive elimination with the pendant alcohol to give the oxacyclic product (usually in modest yields). A parallel strategy, relying on the use of the PIP auxiliary as a directing group, has enabled the activation

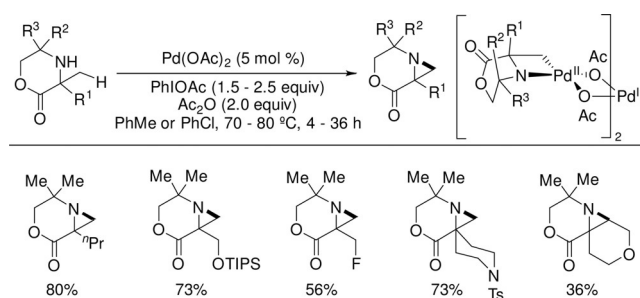


Scheme 4. a) Pd^{II}-catalyzed cyclization of alcohols bearing oxime directing groups to yield cyclic ethers. b) Pd^{II}-catalyzed cyclization of alcohols bearing a chiral amide directing group.

of secondary C–H groups for the assembly of tetrahydrofuran and tetrahydropyran derivatives.^[40]

Using different types of substrates equipped with an amide containing a chiral bidentate directing group, Hong, Baik, and co-workers developed a diastereoselective oxacyclization of aliphatic alcohols (Scheme 4b).^[41]

In contrast to alcohols, free aliphatic amines can be directly cyclized using C(sp³)–H activation reactions. Gaunt and co-workers have demonstrated extensively that appropriately designed α -methylated secondary amines, such as those shown in Scheme 5, can be readily converted into

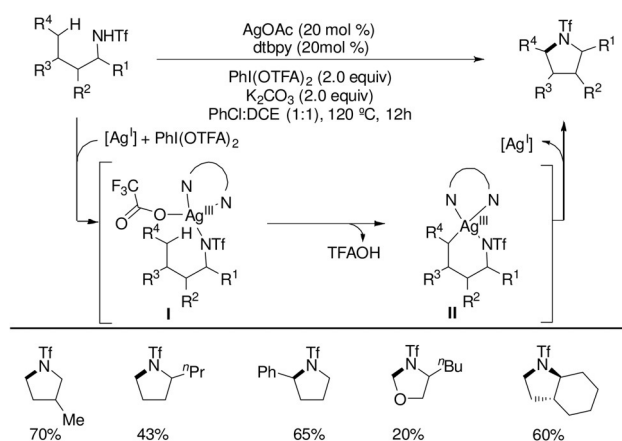


Scheme 5. Pd^{II}-catalyzed aziridination of designed secondary amines.

aziridines.^[42] The reaction involves a Pd-catalyzed activation of the pendant methyl groups to give four-membered cyclopalladated intermediates. The ensuing oxidation of the palladacycle to a Pd^{IV} species followed by reductive elimination yields the aziridine core. Importantly, the introduction of steric bulk around the NH moiety is needed to avoid the formation of off-cycle bis(amine)–palladium complexes. The authors further demonstrated the synthetic potential of this method by opening the aziridine rings with different types of nucleophiles. They also reported a follow-up enantioselective version.^[43]

Introducing a suitable protecting/auxiliary group in the amine seems to facilitate the azacyclization.^[19] Therefore, in 2009, Glorius and co-workers demonstrated that acetyl-protected *ortho*-alkylanilides can be cyclized into the corresponding indolines under Pd^{II} catalysis, although all the reported examples consist of anilides with *ortho-tert*-butyl (or very similar) substituents.^[44] In a related approach, Nadres and Daugulis reported in 2012 a Pd^{II}-catalyzed activation of δ -C–H bonds in selected alkylamides and *ortho*-methylanilides bearing picolinamide bidentate auxiliaries to afford pyrrolidines and isoindolines.^[45] Chen and co-workers extended this approach to the preparation of azetidines and pyrrolidines.^[46]

An alternative entry to pyrrolidines was reported by Shi and co-workers, and involves the use of alkyl triflamides as precursors and silver salts as catalysts. The authors postulate that PhI(OTFA)₂ induces the oxidation of the silver precursor to a Ag^{III} species, which promotes a CMD-like cleavage of primary or secondary benzylic C(sp³)–H bonds of the substrates. Finally, a C–N reductive elimination generates the pyrrolidine core (Scheme 6).^[47]



Scheme 6. Ag^I-catalyzed cyclization of alkyl triflimides to pyrrolidines.

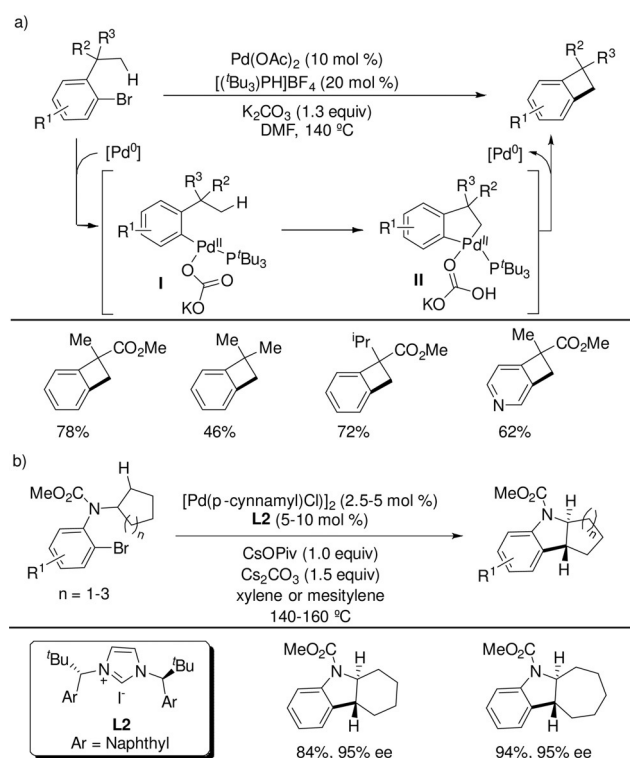
2.3. Carbocyclizations

In addition to metal-catalyzed heterocyclizations, a number of carbocyclization strategies have also been developed for reactions involving the activation of C(sp³)-H bonds. One of the earliest and most prolific approaches is based on the use of aryl halide or pseudohalide precursors (Ar-X) and Pd⁰ catalysts. This approach, pioneered by the group of Dyker,^[48] relies on an initial oxidative addition of Pd⁰ to Ar-X bonds to generate aryl-Pd^{II} species, which promote selective C(sp³)-H activations in nearby alkyl chains. A final reductive elimination from the resulting palladacycles produces the desired carbocycles.

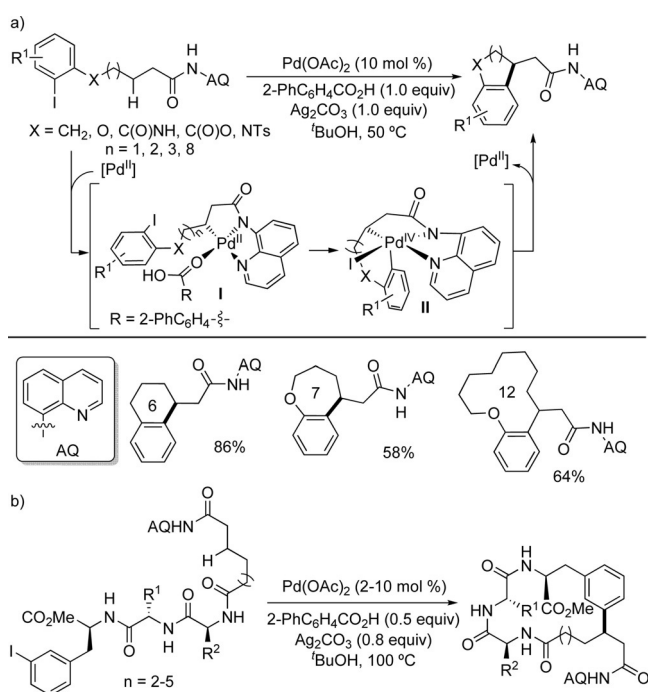
The Baudoin group has been particularly active in exploring the potential of this strategy. Their first studies focused on the construction of benzocyclobutanes from *ortho*-alkyl bromoarenes, as illustrated in Scheme 7a.^[49,50] Similar approaches have since been used for the assembly of a wide range of fused carbocycles and heterocycles of different sizes,^[18,51,52] even in an asymmetric manner. For example, Kündig and co-workers developed a Pd⁰-catalyzed enantioselective carbocyclization of aryl halides for the synthesis of enantioenriched fused indolines by using a chiral NHC ligand (**L2**, Scheme 7b).^[53]

The catalytic carbocyclization sequence can also be triggered by an initial C-H activation through a CMD mechanism, followed by an oxidative addition to an internal aryl halide, to give a Pd^{IV} intermediate (Scheme 8a).^[54] This strategy, which requires substrates bearing 8-aminoquinoline (AQ) auxiliaries, was later used in the macrocyclization of peptide-like architectures, thereby enabling the obtention of macrocycles with up to 37 members (Scheme 8b).^[55] More recently, related carbocyclization approaches that exploit transient directing groups instead of semipermanent auxiliaries have started to emerge.^[56,57]

In the last few years there has been an upsurge in carbocyclization methods based on twofold C-H activations. Taking as reference the seminal work by Dyker on the Pd-catalyzed dimerization/carbocyclization of iodoanisoles through double C-H activation processes,^[58] Baudoin and co-workers developed a versatile method to build cyclo-



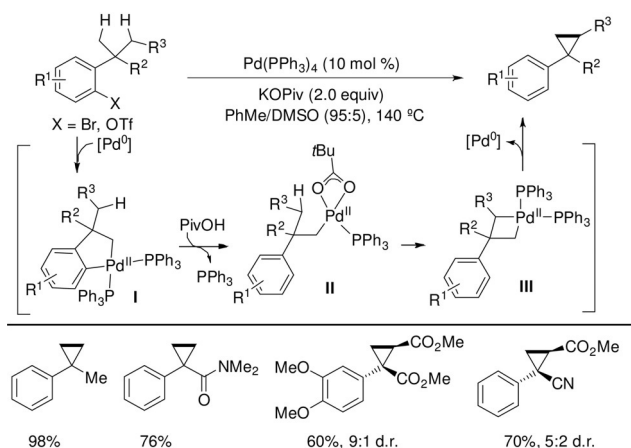
Scheme 7. a) Pd⁰-catalyzed cyclization of aryl bromides to afford benzocyclobutanes through C(sp³)-H activation. b) Pd⁰-catalyzed enantioselective cyclization of aryl bromides to afford fused indoline cores.



Scheme 8. a) Pd^{II}-catalyzed intramolecular arylation of 8-aminoquinoline-containing alkyl chains by chelation-assisted C(sp³)-H activation. Ring sizes are listed in the scheme. b) Pd^{II}-catalyzed macrocyclization of peptide-like structures exemplified with a tripeptide derivative.

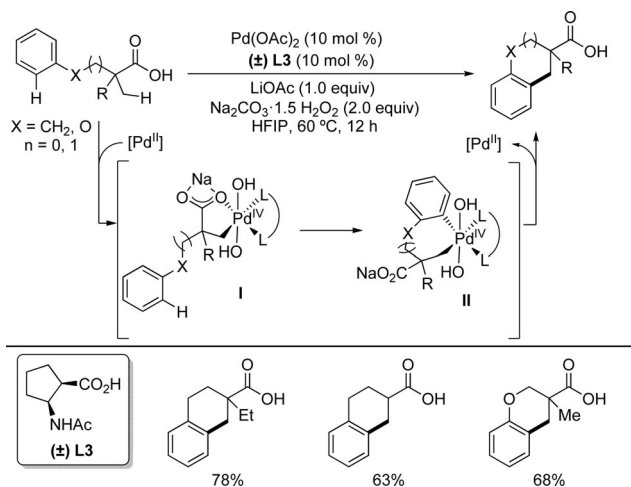
propanes from acyclic precursors using a Pd⁰-promoted C(sp³)-H activation cascade.^[59]

The reaction involves an initial oxidative addition of the aryl halide to generate palladacyclopentane **I**, which evolves by proto-depalladation to give species **II** in a formal 1,4-Pd shift (Scheme 9). This intermediate promotes the cleavage of a C(sp³)-H bond in an alkyl group of the substrate to afford palladacyclobutane **III**, which yields the final cyclopropane by reductive elimination. In substrates containing alkyl chains with β-hydrogen atoms, β-hydride elimination pathways compete with the cyclopropanation. The authors found that the use of pivalates instead of carbonates is key to favor the desired cyclopropanation pathway.



Scheme 9. Pd⁰-catalyzed cyclization of *gem*-dialkyl (pseudo)haloarenes by double C(sp³)-H activation.

Other carbocyclizations relying on double C-H activation processes have also been reported by Yu and co-workers. Their reactions, however, are not initiated by oxidative addition of Pd⁰ to haloarenes, but by a carboxylate-directed C(sp³)-H activation process (Scheme 10).^[60] A subsequent oxidation of the intermediate generates an alkyl-Pd^{IV} com-

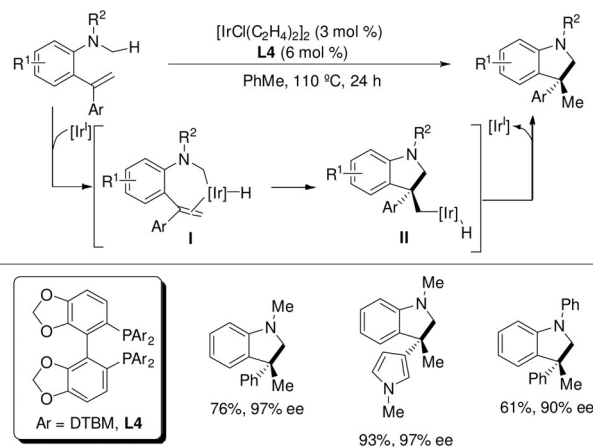


Scheme 10. Pd^{II}-catalyzed cyclization of aryl alkyl carboxylic acids by twofold C-H activation. The oxidized intermediates are indicated.

plex that promotes the C(sp³)-H activation of the arene prior to a ring-forming C-C reductive elimination. The reaction, which is only effective for the activation of methyl groups, was used in a four-step synthesis of indane-containing sesquiterpene (±)-russujaponol D.

In the above reactions, the C(sp³)-H activation step occurs through a CMD-type mechanism and requires electrophilic metal catalysts, in most cases based on Pd^{II}. An alternative for performing the C-H activation step relies on oxidative addition to low-valent transition-metal centers. Indeed, synthetic methods based on C(sp³)-H oxidative additions that lead to metal-hydride intermediates are finding increasing synthetic applications. This is the case for well-known Ru^{II}-, Rh^I-, and Ir^I-catalyzed borylation and silylation reactions,^[61,62] as well as in intermolecular hydrocarbonation processes.^[63] Conversely, intramolecular hydrocarbonations to build cyclic products are much less common. An early contribution was published by Jones et al. in 1986, which demonstrated the viability of assembling indoles from 2,6-dialkylphenylisocyanides^[64,65] using low-valent ruthenium catalysts. Another relevant contribution relying on an iridium-catalyzed hydrocarbonation of alkenes was reported by Sames and co-workers in 2004.^[66]

The Suginome group has recently described elegant examples of carbocyclization reactions to build indolines through the Ir-catalyzed C(sp³)-H activation of methylaniline precursors. The reaction can even be performed in an enantioselective fashion by using chiral BINAP derivatives as ligands (**L4**, Scheme 11).^[67] This concept has been further exploited by the authors to build benzofuran skeletons.^[68]



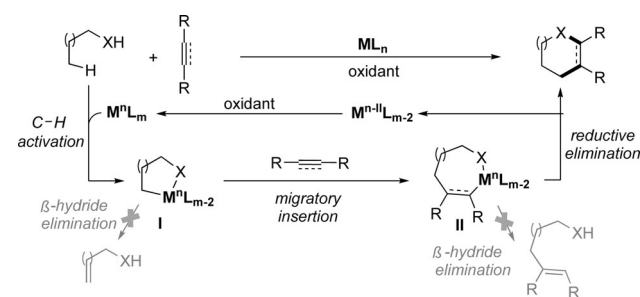
Scheme 11. Ir^I-catalyzed enantioselective cyclization of 2-alkenyl-N-methylanilines to afford indolines.

To conclude this section, we can state that cyclization reactions triggered by metal-promoted C(sp³)-H activations can be ranked among the more promising strategies to build cyclic products from simple acyclic precursors. The progress in this topic has been slow but steady, and, very likely, many new methods will see the light in the years to come.

3. Transition-Metal-Catalyzed Formal Cycloadditions by C(sp³)-H Activation

From a constructive point of view, cycloadditions are even more appealing than cyclizations, owing to their inherent complexity-increasing characteristics. Transition-metal catalysis has demonstrated an enormous potential in the development of formal cycloadditions of unsaturated precursors.^[69–71] In recent years there has been a substantial increase in cycloadditions involving transition-metal-catalyzed C–H activation, with most of the examples so far reported involving the cleavage of C(sp²)-H bonds.^[7] Analogous formal cycloadditions entailing the activation of C(sp³)-H bonds is more challenging, and has been much less developed. In most cases, these reactions follow the general pathways outlined in Scheme 12: A metal-promoted C(sp³)-H activation followed by a migratory insertion of an unsaturated partner, and a final reductive elimination that yields the cycloaddition product. In addition to the intrinsic difficulties of the C–H activation step, the other steps can also be problematic, in part because they present competing β -hydride elimination pathways (Scheme 12).^[72]

Despite these hurdles, methods formally involving such cycloadditions are starting to emerge.



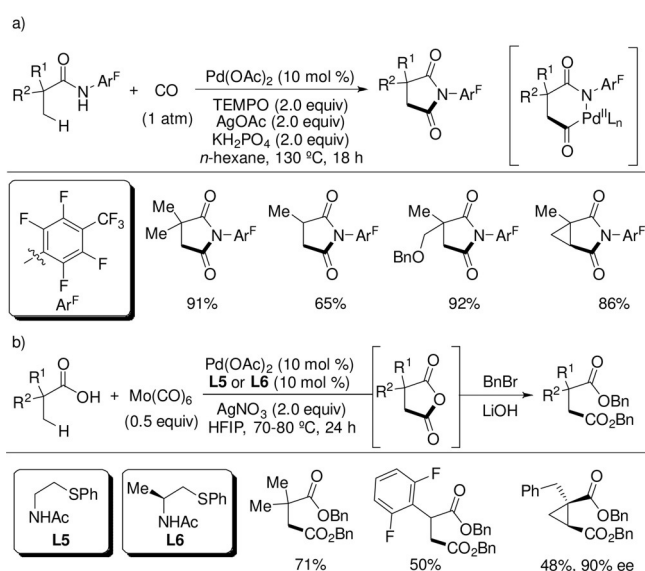
Scheme 12. General mechanistic scenario for transition-metal-catalyzed formal cycloaddition through C(sp³)-H activation processes.

3.1. Formal Cycloadditions with Carbon Monoxide

Among the first examples describing formal cycloadditions involving the activation of C(sp³)-H bonds, those based on the use of carbon monoxide as an annulation partner occupy a prominent position. A wide variety of methods for the construction of succinimides and lactams, usually operating through the mechanistic profile outlined in Scheme 12, have been reported.

The first reports based on this approach appeared more than ten years ago, when Yu and co-workers described a Pd-catalyzed formal (4 + 1) cycloaddition of electron-deficient alkyl amides and CO (Scheme 13a).^[73] The electron-poor nature of the aromatic amide is essential for the C–H activation step.

Related annulations to give succinimides have also been developed using other transition metals, such as ruthenium,^[74] copper,^[75] cobalt,^[76] and nickel.^[77] In some cases, these methods use CO surrogates, such as nitromethane or DMF, as annulation partners. In all these examples, the presence of



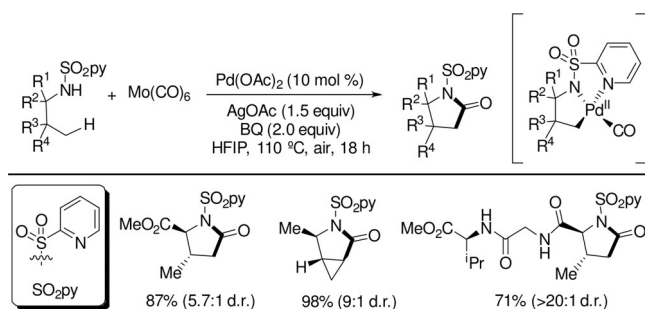
Scheme 13. a) Pd^{II}-catalyzed formal (4 + 1) cycloaddition of alkyl amides. b) Pd^{II}-catalyzed formal (4 + 1) cycloaddition of alkyl carboxylic acids.

coordinating groups appended to the amide nitrogen atom seems crucial for the C(sp³)-H activation step.

Other than amides, aliphatic carboxylic acids have also been reported to participate in Pd^{II}-catalyzed carbonylations. Indeed, Yu and co-workers developed a formal (4 + 1) cycloaddition using Mo(CO)₆ as the CO source and β -aminothioether **L5** as the ligand (Scheme 13b). The reaction products were isolated as acyclic diester derivatives because of the high sensitivity of anhydrides toward hydrolysis.^[78] Moreover, preliminary results of an enantioselective version using the β -aminothioether ligand **L6** have been reported.

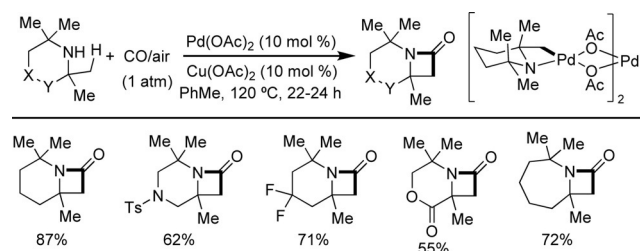
Analogous carbonylations of amine precursors containing auxiliary directing groups (oxalyl- or picolinamides) have recently been reported.^[79,80] Carretero and co-workers have exploited pyridylsulfonyl auxiliaries in alkyl amines to promote their conversion into pyrrolidinones under Pd(OAc)₂ catalysis, using Mo(CO)₆ as a CO surrogate (Scheme 14).^[81]

Gaunt and co-workers delineated alternative carbonylative annulations directly from hindered unprotected amines. They described a practical entry to a variety of β -lactams by Pd^{II}-catalyzed carbonylation of amines under a CO/air



Scheme 14. Pd^{II}-catalyzed formal (4 + 1) cycloaddition of pyridylsulfonyl-protected alkyl amides.

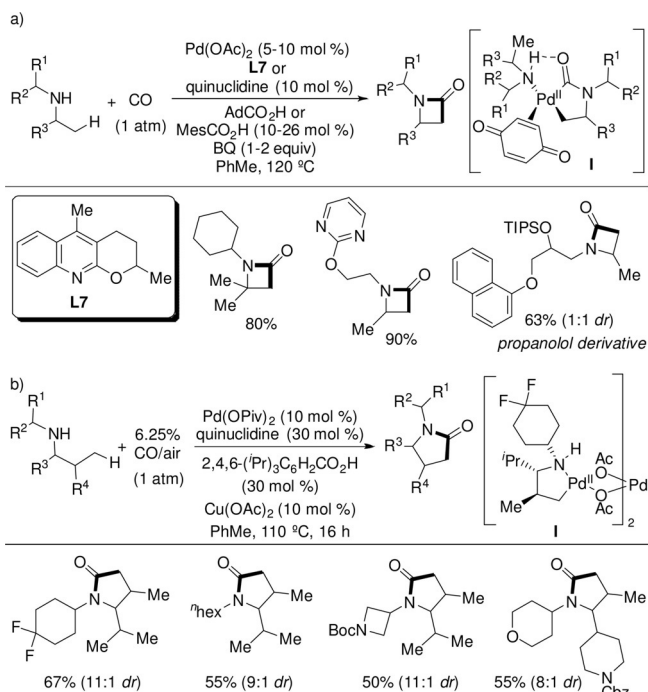
atmosphere (Scheme 15).^[43] The authors were even able to isolate key azapalladacycle intermediates resulting from the C–H activation.



Scheme 15. Pd^{II}-catalyzed C(sp³)-H carbonylation of hindered secondary free amines.

Less-hindered amines containing tertiary, secondary, and even primary carbon atoms can also engage in this type of annulation, although such reactions follow different mechanistic pathways. Computational and experimental studies suggested that the reaction entails the carbonylation of the amine to give an acyl palladium intermediate, which undergoes a C(sp³)-H activation to generate species **I** (Scheme 16a).

After optimization of the reaction parameters, the Gaunt group applied the method to the preparation of a wide range of β -lactams with good to excellent yields (Scheme 16a).^[82] This method can also be used for the late-stage carbonylation of pharmaceuticals and other biologically active products.



Scheme 16. a) Pd^{II}-catalyzed β -carbonylation of secondary bulky amines via carbamoyl-Pd^{II} species. The reaction intermediate **I** was characterized by X-ray diffraction. b) Pd^{II}-catalyzed γ -carbonylation of hindered secondary amines.

These formal (3 + 1) cycloadditions can also be extended to other secondary amines^[83] or α -tertiary amines^[84] that require the activation of β -methylene C–H groups. Further tuning of the reaction conditions allowed the regioselectivity of these processes to be shifted to activate γ -methyl groups of secondary amines and deliver γ -lactams in a formal (4 + 1) cycloaddition (Scheme 16b). To achieve this selectivity it is key to use a reaction atmosphere with a low content of CO (6.25% CO/air mixture), and thus prevent the formation of carbamoyl-Pd species, as these reactions proceed through five-membered palladacycles (species **I**, Scheme 16b).^[85]

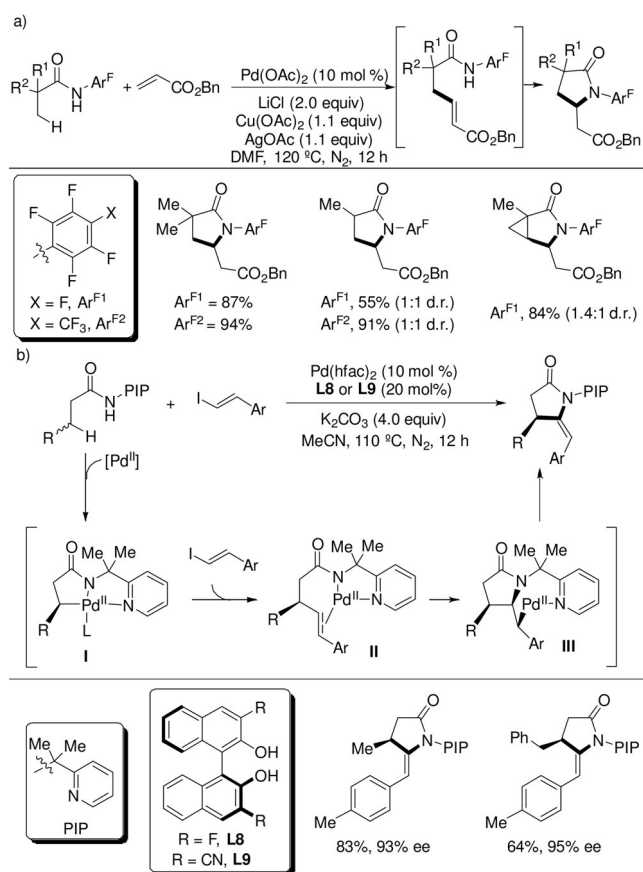
It can be concluded that the carbonylation of C(sp³)-H bonds in formal cycloaddition processes has proven very fruitful for building succinimides, succinic anhydrides, and lactams of different sizes. However, most of these transformations require careful engineering of the substrate to prevent undesired side reactions, which represents a serious limitation in terms of scope and generality. Noticeably, related cycloadditions with CO, involving the formation of two C–C bonds, have not yet been reported.

3.2. Formal Cycloadditions with Alkenes, Dienes, and Allenes

Formal cycloadditions involving the activation of C(sp³)-H bonds but using olefinic partners instead of CO are very attractive (Scheme 11), although they represent a significant challenge. The palladacyclic intermediates resulting from the migratory insertion of the alkene tend to undergo β -hydride elimination processes, which halts the canonical cycloaddition. However, the resulting olefinated adducts can still be converted into cyclic products through an intramolecular Michael-type addition. This was indeed demonstrated by Yu and co-workers in 2010 with the reaction between alkyl amides and acrylates using Pd^{II} catalysts and oxidizing additives. The reaction is initiated by activation of a C(sp³)-H bond in the β position to an amide to give a palladacyclic intermediate, which evolves to the final γ -lactam by the aforementioned Heck-type coupling/Michael addition mechanism (Scheme 17a).^[86] This transformation could be extended to build six-membered rings using amide substrates bearing β -quaternary carbon atoms.^[87]

More recently, Shi and co-workers reported a Pd^{II}-catalyzed alkenylation/cyclization process to build γ -lactams using alkyl amides bearing a pyridyl-isopropylamine directing group (PIP) and alkenyl iodide coupling partners (Scheme 17b). In this case, the Pd catalyst promotes a C(sp³)-H alkenylation of the alkyl amide, followed by a *syn*-aminopalladation (**II** \rightarrow **III**). Finally, a β -hydride elimination step delivers the aza-Wacker cyclized product. The authors also demonstrated that using BINOL derivatives as chiral ligands for Pd enables the reaction to occur with excellent levels of enantioselectivity.^[88, 89]

Compared to amides, related alkenylation/cyclizations of alkyl carboxylic acids have proven more challenging. As indicated in Section 2.1, the C–H activation of these precursors is favored by using alkali metal bases, which exhibit κ^2 -coordination with the acid substrate and prevent poisoning of the catalyst.^[90]

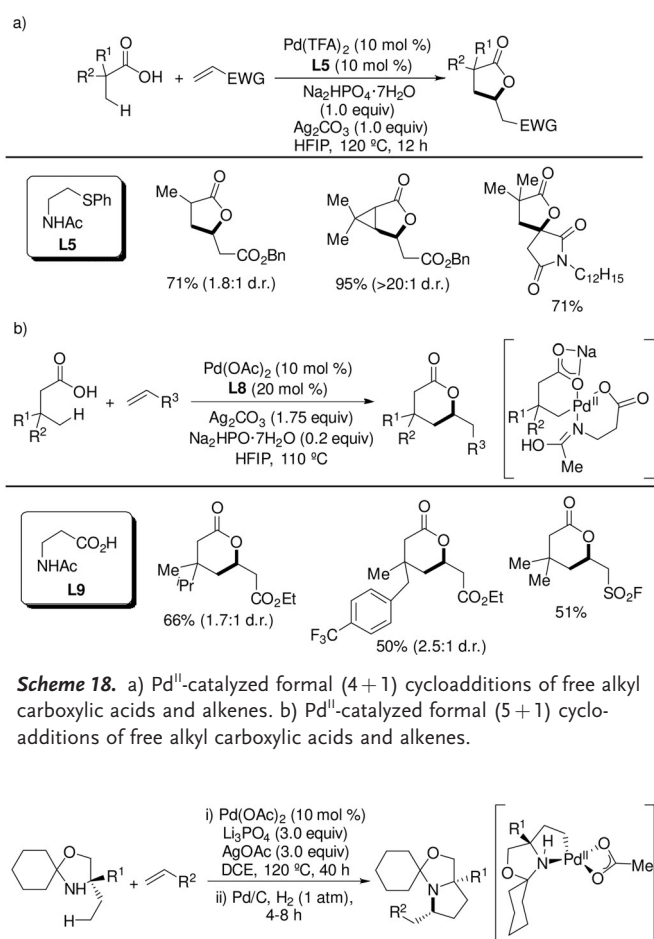


Scheme 17. a) Pd^{II}-catalyzed γ -alkenylation/cyclization of alkyl amides and acrylates. b) Pd^{II}-catalyzed enantioselective γ -alkenylation/aza-Wacker cyclization of alkyl amides and vinyl iodides.

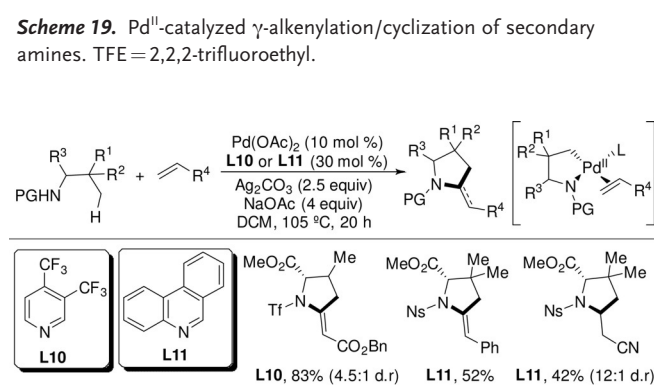
In 2018, Yu and co-workers described a Pd^{II}-catalyzed olefination of free alkyl carboxylic acids with acrylates that was accelerated by the β -aminothioether ligand **L5** and gave the corresponding lactones (Scheme 18a).^[91] The groups of van Gemmeren,^[92] Yu,^[93] and Maiti^[94] have reported similar annulation reactions to produce δ - and ϵ -lactones.^[94] These reactions required the use of suitable amino acids as palladium ligands, and afforded the products in moderate to good yields (Scheme 18b). Interestingly, the reaction did not work with substrates containing non-quaternary β carbon atoms, which suggests there is a need for a Thorpe–Ingold effect to favor the C–H activation step.

Related annulations based on alkenylation/cyclization sequences have been used by the Gaunt group to build fused pyrrolidines from specifically engineered alkyl amines (Scheme 19). Steric effects were key to lock the conformation of the substrate and favor the C–H activation process, which can even take place at room temperature.^[95] In this example, there is a competition between aza-Wacker and aza-Michael processes in the cyclization event and, therefore, the products were better obtained after hydrogenation of the mixture.

The Yu group has also developed a set of pyridine and quinoline ligands that enable similar alkenylation/cyclization processes with triflyl- and nosyl-protected aliphatic amines (Scheme 20).^[96] Interestingly, with acrylate and styrene part-



Scheme 19. Pd^{II}-catalyzed γ -alkenylation/cyclization of secondary amines. TFE = 2,2,2-trifluoroethyl.

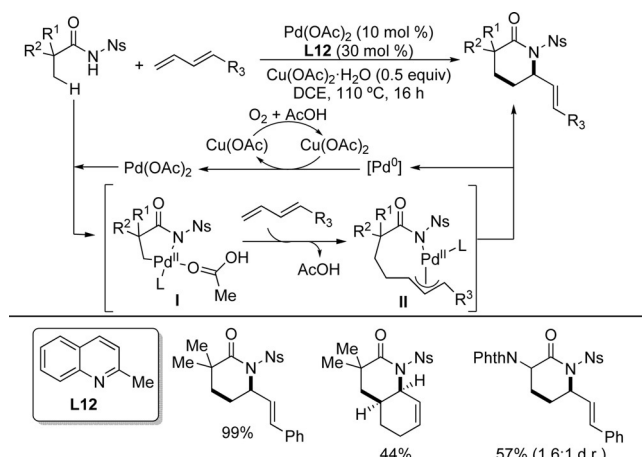


Scheme 20. Pd^{II}-catalyzed γ -alkenylation/cyclization of protected amino acids.

ners, this method affords pyrrolidines with exocyclic unsaturations through aza-Wacker oxidative cyclization.

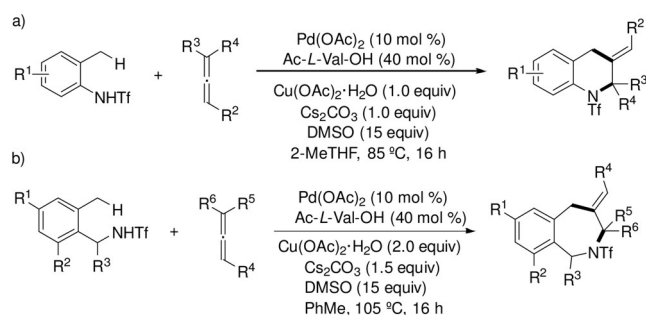
Overall, these olefination/cyclization sequences have unlocked fast synthetic routes to a variety of important classes of heterocycles such as pyrrolidinones, 4,4-disubstituted piperidinones, dihydrofuranones, 4,4-disubstituted tetrahydropyranones, and pyrrolidines. However, they cannot be considered as formal one-step organometallic cycloadditions.

Indeed, the progress in metal-catalyzed ($n+2$) formal cycloadditions has been quite modest. Gulías, Mascareñas, and co-workers recently described a strategy to make piperidones from alkyl amides and dienes that proceeds via canonical carbometalation/reductive elimination processes (Scheme 21).^[97] Preliminary mechanistic studies, which included the isolation of palladacyclic intermediates, revealed the key role of the bulky quinaldine ligand **L12** in facilitating the C(sp³)-H activation and the diene migratory insertion steps.



Scheme 21. Pd^{II}-catalyzed formal (4 + 2) cycloaddition between alkyl amides and dienes.

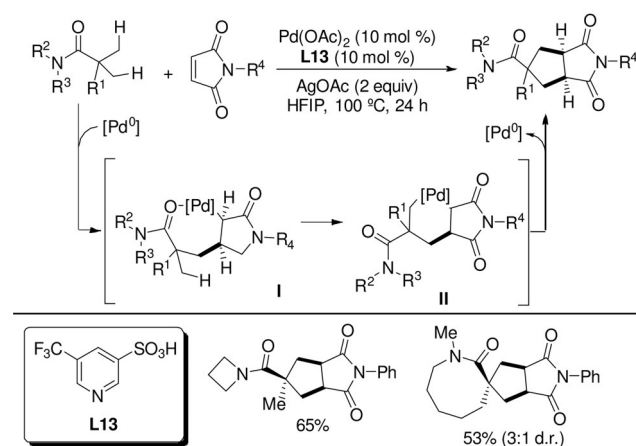
The same group has developed annulations between *ortho*-methylamides and allenes involving the Pd^{II}-catalyzed activation of benzylic methyl groups (Scheme 22a). The use of an α -amino acid ligand is crucial for the success of the reaction. This formal (4 + 2) cycloaddition does not proceed with other unsaturated moieties such as alkenes or alkynes, which underscores the relevance of using allenes as partners. Importantly, this transformation can be extended to *ortho*-methylbenzylamines, although in this case, both *ortho* positions of the aromatic ring need to be appropriately blocked to avoid activation of the aromatic C-H bonds (Scheme 22b). This example represents the first metal-catalyzed formal (5 + 2)



Scheme 22. a) Pd^{II}-catalyzed formal (4 + 2) cycloaddition between *ortho*-methylamides and allenes. b) Pd^{II}-catalyzed formal (5 + 2) cycloaddition between *ortho*-methylbenzylamines and allenes.

2) cycloaddition that involves the activation of a C(sp³)-H bond.^[98]

In all these examples of formal cycloadditions, one of the two bonds formed involves a heteroatom (C-O or C-N bond). Examples of cycloadditions leading to the formation of two C-C bonds were essentially unknown until a recent report by Park and Yu describing a formal (3 + 2) annulation between alkyl amides and maleimides, which operates through a twofold C(sp³)-H activation mechanism.^[99] The reaction requires the use of maleimides as reaction partners, likely because they disfavor potential β -hydride eliminations after the migratory insertion step.^[100] The rigidity of the maleimide scaffold may also facilitate a second cyclopalladation leading to a dialkyl-Pd^{II} species (**II**) that eventually delivers the cycloadduct after C-C reductive elimination (Scheme 23).



Scheme 23. Pd^{II}-catalyzed formal (3 + 2) cycloaddition of alkyl amides and maleimides by double C(sp³)-H activation.

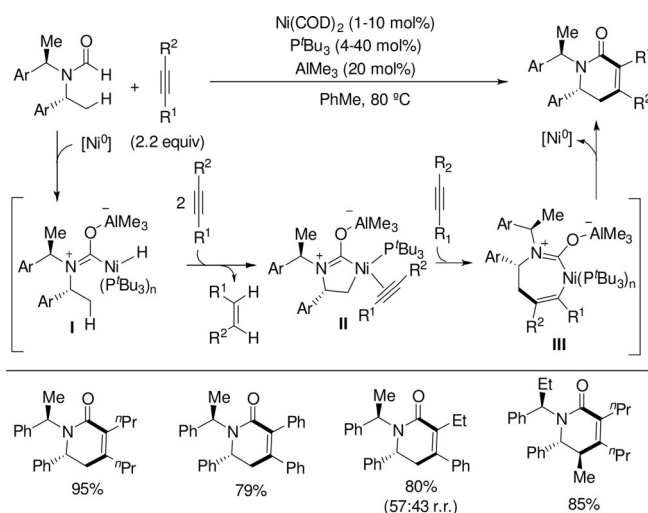
Soon after this seminal report, He and Chatani reported a related formal [3C + 2C] cycloaddition between aromatic amides equipped with bidentate auxiliaries and maleimides to yield fused carbocyclic products.^[101]

3.3. Formal Cycloadditions with Alkynes

Although the number of formal metal-catalyzed cycloadditions initiated by C(alkyl)-H activation, and using CO, alkenes, or allenes as partners, is very scarce, similar reactions with alkynes are even less common.

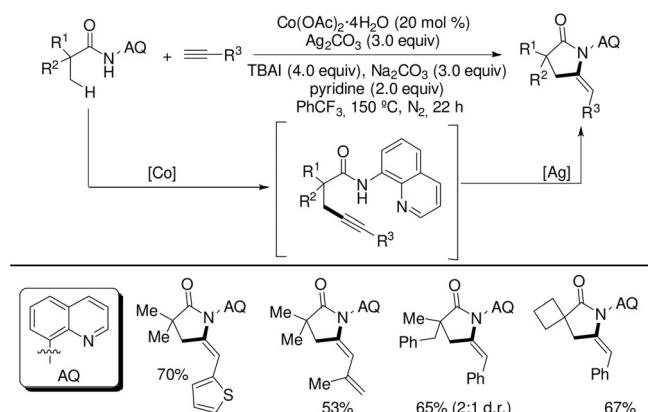
Only one of the examples so far described follows the general mechanistic pathways described in Scheme 12. Nakao, Hiyama et al. described a clever strategy to couple Ni oxidative addition to the C(acyl)-H bonds of *N*-dialkyl formamides with a C(sp³)-H activation to generate nickelacycles that can be trapped by alkynes.

These reactions produce dihydropyridone rings and use Ni⁰ precatalysts, trialkyl phosphine ligands, and trimethylaluminum to facilitate the initial Ni⁰ acyl oxidative addition. The reaction also needs excess alkyne partner, which acts as a sacrificial H₂ acceptor (Scheme 24).^[102]



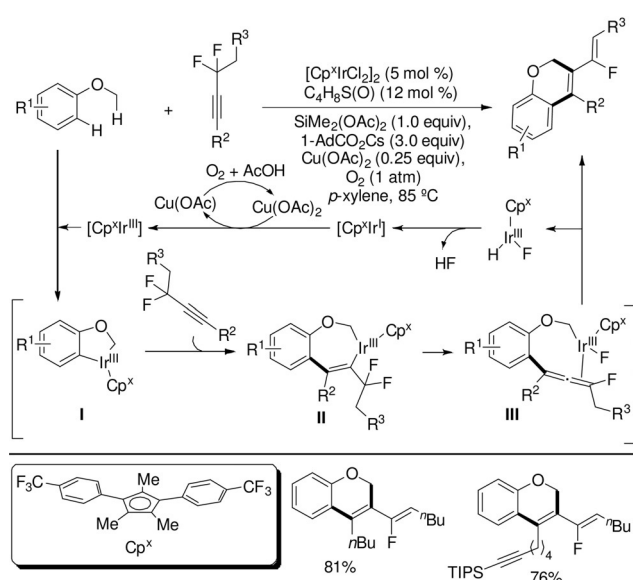
Scheme 24. Ni⁰-catalyzed formal (4 + 2) cycloaddition of *N*-dialkyl formamides and alkynes to afford 2-dihydropyridones.

Other annulation strategies using alkyne partners but taking place through alternative mechanisms are starting to appear in the literature. For example, Zhang and co-workers have reported the assembly of γ -lactam products from amides featuring bidentate directing groups (AQ), by using a bimetallic system consisting of a cobalt catalyst and silver additives.^[103] The reaction occurs through an initial C(sp³)–H alkylation triggered by the cobalt catalyst followed by a silver-mediated cyclization to generate the final γ -lactam (Scheme 25).



Scheme 25. Co^{III}-mediated formal (4 + 1) cycloaddition of alkyl amides and alkynes to afford 5-alkenylisoindolones.

An interesting formal (4C + 2C) cycloaddition promoted by iridium catalysts has also been recently developed by Rovis and co-workers. They demonstrated that anisole derivatives react with *gem*-difluoroalkynes in the presence of a modified [Cp^{*}IrCl₂]₂ catalyst to form chromenes (Scheme 26).^[104] The catalytic cycle postulates a first C(sp²)–H iridation followed by C(sp³)–H cleavage to yield five-membered iridacycle **I** (Scheme 26). This species undergoes migratory insertion of the difluorinated alkyne, followed



Scheme 26. Ir^{III}-catalyzed formal (4 + 2) cycloaddition of anisoles and *gem*-difluoroalkynes to yield fluoroalkenylchromenes.

by a β -fluorine elimination to give fluoroallene intermediate **III**. A subsequent migratory insertion of the allene produces an α -iridated chromene ring that delivers the product upon β -hydride elimination.

4. Conclusion and Outlook

Transition-metal-catalyzed annulations by the activation of inert alkyl C(sp³)–H bonds hold enormous potential to streamline the synthesis of valuable saturated carb- and heterocycles from simple acyclic precursors. Although important breakthroughs have already been made, the progress in the field has been slow, and restricted to very specific types of reactions and substrates. Therefore, there is a clear need to invent and develop new types of approaches that are more general and present a wider scope, avoiding excessive substrate engineering. Furthermore, it is important to invent methods that allow the activation of C–H bonds in moieties other than methyl, as well as reactions catalyzed by more sustainable transition metals. Finally, the implementation of enantioselective variants remains a highly challenging goal. Overall, we foresee a bright future for these methods.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: annulation · C(sp³)-H activation · carbocycles · heterocycles · transition-metal catalysis

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