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# Catalytic Domino Annulations through $\eta^3$ -Allylpalladium Chemistry: a Never-Ending Story

Yang Liu, Julie Oble, Alexandre Pradal\* and Giovanni Poli\*

Dedicated to the memory of our friend and colleague Francois Couty

**Abstract:** Annulative  $\eta^3$ -allylpalladium chemistry has been a longstanding trending research topic since the 80's. Nowadays, this research area is still providing challenges to the catalysis community allowing to develop original and brand new transformations. Several reaction partners have been used as precursors for  $\eta^3$ -allylpalladium species, namely allyl diacetates, allyl monoacetates, 3-acetoxy-2-trimethylsilylmethyl-1-propene (ASMP), alkylidene cyclopropanes (ACPs), vinyl cyclopropanes (VCPs), vinyl aziridines and vinyl epoxides. This minireview is intended to show the recent developments in the field of annulative  $\eta^3$ -allylpalladium chemistry with the emphasis on new reactivity, enantioselective transformations as well as potential applications in total synthesis.

## Introduction.

Out of the huge number of organic compounds present on earth, many of them are – or incorporate – cyclic structures, and some of them are of relevance for steric or electronic properties, biological or pharmacological activity. Furthermore, occurrence of ring-containing compounds in Nature is very high. For this reason, methods for the selective generation of cyclic structures are of utmost importance in organic chemistry and the development of new ones has been the topic of a large number of publications.

Annulation reactions are among the most efficient methods for the generation of cyclic molecules, as pioneered by O. Diels and K. Alder,<sup>[1]</sup> as well as Sir R. Robinson.<sup>[2]</sup> An annulation reaction is defined as the creation of a cyclic molecular entity through the formation of two covalent bonds between two units – being them two separated molecules, or incorporated into a single molecular entity – via a single – concerted or stepwise – process. Many annulation methods have been reported since,<sup>[3]</sup> and this type of reaction clearly constitutes a superior method to build-up cyclic structures from simpler components.<sup>[4]</sup>

In addition, palladium chemistry has been the object of an extremely high number of publications these last decades due to its versatility in a number of transformations such as cross-couplings,<sup>[5]</sup> C-H activations<sup>[6]</sup> and/or annulations.<sup>[7]</sup> As to the latter transformations, many examples involve the transient generation of  $\eta^3$ -allyl intermediates.

This, far from exhaustive, review collects some reported

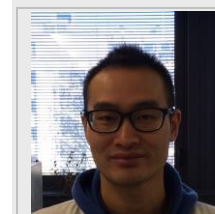
annulation processes taking place through  $\eta^3$ -allylpalladium chemistry. It is organized into two main parts according to the polarity of the interacting reaction partners. Part 1): bis-nucleophile / bis-electrophile [ $\ominus-\ominus/\oplus-\oplus$ ] interactions; part 2): heterodipole / heterodipolarophile [ $\ominus-\oplus/\delta^{\oplus}-\delta^{\ominus}$ ] interactions.<sup>[8]</sup>

## 1. Bis-nucleophile / bis-electrophile [ $\ominus-\ominus/\oplus-\oplus$ ] interactions

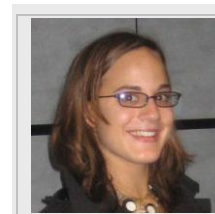
### Bis-allylic system as bis-electrophile.

The palladium-catalyzed allylation of nucleophiles (Pd-AA) is one of the most useful transformations in organic synthesis (Scheme 1, top).<sup>[9,10]</sup> Indeed, this key reaction has been used by chemists in a great number of syntheses, and developed in a

Dr. Yang Liu was born in 1990 in Su Zhou (China). He obtained his B.Sc. at the Shenyang University of Chemical Technology in 2012. Then, he started his graduate studies with Prof. Pei-Qiang Huang at XiaMen University, where his work was focused on the asymmetric total synthesis of loline alkaloids. After three years, he started his doctoral studies with Prof. Giovanni Poli at Sorbonne Université, where his work was focusing on Palladium-catalyzed [3+2]-annulation/domino reactions. After completion of his PhD degree in the summer of 2019, he joined the Medicinal Chemistry department at STA Pharmaceutical Co., Ltd in Chang Zhou, China.



Dr. Julie Oble received in 2007 her PhD degree from the Ecole Polytechnique (Paris, France) under the direction of Drs. Laurence Grimaud and Laurent Elkaim. In 2007, she obtained a one year postdoctoral position in the research group of Prof. André B. Charette at the University of Montréal (Canada). After two further years as a postdoctoral fellow under the supervision of Dr. Emmanuel Lacôte, Prof. Serge Thorimbert and Prof. Bernold Hasenknopf at UPMC, she joined in 2010 the research team of Prof. Giovanni Poli at Sorbonne Université as Assistant Professor. Her research focuses on the development of new metal-catalyzed domino reactions toward the synthesis of heterocycles, homogeneous and quasi-homogeneous catalytic C-H activations, and biomass valorization.



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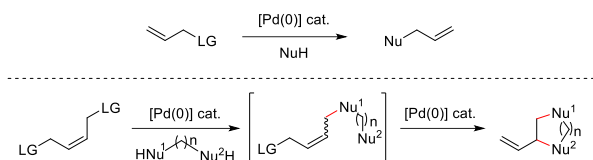
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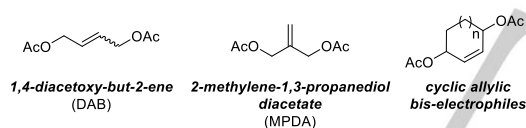
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number of variations, including X–C and C–C bond formations, as well as asymmetric variants (Pd-AAA). In particular, when the substrate is a bis-allylic system, its interaction with a bis-nucleophile may allow accomplishing an annulation reaction via a Pd-catalyzed cascade process (Scheme 1, bottom).



**Scheme 1.** Top: generic Pd-catalyzed allylation. Bottom: generic Pd-catalyzed cascade allylic alkylation using a bis-allylic system and a bis-nucleophile. LG = leaving group.

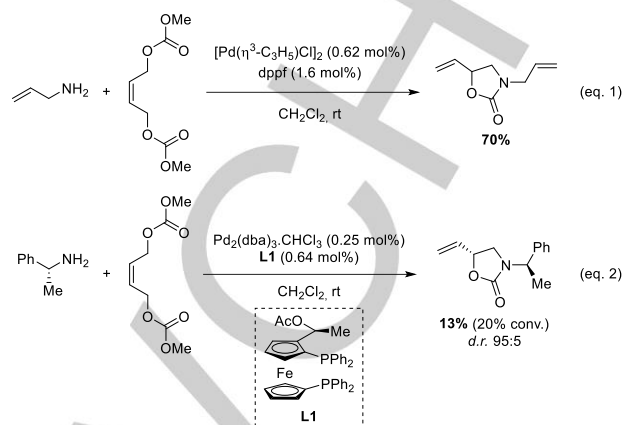
Various combinations of carbon, nitrogen and oxygen bis-nucleophiles have been used for the construction of a variety of vinyl substituted annulated systems. Although this chemistry can in principle lead to a number of regioisomeric products, the use of symmetric electrophiles and/or nucleophiles allowed to avoid such issue, and to adopt this strategy in total syntheses. The following paragraphs will be dealing with two types of bis-allylic electrophiles: acyclic ones, with 1,4-diacetoxybut-2-ene (DAB) and 2-methylene-1,3-propanediol diacetate (MPDA) being the most common (Scheme 2), as well as cyclic ones.



**Scheme 2.** Structures of DAB and MPDA.

Besides carbocycles<sup>[11]</sup> and heterocyclic compounds such as morpholines or piperazines,<sup>[12]</sup> oxazolidinones have been successfully synthesized using a Pd-catalyzed annulation strategy. The group of Tanimori<sup>[13]</sup> described in 2000 and 2003 new procedures for the preparation of oxazolidinones, such type of annulations being previously known only with ketones<sup>[14]</sup> and malonates.<sup>[15]</sup> Mixing 1,4-dimethoxycarbonylbut-2-ene (carbonate analog of DAB) and primary amines in the presence of (allyl)palladium(II) chloride dimer and diphenylphosphinoferrocene (dppf) lead to the formation of a wide range of oxazolidinones with good yields (56–70%). For example, allylamine reacted with 1,4-dimethoxycarbonylbut-2-ene to give the corresponding N-allyloxazolidine with 70% yield (Scheme 3, eq. 1). Two years later,<sup>[16]</sup> the same group expanded the scope of the reaction to more complex amines, and demonstrated that the reaction does not work with anilines, amino-acids or -esters and hydrazines. Furthermore, although no stereoselection could be obtained using a chiral enantiopure amine, good *d.r.* values were obtained by introducing a chiral ligand. The use of Pd<sub>2</sub>(dba)<sub>3</sub>·CHCl<sub>3</sub> and L1 as a chiral ligand led

to the formation of the desired oxazolidine in 13% yield and with a 95:5 *d.r.* (Scheme 3, eq. 2).

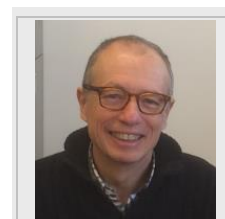


**Scheme 3.** Preparation of oxazolidines by Pd-catalyzed annulation of 1,4-dimethoxycarbonylbut-2-ene and primary amines.

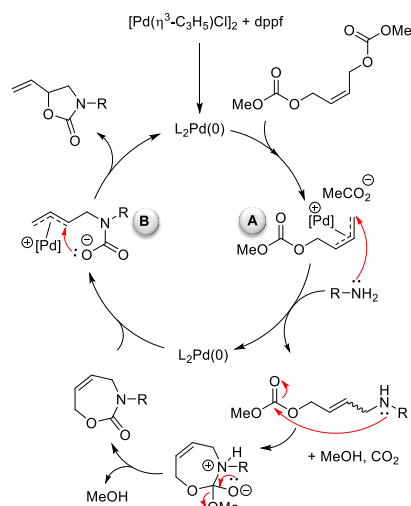
Dr. Alexandre Pradal was born in 1987 in Maisons-Laffitte (France). He obtained his Ph.D in organic chemistry in 2012 from Université Pierre et Marie Curie, where he worked on the development of gold- and platinum-catalyzed stereoselective cycloisomerization reactions under the supervision of Prof. Véronique Michelet and Prof. Patrick Toullec. After postdoctoral stays in the groups of Prof. Gwilherm Evano (ULB, Brussels, Belgium), Prof. Christopher J. Moody (University of Nottingham, Nottingham, UK) and Prof. Vincent Dalla (Normandie Université, Le Havre, France), he was appointed as Chargé de Recherche CNRS at Sorbonne Université in 2016 working with Prof. Giovanni Poli. His research interests include the development of new metal-catalyzed C–H activation reactions, domino reactions, the elucidation of their mechanism and the application of those transformations in the total synthesis of relevant natural products.



Prof. Giovanni Poli was born in Milan in 1956. He received his Laurea in 1980 and then his PhD degree at the University of Milano, under the direction of Professor Carlo Scolastico. In 1986 he continued his scientific education as postdoctoral fellow with Professor Wolfgang Oppolzer at the University of Geneva. After one year as Maître Assistant at the University of Lausanne, he joined the faculty at the University of Florence in 1992 as Associate Professor. In 2000 he reached UPMC (now Sorbonne Université) in Paris as Full Professor. His current interest focuses on the study of innovative transition metal catalyzed transformations, catalytic C–H activation processes, and biomass valorization.

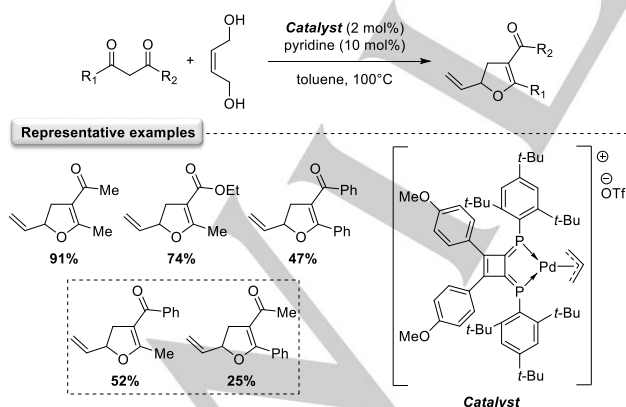


The expected mechanism (Scheme 4)<sup>[17]</sup> involves attack of the primary amine on the  $\eta^3$ -allylpalladium intermediate **A**<sup>[18]</sup> in turn generated by ionization of the bis-electrophile by the *in situ* generated Pd(0) complex. Subsequent cyclization – rather than ionization – leads to an allylic 7-membered carbamate, which undergoes a further ionization to generate the new  $\eta^3$ -allylpalladium intermediate **B**. Finally, a 6-*exo* cyclization gives the desired oxazolidine and the Pd(0) catalyst.



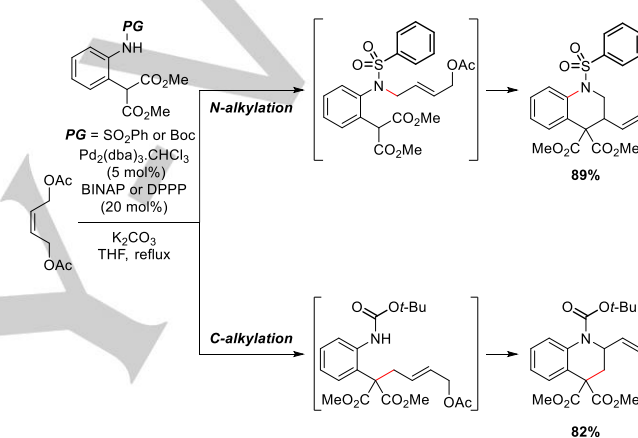
**Scheme 4.** Proposed mechanism for the synthesis of oxazolidines.

Bis-electrophilic reagents other than acetates and carbonates were also considered. For example, the group of Ozawa managed to directly use *cis*-2-butene-1,4-diol to prepare dihydrofurans in moderate to high yields (47–91%) in Pd-catalyzed annulation processes with  $\beta$ -diketones or  $\beta$ -ketoesters (Scheme 5).<sup>[19]</sup> The formation of dihydrofurans from DAB was known for a long time.<sup>[20]</sup>



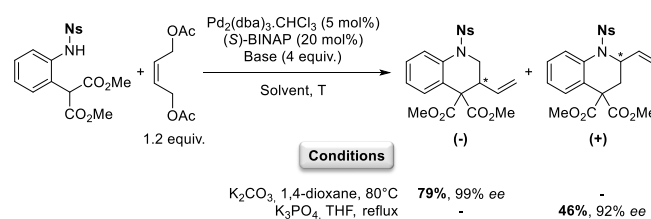
**Scheme 5.** *Cis*-butene-1,4-diol as a bis-electrophile for the synthesis of dihydrofurans.

Tetrahydroquinolines are a class of compounds that can be obtained through a Pd-catalyzed annulation between 2-amidophenyl-malonates and allylic bis-electrophiles.<sup>[21]</sup> For example, the group of Yoshida used this strategy to obtain these heterocycles in a regio- and enantioselective way.<sup>[16,22]</sup> In particular, the reaction could give either sulfonyl-protected tetrahydroquinoline (Scheme 6, top) or Boc-protected tetrahydroquinoline (Scheme 6, bottom) depending on the nature of the protecting group on the starting aniline. After formation of the  $\eta^3$ -allylpalladium intermediate, N-alkylation occurs first if the protecting group is a sulfonamide. Conversely, C-alkylation occurs first if the aniline is protected as a carbamate. This regioselectivity can be explained by the  $pK_a$  difference between the sulfonyl- and carbamate-protecting anilines compared to that of the malonate.



**Scheme 6.** Regioselectivity outcome of the synthesis of tetrahydroquinolines depending on the protecting group on the aniline part. PG = protecting group.

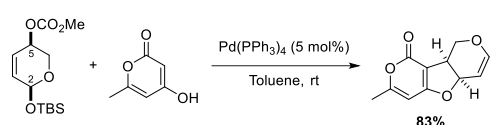
Two years later, they investigated an enantioselective variant by using a chiral diphosphine.<sup>[22]</sup> Thus, using BINAP, a tosyl-protected aniline gave the best results, though, in a low yield (36% yield, 56% ee). However, switching to aniline, which carries a nosyl protecting group, greatly enhanced the enantioselectivity. Each regioisomer (+) and (–) could be selectively isolated depending on the base and the solvent used (Scheme 7). While working with potassium carbonate as the base in 1,4-dioxane at 80°C gave (+) in 79% yield and 99% ee, (–) was isolated in a moderate 46% yield and 92% ee when using potassium phosphate as the base in THF at reflux.





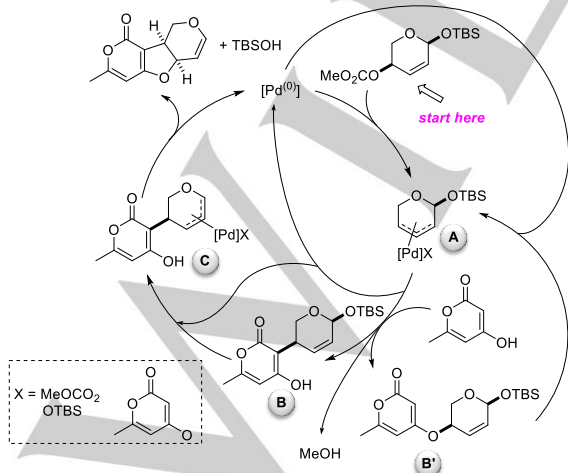
**Scheme 7.** Stereoselective Pd-catalyzed annulation using DAB to afford *trans*-tetrahydroquinolines.

Harvey<sup>[23]</sup> and Tanimori<sup>[24]</sup> reported the use of cyclic allylic bis-electrophiles for the preparation of bicyclic dihydrofurans from bis-nucleophiles such as dimedone, dimethyl-1,3-acetone-dicarboxylate or hydroxypyrones. In particular, the former group demonstrated that by the judicious choice of the leaving groups on the bis-electrophile, the initial C-allylation of the bis-nucleophile could be selectively directed to position 5 of the bis-electrophile and the subsequent O-allylation to position 2 of the bis-electrophile (Scheme 8). As previously observed in similar cases,<sup>[25]</sup> the reaction was stereoconvergent, the *cis*- and *trans*-bis-electrophiles providing only *cis*-fused tricyclic compounds.



**Scheme 8.** Pd-catalyzed methods for the synthesis of polycyclic dihydrofurans.

The mechanism of this transformation<sup>[26]</sup> is expected to be as described below (Scheme 9). Ionization of the bis-electrophile by expulsion of the carbonate anion first generates the transient  $\eta^3$ -allylpalladium intermediate **A**. Then, the carbonate counterion deprotonates the bis-nucleophile, and the resulting enolate reacts with the bis-electrophile via C-alkylation, to give **B**, as well as via O-alkylation, to give intermediate **B'**, which has been isolated and characterized by X-ray diffraction. On the one hand, the former intermediate is the only one that is prone to undergo a second ionization to generate the new  $\eta^3$ -allylpalladium complex **C** by silyloxy anion displacement. An intramolecular O-allylation generates the final tricyclic furan derivative and regenerates the starting Pd(0) complex. On the other hand, the O-allylated intermediate **B'** can be reinjected into the catalytic cycle through reionization by Pd(0).

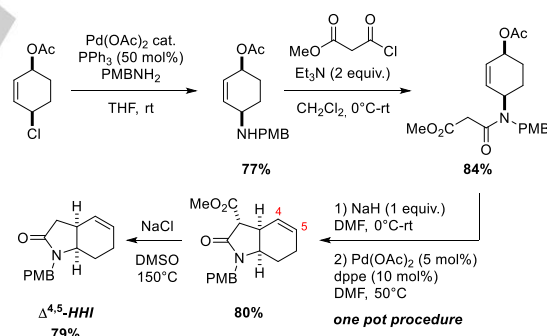


**Scheme 9.** Proposed mechanism for the generation of the *cis*-fused furanic tricyclic compound.

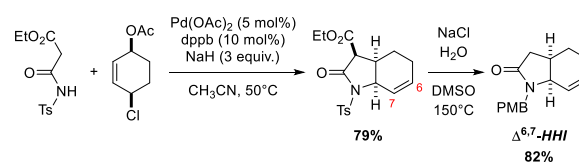
More recently, while studying a route towards the total synthesis of members of the aeruginosin family, our group developed a method to rapidly access the 2-carboxyl-6-hydroxyoctahydroindole (CHOI) core structure found in those natural products.<sup>[27]</sup> Depending on the use of a stepwise or *pseudo*-domino sequence for the preparation of the CHOI core, two different regioisomers of a precursor hexahydroindole (HHI) structure could be isolated (Scheme 10).

The first attempts to access the HHI structure were done via a 4-step process. The allylic chloroacetate bis-electrophile was firstly treated with *p*-methoxybenzylamine in a Pd(0)-catalyzed amination furnishing the PMB-protected allylic amine in 77% yield. The reaction is completely chemoselective, since the  $\eta^3$ -allylpalladium intermediate formed comes exclusively from the release of the chloride anion. Condensation between the allylic amine and methyl malonyl chloride generates the corresponding allylamide in 84% yield. An one-pot intramolecular allylation provided the ester-substituted  $\Delta^{4,5}$ -HHI in 80% yield in the presence of sodium hydride. Therefore, creating the C–N bond before the C–C bond releases the  $\Delta^{4,5}$ -HHI ring (Scheme 10, top). Access to this structure was also possible in one synthetic step (decarboxylation under the Krapcho conditions). The regioisomeric  $\Delta^{6,7}$ -HHI was obtained via a *pseudo*-domino approach, inspired from an old work of Mori *et al.*<sup>[28]</sup> (Scheme 10, bottom).

■ Stepwise strategy to  $\Delta^{4,5}$ -HHI core structure



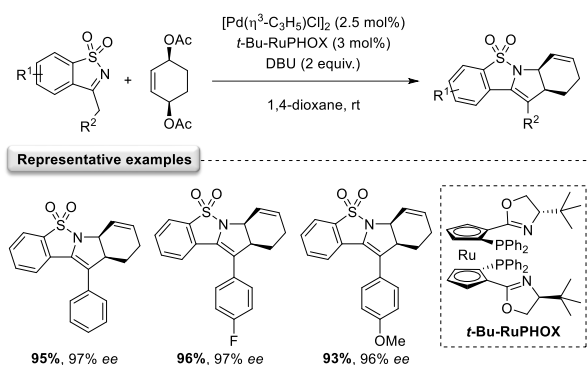
■ Pseudo-domino strategy to  $\Delta^{6,7}$ -HHI core structure



**Scheme 10.** Access to HHI regioisomers by Pd-catalyzed C–N and C–C bond formation from allylic bis-electrophiles.

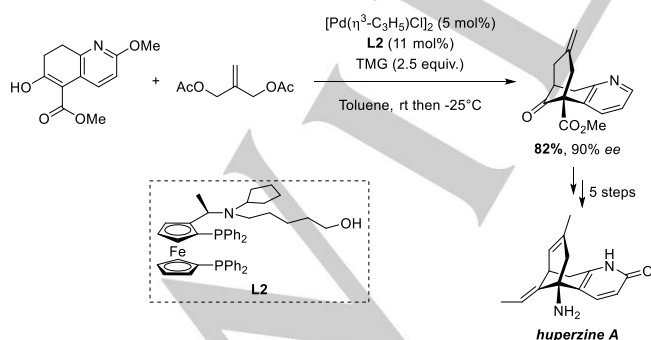
Recently, Liu, Zhang *et al.* reported an enantioselective approach to tetracyclic scaffolds via annulation between

1 sulfonylimine-derived bis-nucleophiles and cyclic allylic bis-  
2 electrophiles.<sup>[29]</sup> Excellent enantioselectivities (*ee* 90-99.8%) of  
3 the targeted tetracyclic sulfonamides were obtained using the  
4 catalytic system [allylpalladium(II) chloride dimer / *t*-Bu-  
5 RuPHOX] and when the active methylene is stabilized by an aryl  
6 ( $R^2$ ) group (Scheme 11). Lower enantioselectivities (68%) were  
7 obtained when the bis-electrophile is a cyclopentene derivative.  
8 Lower yields (45%) were also obtained when the bis-electrophile  
9 is a cycloheptene derivative.



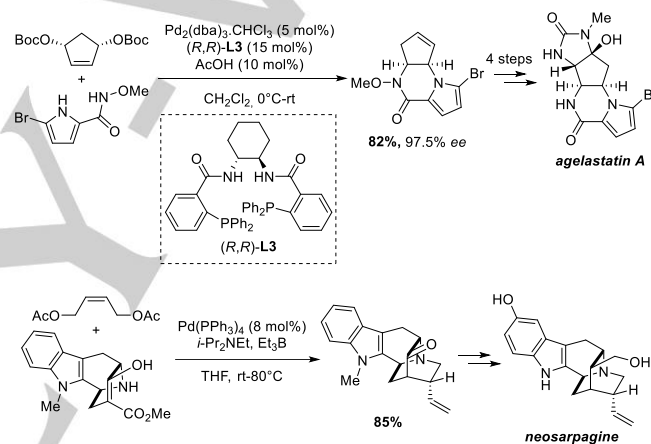
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24 **Scheme 11.** Enantioselective route to tetracyclic sulfonamides by Pd-  
25 catalyzed annulation of sulfonimines with cyclic allylic bis-electrophiles.

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28 The key step in the enantioselective total synthesis of  
29 huperzine A reported by the group of Bai is a Pd-catalyzed  
30 annulation of an allylic bis-electrophile.<sup>[30]</sup> Although the Trost  
31 DACH ligands were reported to give excellent  
32 enantioselectivities in the Pd-catalyzed allylation of  $\alpha$ -alkyl  $\beta$ -  
33 ketoesters<sup>[31]</sup> and other annulation reactions,<sup>[32]</sup> in this specific  
34 case good enantioselectivities were obtained only with the  
35 ferrocenylphosphines ligands developed by Hayashi.<sup>[33]</sup>  
36 Specifically, the catalytic system [(allyl)Pd(II)Cl]<sub>2</sub> / ligand **L2**  
37 gave the best results in terms of yield and enantioselectivity for  
38 the synthesis of the bridged  $\beta$ -ketoester precursor, which is an  
39 advanced precursor of the target molecule (Scheme 12).



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52 **Scheme 12.** Enantioselective preparation of bridged  $\beta$ -ketoesters via a Pd-  
53 catalyzed annulation towards in route to the total synthesis of huperzine A.  
54 TMG = tetramethylguanidine.

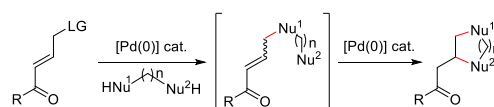
The preparation of even more complex structures was  
additionally illustrated by the group of Trost, who showed the  
power of this method in the total synthesis of agelastatin A.<sup>[34]</sup>  
The Pd-catalyzed annulation between the Weinreb amide of a 2-  
carboxypyrrole and the diBoc derivative of *cis*-cyclopent-4-ene-  
1,3-diol in the presence of the DACH chiral ligand (*R,R*)-**L3** gave  
the desired tricyclic bromopyrrole in 82% yield and 97.5% *ee*  
(Scheme 13, top). Interestingly, the reaction tolerates the  
presence of a bromine atom on the pyrrole ring without  
competing oxidative addition to the *in situ* formed Pd(0) species.  
Another example of molecular complexity straightforwardly  
obtained through a Pd-catalyzed annulation has been reported  
by the group of Cook while developing a cascade sequence  
toward the core structure of neosarpagine.<sup>[35]</sup> In this case, the  
bridged polycyclic indole derivative is the result of an annulation  
between a cyclic  $\beta$ -keto  $\gamma$ -amino ester bis-nucleophile and DAB  
bis-electrophile (Scheme 13, bottom).



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58 **Scheme 13.** Generation of complex molecular scaffolds in route to the  
59 synthesis of the natural products agelastatin A and neosarpagine.

### 60 Michael acceptor bearing an allylic leaving group as bis-electrophile.

A bis-electrophilic substrate can also be constituted by an  
electron-poor alkene bearing an allylic leaving group. In this  
case, an appropriate bis-nucleophile can undergo a first Pd-  
catalyzed allylation followed by a Michael-type addition (Scheme  
14).

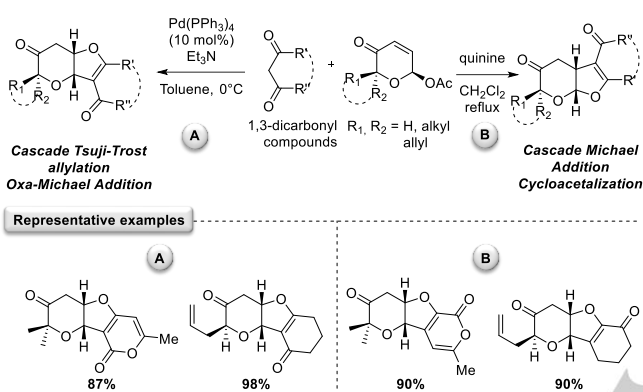


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64 **Scheme 14.** Generic annulation between a bis-nucleophile and a Michael  
65 acceptor carrying an allylic leaving group.

Despite the number of palladium-catalyzed annulations  
reported, Pd-catalyzed allylation / Michael sequences are still

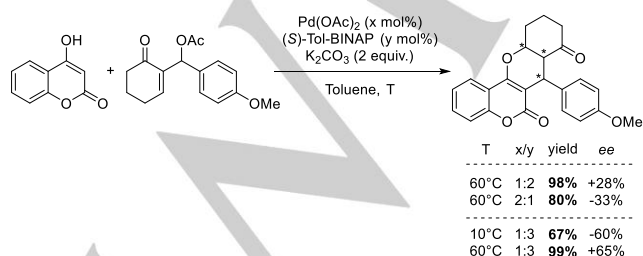
1 rare. Here below are shown recent examples describing the  
2 preparation of fuopyranones, tetracyclic coumarins, polycyclic  
3 lactams, dihydrofurans and bicyclononanes.

4 In 2016, Tong reported the synthesis of fuopyranones  
5 through Pd-catalyzed oxa-[3+2]-annulation between acetoxy-2-  
6 pyranones and 1,3-dicarbonyl compounds. The annulation  
7 involves a palladium-catalyzed allylation followed by an  
8 intramolecular oxa-Michael reaction (Scheme 15, left).<sup>[36]</sup> The  
9 authors also found that the use of quinine as catalyst instead of  
10 the palladium system affords regioisomeric fuopyranones,  
11 deriving from an intermolecular Michael addition followed by  
12  $S_N2$ -type cycloacetalization (Scheme 15, right).



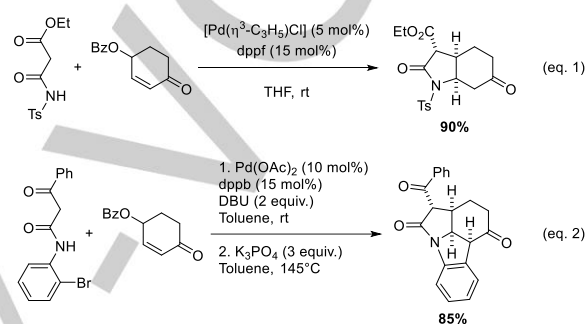
**Scheme 15.** [3+2]-C-C/O-C bond-forming annulation for synthesis of fuopyranones derivatives.

34 4-Hydroxycoumarins have also been recently used as bis-  
35 nucleophiles in Pd-catalyzed domino allylation / oxa-Michael  
36 addition. In particular, the group of Chen and Yang discovered  
37 that the enantioselectivity of the reaction was dependent on the  
38 reaction temperature<sup>[37]</sup> as well as on the Pd/chiral ligand  
39 ratio.<sup>[38]</sup> Thus, when working at 60°C and with a Pd/ligand  
40 ratio of 1:2, the corresponding (+)-tetracyclic coumarin derivative  
41 was obtained in 28% ee, whereas using a reversed 2:1 Pd/ligand  
42 ratio, the (-)-enantiomer was isolated in 33% ee. Furthermore,  
43 using a Pd/ligand ratio of 1:3, and performing the reaction at  
44 60°C affords the (+)-tetracyclic coumarin in 65% ee, while  
45 performing the reaction at 10°C, gives the reversed enantiomer  
46 in 60% ee (Scheme 16).



**Scheme 16.** Pd/ligand ratio-dependent and temperature-dependent enantioselectivity reversal in Pd-catalyzed domino allylation / oxa-Michael reaction.

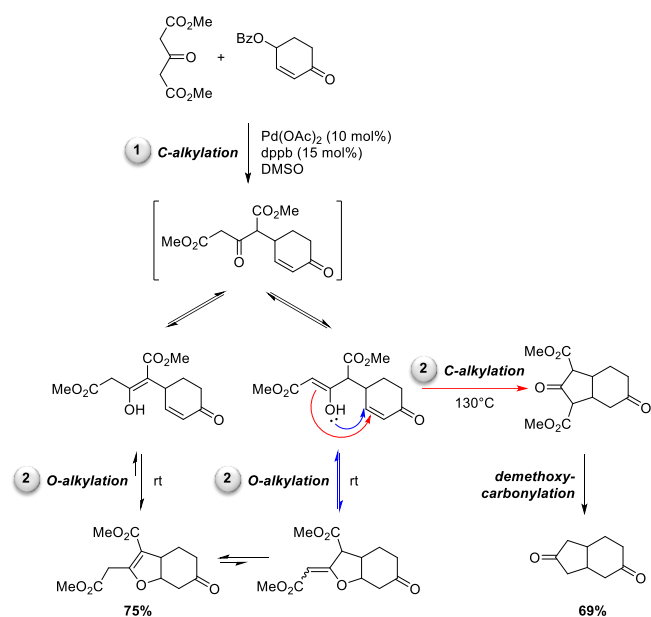
10 In the frame of our studies on  $\eta^3$ -allylpalladium chemistry  
11 applied to domino transformations,<sup>[27]</sup> our group developed an  
12 approach to bicyclic and tetracyclic lactams where we were able  
13 to control the chronology of the C-C and C-N bond-forming  
14 steps in a domino allylic alkylation / aza-Michael sequence.<sup>[39]</sup>  
15 Starting from ethoxycarbonyl N-tosyl acetamide as bis-  
16 nucleophile and  $\gamma$ -benzyloxycyclohexenone as bis-electrophile,  
17 the bicyclic lactam could be regio- and stereoselectively  
18 obtained in 90% yield using the catalytic system [[allylPd(II)Cl]<sub>2</sub>  
19 (5 mol%) / dppf (15 mol%)] at room temperature (Scheme 17, eq.  
20 1). The introduction of 2 equiv. of DBU was necessary with N-  
21 aryl, N-alkyl and N-Boc bis-nucleophiles.



**Scheme 17.** Preparation of polycyclic lactams via a) Top: Pd-catalyzed allylation / Michael addition domino sequence; b) Bottom: Pd-catalyzed allylation / Michael addition / Pd-catalyzed ketone arylation (ALAMAR) domino sequence. dppf = diphenylphosphinoferrocene; dppb = diphenylphosphinobutane; DBU = 1,8-Diazabicyclo[5.4.0]undec-7-ene.

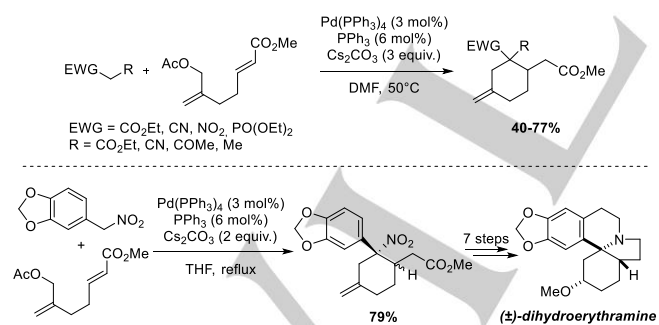
Building of more structurally complex lactams was also  
possible using bis-nucleophiles bearing *o*-haloaryl or *o*-  
halobenzyl moieties on the N-amide function through an  
allylation / aza-Michael / arylation] (ALAMAR) domino sequence.  
For instance, the tetracyclic lactam could be isolated in 85%  
yield from an N-*o*-bromophenyl substituted  $\beta$ -ketoamide  
(Scheme 17, eq. 2).

Our group also reported the Pd-catalyzed annulative domino  
processes between dimethyl-3-oxoglutarate as bis-nucleophile  
and cyclic  $\gamma$ -oxy- $\alpha,\beta$ -unsaturated ketones as bis-electrophiles.<sup>[40]</sup>  
In particular, we discovered that either dihydrofuran or  
bicyclo[4.3.0]nonane derivatives could be obtained at will using  
the same catalytic system, just by playing with the reaction  
temperature. The generation of these two different products has  
been rationalized on the basis of a reversible intramolecular O-  
1,4-addition of the allylation product at rt versus an irreversible C-  
1,4-addition / demethoxycarbonylation at high temperature  
(Scheme 18).



**Scheme 18.** Mechanistic rationale for the annulation with dimethyl-3-oxoglutarate as the bis-nucleophile.

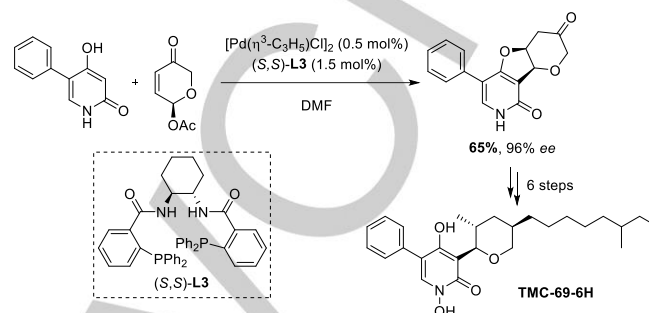
The power of the above method has been cleverly exploited in the synthesis of complex natural products, which allowed to put into practice straightforward synthetic strategies.<sup>[41]</sup> In 1998 and 2003, the Desmaële group reported a palladium-catalyzed allylation followed by spontaneous intramolecular Michael addition.<sup>[42]</sup> Thus, a variety of combinations between active methylene compounds and methyl 6-acetoxymethyl-hepta-2,6-dienoate were investigated, which provided a new access to methylene cyclohexane derivatives. The authors applied this strategy to the synthesis of erythramine, an alkaloid of the family of erythrines (Scheme 19).<sup>[43]</sup>



**Scheme 19.** Pd-catalyzed annulation of methyl 6-acetoxymethyl-hepta-2,6-dienoate with active methylene compounds – towards the total synthesis of (±)-dihydroerythramine.

In 2004, the group of Fürstner achieved the total synthesis of the antitumor agent TMC-69-6H.<sup>[44]</sup> The key step of this synthesis was a Pd-catalyzed [3+2]-C-C/O-C bond-forming

annulation between 4-hydroxy-2-pyridone and a pyranil acetate, which involved a palladium-catalyzed C-allylation followed by a spontaneous oxa-Michael reaction. In the presence of the chiral ligand (S,S)-L3 and [allylPd(II)Cl]<sub>2</sub> the key tricyclic pyridone was obtained in 65% yield and an excellent enantioselectivity (Scheme 20).

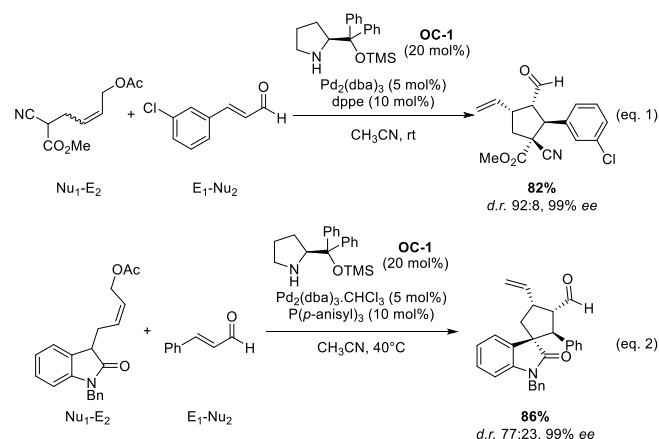


**Scheme 20.** Pd-catalyzed [3+2]-C-C/O-C bond-forming annulation for synthesis of TMC-69-6H.

## 2. Heterodipole / heterodipolarophile [⊖—⊕/δ⊖—δ⊕] interactions.

### Organocatalyst to generate a dipolarophile.

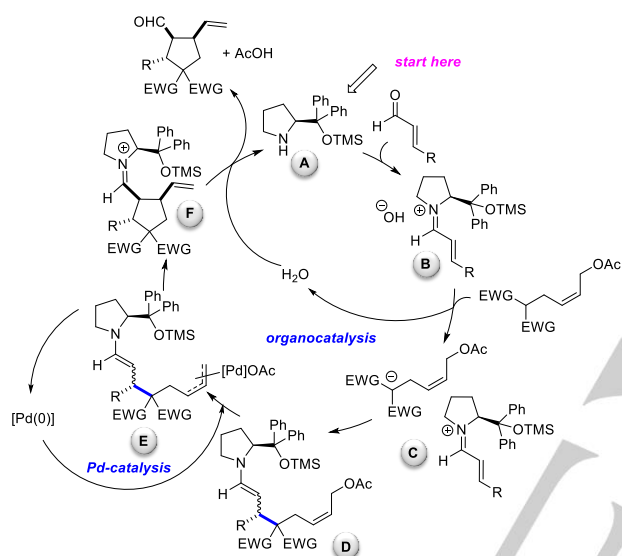
The group of Córdova recently reported a couple of highly enantioselective annulative domino allylation / Michael sequences based on the combined use of palladium- and organo-catalysis – like prolinol derivative **OC-1**. The former example deals with the synthesis of vinylcyclopentane structures (Scheme 21, eq. 1)<sup>[45]</sup> while the latter generates vinylcyclopentane-containing spirocyclic oxindoles<sup>[46]</sup> (Scheme 21, eq. 2).



**Scheme 21.** Synergistic catalysis as a strategy for the highly enantioselective preparation of vinylcyclopentanes as reported by Córdova *et al.*



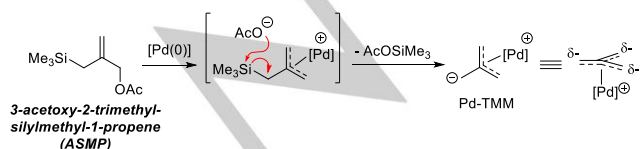
The mechanism of these transformations is expected to be as follows (Scheme 22). Condensation between the Hayashi-Jørgensen's<sup>471</sup> prolinol derivative **A** and the  $\alpha,\beta$ -unsaturated aldehyde generates the iminium ion **B**, whose hydroxide counterion can deprotonate the activated methylene to generate the corresponding enolate **C**. Conjugate addition of this latter to the  $\alpha,\beta$ -unsaturated iminium ion generates the new enamine intermediate **D**. Ionization of the allylic acetate moiety of **E** by the Pd(0) complex generates the corresponding enamine  $\pi$ -allylpalladium complex **E**, which undergoes an intramolecular allylation to provide iminium ion **F**. Hydrolysis of this latter regenerates the organocatalyst **A** and provides the desired cyclopentane derivative.



**Scheme 22.** Mechanism proposal showing the synergy between organocatalysis and palladium catalysis.

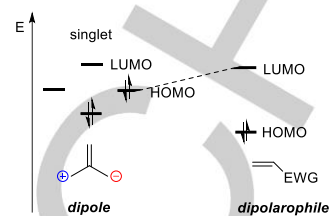
### 3-Acetoxy-2-trimethylsilylmethyl-1-propene as heterodipole.

Pd-catalyzed [3+2]-annulation reactions from 3-acetoxy-2-trimethylsilylmethyl-1-propene (ASMP) are one of the most effective methods for the synthesis of five-membered carbocycles and heterocycles. Indeed, the interaction between 3-acetoxy-2-trimethylsilylmethyl-1-propene and a Pd(0) complex generates a zwitterionic complex (Pd-TMM) (Scheme 23).<sup>[48]</sup> The positive charge is stabilized by palladium, which prevents ring closing to methyldiene cyclopropane and Pd(0).



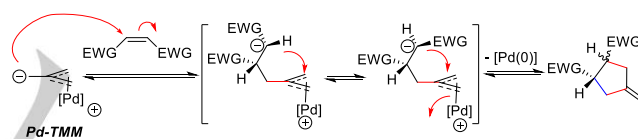
**Scheme 23.** Generation of TMM-Pd.

Furthermore, this stable 1,3-dipole favors the singlet state, which has a nucleophilic nature and reacts with a number of electrophilic dipolarophiles to provide five-membered ring systems (Figure 1).



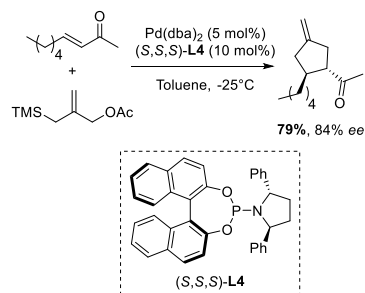
**Figure 1.** Qualitative molecular orbital interaction diagram between the  $\pi$ -system of Pd-TMM and that of a generic electrophilic dipolarophile.

Pd-TMM, generated *in situ* from ASMP, gives  $[3_{2\sigma}+2_{2\pi}]$  cycloadditions with a number of electron-deficient olefins. For example, the reaction with dimethyl fumarate led to exclusively the *trans* cycloadduct, whereas the reaction with dimethyl maleate produced *cis/trans* mixtures of methylene cyclopentanes. This lack of stereospecificity suggests a stepwise, non-concerted mechanism (Scheme 24). The Pd-TMM species is a 1,3-dipole, prone to undergo [3+2]-cycloadditions with a number of dipolarophiles,<sup>[49]</sup> as exemplified through the total synthesis of several natural and pharmaceutical products within the last two decades.<sup>[50]</sup>



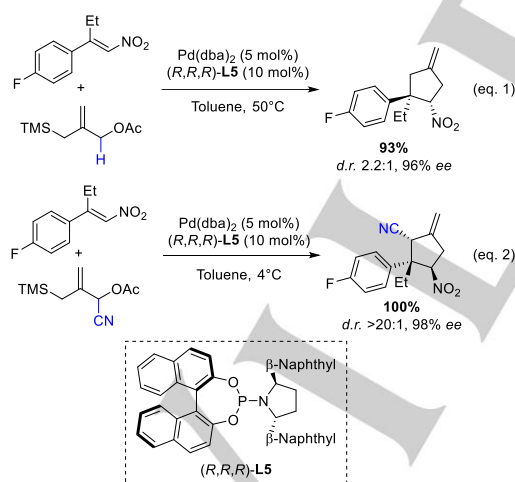
**Scheme 24.** Stepwise non-stereospecific mechanism in the cycloaddition of Pd-TMM.

The pioneering studies on enantioselective [3+2]-cycloadditions<sup>[51]</sup> involving Pd-TMM 1,3-dipoles were based on covalently linked chiral auxiliaries.<sup>[52]</sup> At that time, the design of chiral ligands was considered impractical, as the enantiodetermining step of the reaction was assumed to be the allylic substitution on the ionized Pd-TMM intermediate. However, using chiral phosphoramidite ligands<sup>[53]</sup>, Trost managed to obtain good yields (63-84%) and enantioselections (58-84% ee)<sup>[54]</sup> in the cycloaddition between Pd-TMM and  $\alpha,\beta$ -unsaturated carbonyl derivatives (ketones, esters, nitriles) to afford exo-methylene cyclopentanes (Scheme 25).



**Scheme 25.** Enantioselective catalysis in [3+2]-cycloadditions of Pd-TMM complexes in the presence of chiral phosphoramidites.

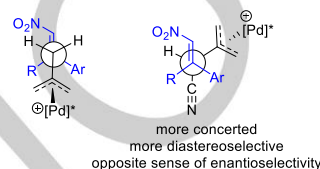
Electron-poor alkenes such as trifluoromethylalkenes<sup>[55]</sup> and nitroalkenes<sup>[56]</sup> have been used as substrates in diastereo- and enantioselective Pd-catalyzed [3+2]-cycloadditions. In all cases, excellent diastereomeric ratios and enantiomeric excesses were obtained in the presence of defined chiral palladium catalysts. Within the study on the use of disubstituted nitroalkenes as the dipolarophile,<sup>[56b]</sup> the authors investigated the influence of the substitution of the Pd-TMM precursor on the stereochemistry of the final product. From ASMP, a methylenecyclopropane bearing a 4-fluorophenyl substituent has been prepared with 93% yield, a diastereomeric ratio of 2.2:1 and a 96% ee of the major diastereoisomer (Scheme 26, eq. 1). If the 1,3-dipole precursor is substituted with a nitrile function, the stereochemistry of the product is completely reversed, as can be seen in the corresponding cycloaddition adduct obtained in a quantitative yield, in a fully diastereoselective fashion (*d.r.* >20:1) and with 98% ee (Scheme 26, eq. 2).



**Scheme 26.** Influence of the substitution of the Pd-TMM precursor on the stereochemistry of the [3+2]-cycloaddition product.

The remarkable different diastereoselectivity of these two reactions has been rationalized assuming that in the case of simple ASMP the favored stereodetermining approach between the reaction partners features an antiperiplanar disposition

between the cationic Pd-TMM moiety and the C(sp<sup>2</sup>) atom bearing the charged nitro function of the nitroalkene (Scheme 27). Conversely, in the case of the more stabilized nitrile-substituted ASMP (ASMP-CN), the favored stereodetermining approach features an antiperiplanar disposition between the nitrile function of ASMP-CN and the C(sp<sup>2</sup>) bearing the nitro function. Such a different disposition implies a more concerted, yet asynchronous, mechanism with respect to the previous case that can lead to increased diastereoselectivity.

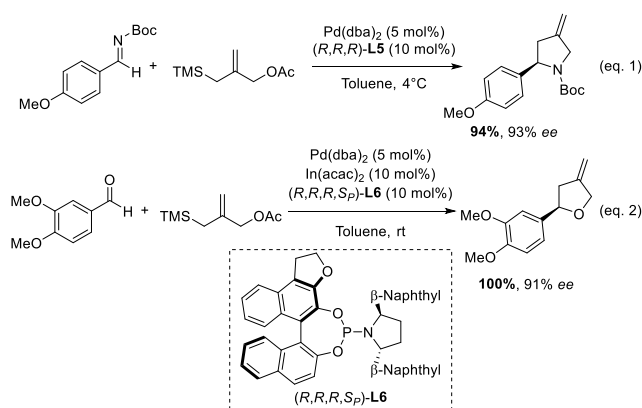


**Scheme 27.** Model accounting for the different level of diastereoselectivity between ASMP and ASMP-CN in cycloaddition with nitroalkenes.

The same group extended the scope of the dipolarophiles to imines<sup>[57]</sup> and aldehydes<sup>[58]</sup> for the preparation of pyrrolidine and tetrahydrofuran derivatives, respectively.<sup>[59]</sup> In the presence of 5 mol% of Pd(*dba*)<sub>2</sub> and 10 mol% of ligand (*R,R,R*)-L5, pyrrolidines were isolated in good to excellent yields (60-96%) and excellent enantioselectivities (85-93%) (Scheme 28, eq. 1).

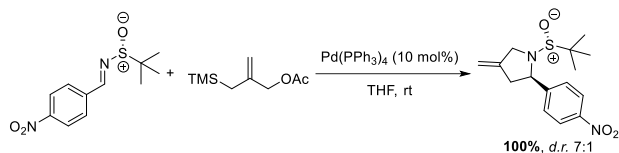
Furthermore, a careful design of phosphoramidites from *o*-substituted BINOL derivatives, allowed them to obtain tetrahydrofuran scaffolds in good to excellent yields (62-100%) and with good to excellent enantioselectivities (Scheme 28, eq. 2). In this case, the introduction of a Lewis acid, to activate the aldehyde, was necessary.<sup>[60]</sup>

Ligand (*R,R,R,S<sub>p</sub>*)-L6 turned out to be successful in the enantioselective cycloaddition of the more challenging ketones, too.<sup>[61]</sup> The concerns associated to this functional group are due to: i) its problematic face discrimination; ii) its limited electrophilicity, iii) the presence of alkyl substituents. Worthy of note, the enantioselectivity turned out to be mainly controlled by the stereochemistry of the phosphorous atom.



**Scheme 28.** Examples for the synthesis of pyrrolidines and tetrahydrofurans by a Pd-catalyzed [3+2]-cycloaddition from ASMP and imines or aldehydes.

Otherwise, the group of Stockman recently reported a diastereoselective Pd-catalyzed [3+2]-cycloadditions between enantiopure *tert*-butane sulfinimines and ASMP leading to pyrrolidines with good diastereoisomeric ratios<sup>[62]</sup> (Scheme 29).

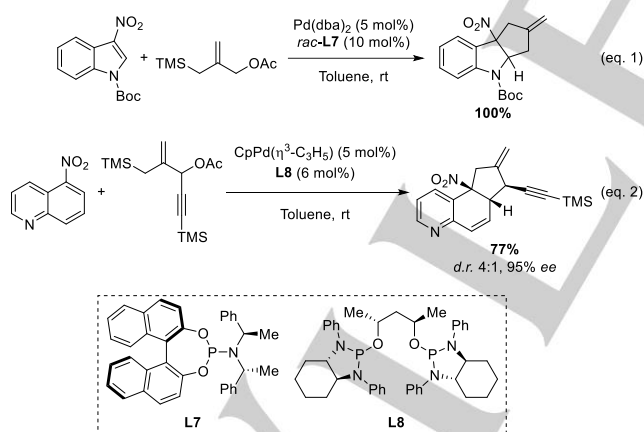


**Scheme 29.** Example of the diastereoselective preparation of pyrrolidines starting from *tert*-butanesulfinimines.

Besides investigations on the use of other dipolarophiles such as isocyanates<sup>[63]</sup> or carbon dioxide,<sup>[64]</sup> new reactivities with regard to Pd-catalyzed [3+2]-cycloaddition reactions have been recently highlighted.

For instance, the group of Trost found that nitroarenes could be used as dipolarophiles in dearomative Pd-catalyzed [3+2]-cycloaddition procedures.<sup>[65]</sup> They showed that the reaction was efficient with nitroquinolines, nitroindoles, nitro-*N*-tosylpyrroles and electron-poor arenes such as nitrobenzenes and benzonitriles. For instance, Boc-protected tricyclic indoline could be isolated in a quantitative yield (Scheme 30, eq. 1).

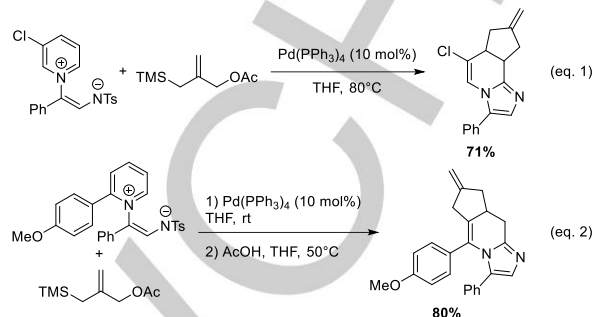
An enantioselective variant could be also developed starting from alkyne-substituted ASMP in the presence of the chiral enantiopure bidentate ligand **L8**, giving the desired tricyclic pyridine derivative in 77% yield and 95% ee for the major diastereoisomer (Scheme 30, eq. 2).



**Scheme 30.** Dearomative Pd-catalyzed [3+2]-cycloaddition of nitroarenes.

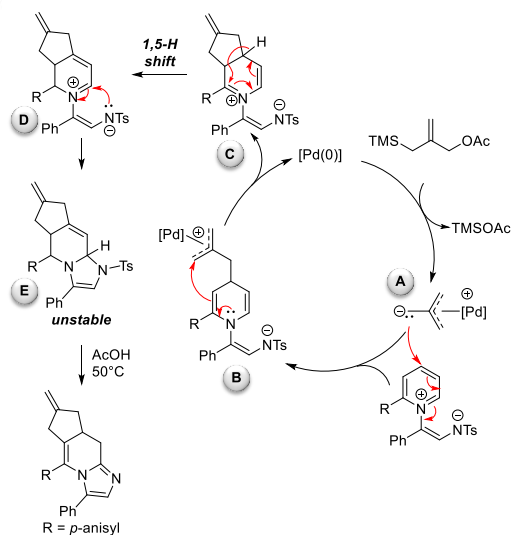
More recently, the group of Baik and Yoo reported a cascade reaction to access cyclopentane-fused heterocycles via a [3+2]-cycloaddition reaction between Pd-TMM and a zwitterionic pyridinium substrate.<sup>[66]</sup> With this cascade approach, imidazodihydro-[2H]-pyridines were isolated in moderate to excellent yields (58-99%) when using *meta*-chloro-substituted

pyridinium moieties (Scheme 31, eq. 1). Likewise, regioisomeric imidazodihydro-[2H]-pyridines were obtained in moderate to good yields (41-85%) after AcOH addition, to bring about a stabilizing double bond shift (Scheme 31, eq. 2).



**Scheme 31.** Regioselective cascade reactions involving a Pd-catalyzed [3+2]-cycloaddition followed eventually by an intramolecular cyclization.

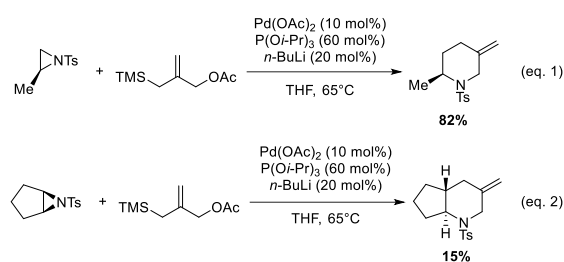
The authors proposed a mechanism (Scheme 32) explaining the formation of the imidazodihydro-[2H]-pyridine shown in equation 2 of Scheme 31. After generation of the Pd-TMM 1,3-dipole **A**, the carbanion attacks the C4-position of the pyridinium ring forming η<sup>3</sup>-allyl palladium species **B**. Following cyclization generates the dihydropyridinium intermediate **C**. After 1,5-H shift, the resulting pyridinium zwitterion **D** undergoes intramolecular addition by the tosylamide anion to give the tricyclic adduct **E**. Addition of AcOH brings about double bond isomerization the more stable imidazodihydro-[2H]-pyridine.



**Scheme 32.** Proposed mechanism for the generation of imidazodihydro-[2H]-pyridines.

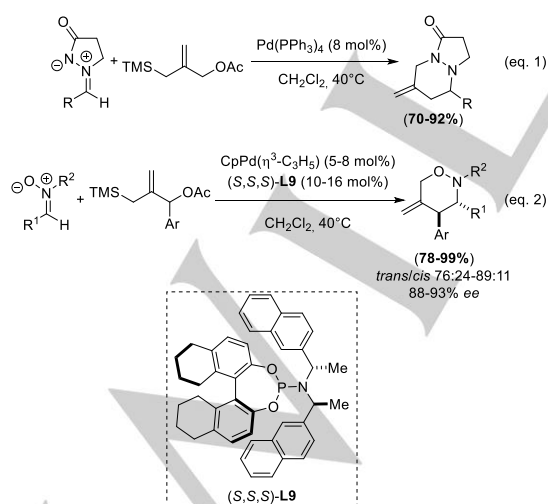
The interaction between Pd-TMM and some 1,3-dipoles, normally used in [3+2]-cycloadditions with classical

dipolarophiles, gives rise to [3+3]-cycloadditions. In the early 2000s, the group of Harrity reported the synthesis of piperidines through a [3+3]-cycloaddition reaction between Pd-TMM and aziridines.<sup>[67]</sup> The reaction proved to be efficient when starting from mono- as well as 1,1-disubstituted-N-tosylaziridines (Scheme 33, eq. 1), but not from fused bicyclic aziridines (Scheme 33, eq. 2). The same group applied this chemistry to the total synthesis of *Nuphar* alkaloids<sup>[68]</sup> as well as the alkaloid (-)-217 A.<sup>[69]</sup>



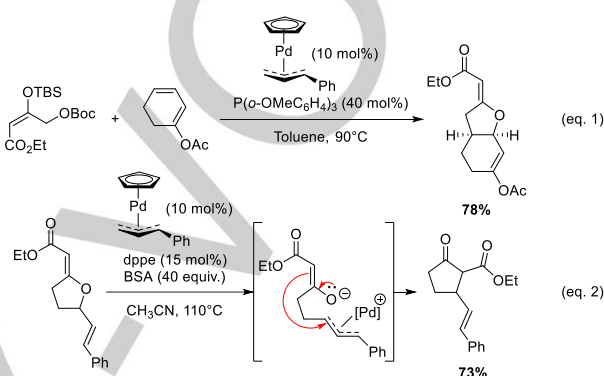
**Scheme 33.** Examples of Pd-catalyzed [3+3]-cycloaddition from ASMP and aziridines.

In 2006, the group of Hayashi<sup>[70]</sup> reported the synthesis of hexahydropyridazines through a [3+3]-cycloaddition between TMM-Pd and 1-alkylidene-3-oxo-pyrazolidin-1-ium-2-ides,<sup>[71]</sup> which are stable azomethine imines.<sup>[72]</sup> Except when the azomethine imines are substituted with a *tert*-butyl group, the desired hexahydropyridazines were isolated in very good yields (70-92%) (Scheme 34, eq. 1). The same group reported an enantioselective [3+3]-cycloaddition between nitrones and aryl-substituted substituted ASMP.<sup>[73]</sup> Using ligand (*S,S,S*)-**L9** (Scheme 34, eq. 2), exomethylene-1,2-oxazines were obtained in excellent yields (78-99%), good *trans/cis* ratio (76:24 to 89:11) and excellent enantioselectivities (89-93% *ee*).



**Scheme 34.** [3+3]-cycloaddition reactions from azomethine imines and nitrones.

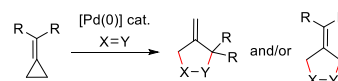
Very recently, the group of Trost extended the use of zwitterionic dipoles to oxyallylpalladium cations generated from silyloxyallylcarbonates.<sup>[74]</sup> By mixing these highly reactive species with linear or cyclic dienes, various tetrahydrofuran derivatives could be efficiently prepared via a [3+2]-cycloaddition procedure (Scheme 35, eq. 1). Under close reaction conditions, they also reported that cyclopentanones could be prepared from the former tetrahydrofurans by a palladium-catalyzed isomerization involving the formation of a new dipole by ring opening (Scheme 35, eq. 2).



**Scheme 35.** Examples of Pd-catalyzed [3+2]-cycloaddition through oxyallyl cations.

#### Alkylidene or vinyl cyclopropanes as heterodipoles.

Under Pd(0)-catalysis, it is also possible to obtain cycloaddition adducts from the interaction between alkylidene cyclopropanes (ACPs), or methylene cyclopropanes (MCPs) when R = H), and alkenes or carbonyl derivatives (X=Y) (Scheme 36).

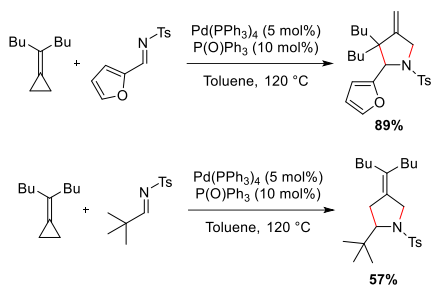


**Scheme 36.** Pd-catalyzed cycloaddition between alkylidene cyclopropanes and alkenes or carbonyl derivatives.

This chemistry was pioneered by Binger and co-workers,<sup>[75]</sup> who studied  $\alpha,\beta$ -unsaturated esters as dipolarophiles. Yamamoto, later reported analogous Pd-catalyzed [3+2]-cycloadditions between methylene cyclopropanes and aldehydes or *N*-tosylimines (Scheme 37, top).<sup>[76]</sup>

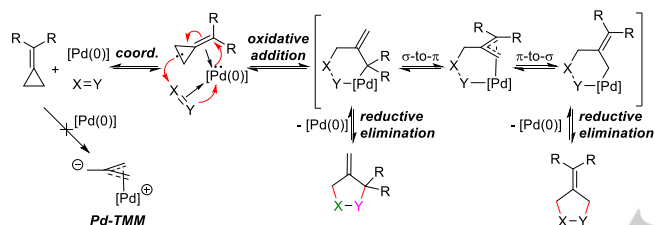
Although at a first glance it is tempting to think at a mechanism involving the previously described zwitterionic Pd-TMM complexes, these two approaches are distinct. Indeed, for example, alkylidene cyclopropanes substituted at the *exo* alkene led to different regioisomers depending on the dipolarophile (Scheme 37, bottom).<sup>[76b,77]</sup>





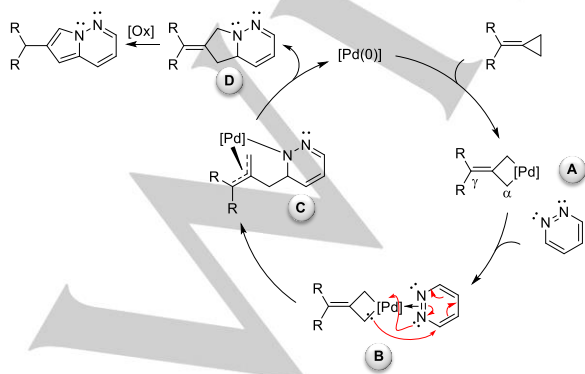
**Scheme 37.** Pd-catalyzed [3+2]-cycloaddition of methylene cyclopropanes leading to different regioisomers.

These results suggest that the mechanism of this transformation involves a rapid  $\sigma$ - $\pi$ - $\sigma$  scrambling between the  $\sigma$ -allylpalladium complexes (Scheme 38).



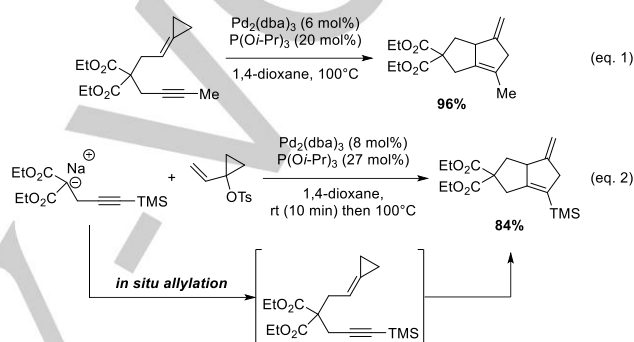
**Scheme 38.** The mechanism of the Pd-catalyzed cycloaddition between methylene cyclopropanes and alkenes.

Besides the work reported on the synthesis of tetrahydrofurans,<sup>[76a]</sup> pyrrolidines,<sup>[76b-c]</sup> and lactones<sup>[78]</sup>, 5-azaindoline derivatives have been made accessible by a Pd-catalyzed formal [3+2]-cycloaddition with ACPs in the presence of 5 mol% of palladium(0) tetrakis(triphenyl)phosphine.<sup>[79]</sup> The proposed mechanism<sup>[80]</sup> involves an initial oxidative addition of the distal C-C bond of the alkylidene cyclopropane to the Pd(0) catalyst to afford the palladocyclobutane **A** (Scheme 39). Subsequent interaction with pyridazine generates the  $\pi$ -allylpalladium intermediate **C**. A reductive elimination step then provides the bicyclic product **D**, which readily oxidizes to furnish the desired 5-azaindoline.



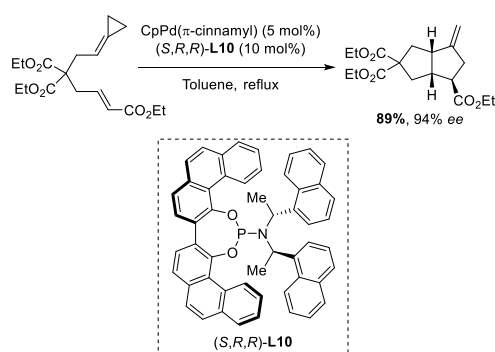
**Scheme 39.** Proposed mechanism for the generation of 5-azaindoline derivatives by Pd(0)-catalyzed formal [3+2]-cycloaddition of ACPs.

The group of Mascareñas reported the cycloaddition between ACPs and alkynes.<sup>[81]</sup> In the presence of Pd<sub>2</sub>(dba)<sub>3</sub> and tri-*iso*-propylphosphite as the ligand, bicyclo[3.3.0]octenes were obtained with good to excellent yields (65-96%) within a short reaction time (Scheme 40, eq. 1). As alkylidene cyclopropanes can be prepared from cyclopropyl vinyl tosylate and functionalized malonates via Pd(0)-catalysis,<sup>[82]</sup> the authors showed that the domino allylation / [3+2]-cycloaddition could be performed efficiently (Scheme 40, eq. 2).



**Scheme 40.** Examples of Pd-catalyzed intramolecular [3+2]-cycloaddition of ACPs with alkynes.

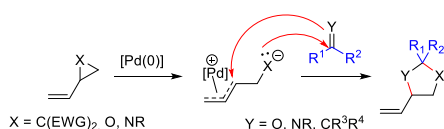
An enantioselective version of the above [3+2]-cycloaddition has been later reported by the same group starting from unsaturated ACPs.<sup>[83]</sup> The best results were obtained by using the bulky phosphoramidite ligand (*S,R,R*)-**L10** (Scheme 41). When the dipolarophile bears a conjugated diene instead of an electron-poor alkene, the [4+3]-cycloaddition is the favored over the [3+2].



**Scheme 41.** Enantioselective generation of bicyclo[3.3.0]octanes via Pd(0)-catalyzed [3+2]-cycloaddition with an alkylidene cyclopropane.

**Vinyl-aziridines, -oxiranes and -cyclopropanes as heterodipoles.**

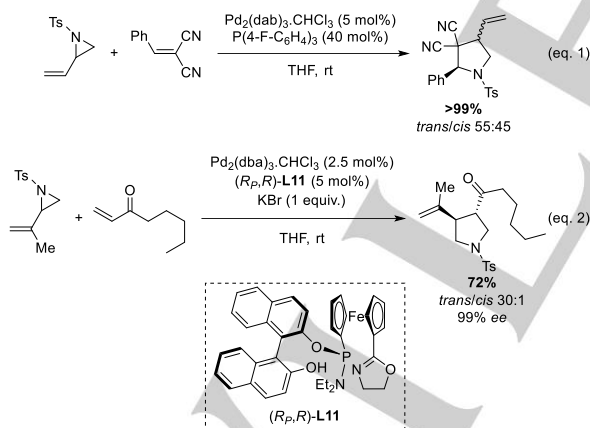
The Pd-catalyzed [3+2]-annulation of 1,3-dipolar species generated from vinyl aziridines, vinyl oxiranes and vinyl cyclopropanes (VCPs) and dipolarophiles has become a highly efficient strategy for the synthesis of five membered ring compounds. With these coupling partners, the  $n^3$ -allyldipoles are prepared by a Pd(0)-induced ring opening of the 3-membered cycle (Scheme 42). Other related examples involve vinylcarbonates<sup>[84]</sup> and vinylcarbamates.<sup>[85]</sup>



**Scheme 42.** General reactivity pattern of VCPs, vinyl epoxides and vinyl aziridines under Pd(0)-catalysis.

Since the seminal work of Tsuji<sup>[86]</sup> *et al.* on the [3+2]-cycloaddition process between VCPs and  $\alpha,\beta$ -unsaturated carbonyl derivatives and reports made after,<sup>[87]</sup> several groups transposed this strategy to vinyl epoxides and vinyl aziridines for the synthesis of tetrahydrofurans and pyrrolidines, respectively.

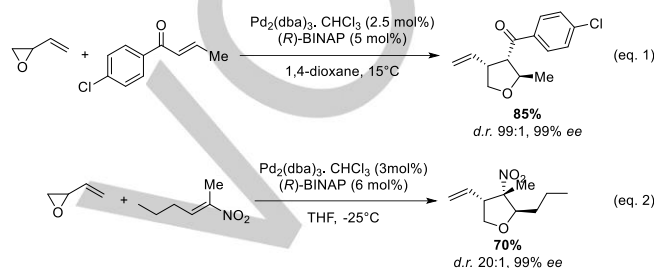
In 2002, the group of Yamamoto reported an original method to prepare pyrrolidines through a [3+2]-annulation between vinyl aziridines and electron-deficient alkenes (Scheme 43, eq. 1).<sup>[88]</sup> In this work, only alkenes bearing two electron-withdrawing groups were successful in the annulation. However, inspired by the work of Aggarwal *et al.* on the total synthesis of (-)- $\alpha$ -kainic acid,<sup>[89]</sup> Ding and Hou later found appropriate reaction conditions to react less electron-poor alkenes<sup>[90]</sup> (Scheme 43, eq. 2).



**Scheme 43.** Evolution of the alkene reactivity in Pd-catalyzed [3+2]-annulations with vinyl aziridines.

A year later, the same group expanded the scope of the transformation to  $\alpha,\beta$ -unsaturated ketones bearing one extra substituent on the alkene moiety.<sup>[91]</sup> In that case, vinyl epoxides were engaged as reaction partner leading to tetrahydrofurans in very good yields as well as excellent diastereo- and

enantioselectivities in the presence of (*R*)-BINAP (Scheme 44, eq. 1). They also reported the enantioselective preparation of tetrahydrofurans from vinyl epoxides and more substituted alkenes.<sup>[92]</sup> This was made possible thanks to the use of trisubstituted nitroalkenes instead of trisubstituted enones, acrylates or acrylonitriles. For example, a 3-nitro-4-vinyl tetrahydrofuran derivative could be isolated in 70% yield, and an excellent diastereoisomeric ratio of 20:1 and 99% ee for the major diastereoisomer in the presence of (*R*)-BINAP as the chiral ligand (Scheme 44, eq. 2).



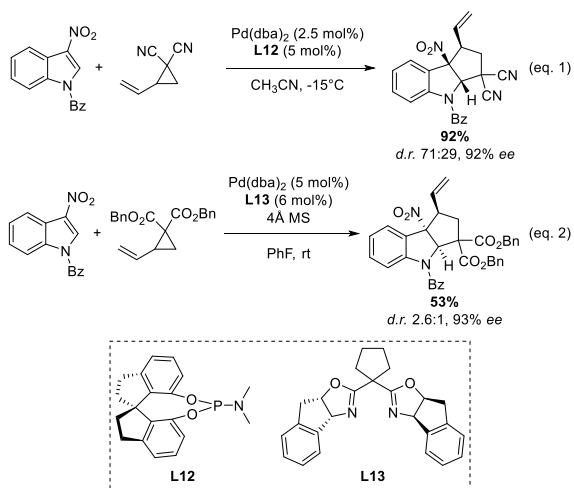
**Scheme 44.** Pd(0)-catalyzed [3+2]-cycloaddition reactions of more substituted and less reactive alkenes.

Inspired by the number of organocatalyzed reactions, including the ones reported by Córdova *et al.*<sup>[45,46]</sup> on the stereoselective preparation of enantiopure cyclopentanes from allyl monoacetate dipoles, the group of Ratovelomanana-Vidal, Michelet and Vitale<sup>[93]</sup> as well as the groups of Jørgensen<sup>[94]</sup> and Rios<sup>[95]</sup> independently reported an enantioselective Pd(0)-catalyzed [3+2]-cycloaddition between enals and VCPs under synergistic catalysis.

Starting from the bis-nitrile-substituted VCP, Ratovelomanana-Vidal, Michelet, Vitale *et al.* reported the use of *p*-nitrobenzoic acid as an additive, to avoid the polymerization of the VCP,<sup>[96]</sup> obtaining the vinyl cyclopentane labelled **a** as a major diastereoisomer in 83% yield and more than 99% ee under conditions A (Scheme 45, eq. 1). Using a similar catalytic system, but with benzoic acid instead of *p*-nitrobenzoic acid, the group of Jørgensen was able to obtain the vinylcyclopentane **a** as the major diastereoisomer with 90% yield and more than 99% ee under conditions B (Scheme 45, eq. 1).

Starting from a different VCP, Rios and Meazza managed to obtain the desired spiro-vinyl cyclopentane in 87% yield and an excellent 99% ee without using an acid additive (Scheme 45, eq. 2).

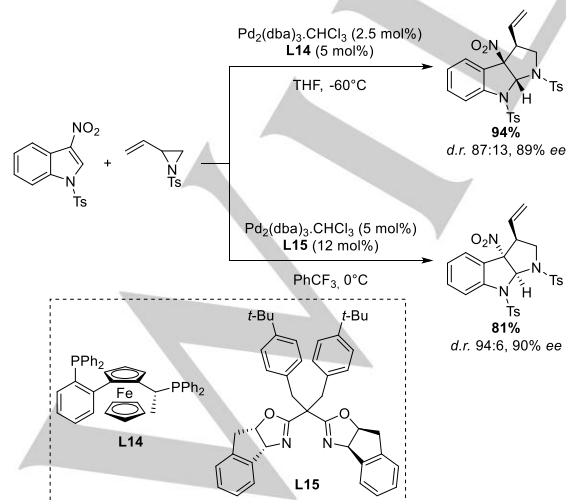




**Scheme 48.** Enantioselective Pd-catalyzed [3+2]-cycloaddition of VCPs with 3-nitroindole.

By replacing the VCP by a vinyl aziridine, the group of Ryan and Hyland managed to prepare pyrroloindolines,<sup>[100]</sup> whose skeletons are found in a large number of natural products such as psychotrimine or psychotriazine. The *cis* or *trans* diastereoisomers could be selectively prepared depending on the substitution of the aromatic ring of the 3-nitroindole. When the indole ring is substituted at C-4, then the *cis*-isomer is the major one. In all the other cases, the *trans* diastereoisomer is the favored one.

Enantioselective versions of the formation of pyrroloindolines have been also reported by the group of Ding and Hou<sup>[101]</sup> as well as the group of Wang.<sup>[99b]</sup> Depending on the ligand used, either the *cis* or the *trans* isomer could be obtained. The ferrocenyl ligand **L14** has been used by Ding, Hou *et al.* to generate a vinyl pyrroloindoline for example with 94% yield and 89% ee (Scheme 49, top). The *trans* diastereoisomer has been obtained thanks to the use of the indane-BOX ligand **L15** by the group of Wang in 81% yield and 90% ee (Scheme 49, bottom).



**Scheme 49.** Diastereo- and enantioselective synthesis of pyrroloindolines via Pd(0)-catalyzed [3+2]-cycloaddition of vinyl aziridines and 3-nitroindoles.

This type of chemistry can be expanded to other types of cycloadditions other than [3+2] such as [6+4]-cycloadditions<sup>[102]</sup> or [5+3] cycloadditions for instance.<sup>[103]</sup>

This non-exhaustive minireview intended to give recent developments in the use of  $\eta^3$ -allylpalladium chemistry for domino annulative reactions. The numerous examples in annulations and cycloadditions, the enantioselective variants developed as well as the various applications in total synthesis showed that this chemistry, pioneered in the 60's, is still a great inspiration for a huge number of groups. Certainly, this field of research will still continue in the upcoming decades to generate new developments.

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- [1] O. Diels, K. Alder, *Liebigs Ann. Chem.* **1928**, 460, 98-122.
- [2] W. S. Rapson, R. Robinson, *J. Chem. Soc.* **1935**, 1285-1288.
- [3] For a selection of ancient reviews, see: a) B. P. Mundy, *J. Chem. Ed.* **1973**, 50, 110-113; b) M. E. Jung, *Tetrahedron* **1976**, 32, 3-31; c) R. L. Danheiser, *J. Am. Chem. Soc.* **1982**, 104, 7670-7672; d) C. P. Curran, M.-H. Chen, E. Spletzer, C. M. Seong, C.-T. Chang, *J. Am. Chem. Soc.* **1989**, 111, 8872-8878; e) P. Muller, *Pure Appl. Chem.* **1994**, 66, 1107-1184. See also e) IUPAC. Compendium of Chemical Terminology, 2nd ed. (the "Gold Book"). DOI: <https://doi.org/10.1351/goldbook.A00367>.
- [4] For example, see: F. Gallier, A. Martel, G. Dujardin, *Angew. Chem. Int. Ed.* **2017**, 56, 12424-12458; *Angew. Chem.* **2017**, 129, 12598-12633.
- [5] For a selection of reviews, see: a) C. C. C. Johansson Seechurn, M. O. Kitching, T. J. Colacot, V. Snieckus, *Angew. Chem. Int. Ed.* **2012**, 51, 5062-5085; *Angew. Chem.* **2012**, 124, 5150-5174; b) A. F. P. Biajoli, C. S. Schwalm, J. Limberger, T. S. Claudino, A. L. Monteiro, *J. Braz. Chem. Soc.* **2014**, 25, 2186-2214; c) D. Roy, Y. Uozumi, *Adv. Synth. Catal.* **2018**, 360, 602-625.
- [6] For a selection of recent reviews, see: a) F. Roudesly, J. Oble, G. Poli, *J. Mol. Catal. A* **2017**, 426, 275-296; b) J. He, M. Wasa, K. S. L. Chan, Q. Shao, J.-Q. Yu, *Chem. Rev.* **2017**, 117, 8754-8786; c) R. R. Karimov, J. F. Hartwig, *Angew. Chem. Int. Ed.* **2018**, 57, 4234-4241; d) T. Gensch, M. J. James, T. Dalton, F. Glorius, *Angew. Chem. Int. Ed.* **2018**, 57, 2296-2306; *Angew. Chem.* **2018**, 130, 2318-2328; e) J. Le Bras, J. Muzart, *Eur. J. Org. Chem.* **2018**, 1176-1203.
- [7] For selected reviews, see: a) E. M. Beccali, G. Brogini, M. Martinelli, S. Sottocornola, *Chem. Rev.* **2007**, 107, 5318-5365; b) X.-F. Wu, H. Neumann, M. Beller, *Chem. Rev.* **2013**, 113, 1-35; c) K. C. Majumdar, S. Samanta, B. Sinha, *Synthesis* **2012**, 44, 817-847.

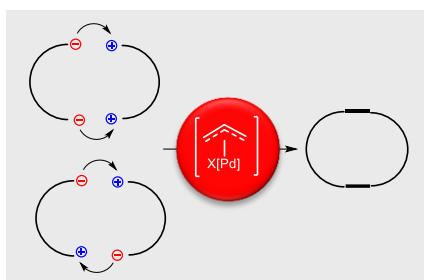


- [8] Reactions between bis-nucleophiles bearing an aryl- or a vinyl halide and dienes, cyclic alkenes, allenes or alkynes as bis-electrophiles will be excluded from this minireview as this topic has been already covered by two reviews: a) R. C. Larock, *J. Organomet. Chem.* **1999**, 576, 111-124. b) G. Zeni, R. C. Larock, *Chem. Rev.* **2006**, 106, 4644-4680.
- [9] For the pioneering works on the Pd-catalyzed allylation, see: a) J. Tsuji, H. Takahashi, M. Morikawa, *Tetrahedron Lett.* **1965**, 49, 4387-4388; b) B. M. Trost, T. J. Fullerton, *J. Am. Chem. Soc.* **1973**, 95, 292-294.
- [10] a) J. Tsuji, H. Takahashi, M. Morikawa, *Tetrahedron Lett.* **1965**, 6, 4387-4388. For reviews, see: b) G. Poli, G. Prestat, F. Liron, C. Kammerer-Pentier, U. Kazmaier, *Top. Organomet. Chem.* **2012**, 38, 1-63; c) B. M. Trost, *Acc. Chem. Res.* **1980**, 13, 385-393. d) B. M. Trost, M. L. Crawley, *Chem. Rev.* **2003**, 103, 2921-2944.
- [11] For an example, see: F. Buono, A. Tenaglia, *J. Org. Chem.* **2000**, 65, 3869-3874.
- [12] For recent examples on the synthesis of morpholines and piperazines, see: a) H. Nakano, J.-I. Yokoyama, R. Fujita, H. Hongo, *Tetrahedron Lett.* **2002**, 43, 7761-7764; b) K. Ito, Y. Imahayashi, T. Kuroda, S. Eno, B. Saito, T. Katsuki, *Tetrahedron Lett.* **2004**, 45, 7277-7281.
- [13] a) S. Tanimori, M. Kirihata, *Tetrahedron Lett.* **2000**, 41, 6785-6788; b) S. Tanimori, U. Inaba, Y. Kato, M. Kirihata, *Tetrahedron* **2003**, 59, 3745-3751.
- [14] T. Hayashi, A. Yamamoto, Y. Ito, *Tetrahedron Lett.* **1988**, 29, 669-672.
- [15] I. Shimizu, Y. Ohashi, J. Tsuji, *Tetrahedron Lett.* **1985**, 26, 3049-3052.
- [16] M. Yoshida, Y. Maeyama, K. Shishido, *Tetrahedron* **2012**, 68, 9962-9972.
- [17] Throughout this review, brackets around palladium atom in the notation of a generic (charged or neutral) metal complex intend to render implicit the formally dative ligands. An asterisk next to the brackets indicates the presence of a chiral (usually enantiopure) ligand.
- [18] Amatore, Jutand and Moreno-Mañas demonstrated that oxidative addition from allylic carbonates is a reversible process, thereby confirming that  $\eta^3$ -allyl palladium alkoxycarbonates do not undergo spontaneous decarboxylation. See: A. Amatore, S. Gamez, A. Jutand, G. Meyer, M. Moreno-Manas, L. Morral, R. Pleixats, *Chem. Eur. J.* **2000**, 6, 3372-3376.
- [19] H. Murakami, Y. Matsui, F. Ozawa, M. Yoshifuji, *J. Organomet. Chem.* **2006**, 691, 3151-3156.
- [20] a) T. Hayashi, A. Yamamoto, Y. Ito, *Tetrahedron Lett.* **1988**, 29, 669-672; b) T. Hayashi, A. Ohno, A.S.-J. Lu, Y. Matsumoto, E. Fukuyo, K. Yanagi, *J. Am. Chem. Soc.* **1994**, 116, 4221-4226; c) M. Sakamoto, I. Shimizu, A. Yamamoto, *Bull. Chem. Soc. Jpn.* **1996**, 69, 1065-1078; d) N. Nomura, K. Tsurugi, M. Okada, *Angew. Chem. Int. Ed.* **2001**, 40, 1932-1934; *Angew. Chem.* **2001**, 113, 1986-1989.
- [21] Enantiopure tetrahydroquinolines can also be prepared by cycloaddition between electron-poor alkenes and palladium-polarized aza-o-xyllylenes obtained by ring opening of vinylbenzoxazinones, see: C. Wang, J. A. Tunge, *J. Am. Chem. Soc.* **2008**, 130, 8118-8119.
- [22] M. Yoshida, Y. Maeyama, K. Shishido, *Tetrahedron Lett.* **2010**, 51, 6008-6010.
- [23] M. J. Bartlett, C. A. Turner, J. E. Harvey, *Org. Lett.* **2013**, 15, 2430-2433.
- [24] S. Tanimori, Y. Kato, M. Kirihata, *Synthesis* **2006**, 5, 865-869.
- [25] a) S. Lemaire, G. Giambastiani, G. Prestat, G. Poli, *Eur. J. Org. Chem.* **2004**, 2840-2847; b) C. Kammerer, G. Prestat, D. Madec, G. Poli, *Acc. Chem. Res.* **2014**, 47, 3439-3447.
- [26] The proposed mechanism slightly differs from that proposed by the authors of the quoted article.
- [27] Z. Mao, E. Martini, G. Prestat, J. Oble, P.-Q. Huang, G. Poli, *Tetrahedron Lett.* **2017**, 58, 4174-4178.
- [28] H. Yoshizaki, H. Satoh, Y. Sato, S. Nukui, M. Shibasaki, M. Mori, *J. Org. Chem.* **1995**, 60, 2016-2021.
- [29] Q. An, D. Liu, J. Shen, Y. Liu, W. Zhang, *Org. Lett.* **2017**, 19, 238-241.
- [30] X.-C. He, B. Wang, G. Yu, D. Bai, *Tetrahedron: Asymmetry* **2001**, 12, 3213-3216.
- [31] B. M. Trost, R. Radinov, E. M. Grenzer, *J. Am. Chem. Soc.* **1997**, 119, 7879-7880.
- [32] S. Kaneko, T. Yashino, T. Katoh, S. Terashima, *Tetrahedron* **1998**, 54, 5471-5484.
- [33] T. Hayashi, K. Kanehira, T. Hagihara, M. Kumada, *J. Org. Chem.* **1988**, 53, 113-120.
- [34] B. M. Trost, G. Dong, *Chem. Eur. J.* **2009**, 15, 6910-6919.
- [35] X. Liao, S. Huang, H. Zhou, D. Parrish, J. M. Cook, *Org. Lett.* **2007**, 9, 1469-1471.
- [36] J. Yu, H. Ma, H. Yao, H. Cheng, R. Tong, *Org. Chem. Front.* **2016**, 3, 714-719.
- [37] S. Wang, J. Xiao, J. Li, H. Xiang, C. Wang, X. Chen, R. G. Carter, H. Yang, *Chem. Commun.* **2017**, 53, 4441-4444.
- [38] J. Li, S.-S. Wang, P.-J. Xia, Q.-L. Zhao, J.-A. Xiao, H.-Y. Xiang, X.-Q. Chen, H. Yang, *Eur. J. Org. Chem.* **2017**, 6961-6965.
- [39] Y. Liu, Z. Mao, A. Pradal, P.-Q. Huang, J. Oble, G. Poli, *Org. Lett.* **2018**, 20, 4057-4061.
- [40] Y. Liu, J. Oble, G. Poli, *Beilstein J. Org. Chem.* **2019**, 15, 1107-1115.
- [41] For a review, see: B. M. Trost, M. L. Crawley, *Chem. Rev.* **2003**, 103, 2921-2943.
- [42] a) C. Jousse, D. Mainguy, D. Desmaële, *Tetrahedron Lett.* **1998**, 39, 1349-1352; b) C. Jousse-Karinthi, F. Zouhiri, J. Mahuteau, D. Desmaële, *Tetrahedron* **2003**, 59, 2093-2099.
- [43] C. Jousse-Karinthi, C. Riche, A. Chironi, D. Desmaële, *Eur. J. Org. Chem.* **2001**, 3631-3640.
- [44] A. Fürstner, F. Feyen, H. Prinz, H. Waldmann, *Tetrahedron* **2004**, 60, 9543-9558.
- [45] G. Ma, S. Afewerki, L. Deiana, C. Palo-Nieto, L. Liu, J. Sun, I. Ibrahim, A. Córdova, *Angew. Chem. Int. Ed.* **2013**, 52, 6050-6054; *Angew. Chem.* **2013**, 125, 6166-6170.
- [46] S. Afewerki, G. Ma, I. Ibrahim, L. Liu, J. Sun, A. Córdova, *ACS Catal.* **2015**, 5, 1266-1272.
- [47] a) Y. Hayashi, H. Gotoh, T. Hayashi, M. Shoji, *Angew. Chem. Int. Ed.* **2005**, 44, 4212-4215; *Angew. Chem.* **2005**, 117, 4284-4287; b) M. Marigo, T. C. Wabnitz, D. Fielenbach, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2005**, 44, 794-797; *Angew. Chem.* **2005**, 117, 804-807.
- [48] a) B. M. Trost, D. M. T. Chan, *J. Am. Chem. Soc.* **1979**, 101, 6429-6432; b) B. M. Trost, *Angew. Chem. Int. Ed.* **1986**, 25, 1-20; *Angew. Chem.* **1986**, 98, 1-20; For reviews, see: c) M. Lautens, W. Klute, W. Tam, *Chem. Rev.* **1996**, 96, 49-92; d) B. M. Trost, *Pure Appl. Chem.* **1988**, 60, 1615-1626; e) S. Yamago, E. Nakamura, *Org. React.* **2003**, 61, 1-217.
- [49] For reviews, see: a) D. M. T. Chan in *Cycloaddition Reactions in Organic Synthesis* (Eds.: S. Kobayashi, K. A. Jørgensen), Wiley-VCH, Weinheim, **2002**, pp. 57-84; b) I. Kumar, *RSC Adv.* **2014**, 4, 16397-16408.
- [50] For selected examples, see: a) **(+)-brefeldin A**: B. M. Trost, M. L. Crawley, *J. Am. Chem. Soc.* **2002**, 124, 9328-9329; b) **(+)-sulcatine G**: D. F. Taber, K. J. Frankowski, *J. Org. Chem.* **2005**, 70, 6417-6421; c) **auerothin and analogues**: M. F. Jacobsen, J. E. Moses, R. M. Adlington, J. E. Baldwin, *Tetrahedron* **2006**, 62, 1675-1689; d) **pinnaic acid**: S. Xu, H. Arimoto, D. Uemura, *Angew. Chem. Int. Ed.* **2007**, 46, 5746-5749; *Angew. Chem.* **2007**, 119, 5848-5851.
- [51] A cycloaddition is a reaction in which two or more unsaturated units – being them two separated molecules, or incorporated into a single molecular entity – combine with the formation of a cyclic adduct with a net reduction of the bond multiplicity. Therefore, a cycloaddition reaction may be regarded as a particular type of annulation reaction.
- [52] B. M. Trost, B. Yang, M. L. Miller, *J. Am. Chem. Soc.* **1989**, 111, 6482-6484.

- [53] B. L. Feringa, *Acc. Chem. Res.* **2000**, *33*, 346.
- [54] B. M. Trost, J. P. Stambuli, S. M. Silverman, U. Schwörer, *J. Am. Chem. Soc.* **2006**, *128*, 13328-13329.
- [55] B. M. Trost, L. Debien, *J. Am. Chem. Soc.* **2015**, *37*, 11606-11609.
- [56] a) B. M. Trost, D. A. Bringley, P. S. Seng, *Org. Lett.* **2012**, *14*, 234-237; b) B. M. Trost, D. A. Bringley, B. M. O'Keefe, *Org. Lett.* **2013**, *15*, 5630-5633.
- [57] a) B. M. Trost, S. M. Silverman, J. P. Stambuli, *J. Am. Chem. Soc.* **2007**, *129*, 12398-12399; b) B. M. Trost, S. M. Silverman, *J. Am. Chem. Soc.* **2012**, *134*, 4941-4954.
- [58] B. M. Trost, D. A. Bringley, S. M. Silverman, *J. Am. Chem. Soc.* **2011**, *133*, 7664-7667.
- [59] L. M. Harwood, R. J. Vickers in *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products* (Eds.: A. Padwa, W. H. Pearson), John Wiley & Sons, Inc., New-York, **2002**, pp. 169-252.
- [60] a) B. M. Trost, S. A. King, T. Schmidt, *J. Am. Chem. Soc.* **1992**, *114*, 7903-7904; b) B. M. Trost, S. Sharma, T. Schmidt, *Tetrahedron Lett.* **1993**, *34*, 7183-7186.
- [61] B. M. Trost, D. A. Bingley, *Angew. Chem. Int. Ed.* **2013**, *52*, 4466-4469; *Angew. Chem.* **2013**, *125*, 4562-4565.
- [62] G. Procopiou, W. Lewis, G. Harbottle, R. A. Stockman, *Org. Lett.* **2013**, *15*, 2030-2033.
- [63] M. Kjjajic, T. Schlatter, R. Breinbauer, *Synlett* **2019**, *30*, 581-585.
- [64] G. E. Greco, B. L. Gleason, T. A. Lowery, M. J. Kier, L. B. Hollander, S. Z. Gibbs, A. D. Worthy, *Org. Lett.* **2007**, *9*, 3817-3820.
- [65] B. M. Trost, V. Ehmke, B. M. O'Keefe, D. A. Bringley, *J. Am. Chem. Soc.* **2014**, *136*, 8213-8216.
- [66] D. Ko, S.-Y. Baek, J. Y. Shim, J. Y. Lee, M.-H. Baik, E. J. Yoo, *Org. Lett.* **2019**, *21*, 3998-4002.
- [67] a) S. J. Hedley, W. J. Moran, A. H. G. P. Prenzel, D. A. Price, J. P. A. Harrity, *Synlett* **2001**, 1596-1598; b) S. J. Hedley, W. J. Moran, D. A. Price, J. P. A. Harrity, *J. Org. Chem.* **2003**, *68*, 4286-4292.
- [68] K. M. Goodenough, W. J. Moran, P. Raubo, J. P. A. Harrity, *J. Org. Chem.* **2005**, *70*, 207-213.
- [69] N. C. Mancey, N. Sandon, A.-L. Auvinet, R. J. Butlin, W. Czechizky, J. P. A. Harrity, *Chem. Commun.* **2011**, *47*, 9804-9806.
- [70] R. Shintani, T. Hayashi, *J. Am. Chem. Soc.* **2006**, *128*, 6330-6331.
- [71] a) H. Dorn, A. Otto, *Chem. Ber.* **1968**, *101*, 3287-3301; b) H. Dorn, A. Otto, *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 214-215; *Angew. Chem.* **1968**, *80*, 196.
- [72] For a selection of articles, see: a) A. Suárez, C. W. Downey, G. C. Fu, *J. Am. Chem. Soc.* **2005**, *127*, 11244-11245; b) L. Pezdirc, V. Jovanovski, B. Bevk, R. Jakse, S. Pirc, A. Meden, B. Stanovnik, J. Svete, *Tetrahedron* **2005**, *60*, 3977-3990.
- [73] R. Shintani, S. Park, W.-L. Duan, T. Hayashi, *Angew. Chem. Int. Ed.* **2007**, *46*, 5901-5903; *Angew. Chem.* **2007**, *119*, 6005-6007.
- [74] B. M. Trost, Z. Huang, G. M. Murhade, *Science* **2018**, *362*, 564-568.
- [75] a) P. Binger, U. Schuchardt, *Angew. Chem. Int. Ed.* **1977**, *16*, 249-250; *Angew. Chem.* **1977**, *89*, 254-255; b) P. Binger, U. Schuchardt, *Chem. Ber.* **1981**, *114*, 3313-3324; For a review, see: c) P. Binger, H. M. Büch, *Top. Curr. Chem.* **1987**, *135*, 77-151.
- [76] a) I. Nakamura, B. H. Oh, S. Saito, Y. Yamamoto, *Angew. Chem. Int. Ed.* **2001**, *40*, 1298-1230; *Angew. Chem.* **2001**, *113*, 1338-1340; b) B. H. Oh, I. Nakamura, S. Saito, Y. Yamamoto, *Tetrahedron Lett.* **2001**, *42*, 6203-6205; c) B. H. Oh, I. Nakamura, S. Saito, Y. Yamamoto, *Heterocycles* **2003**, *61*, 247-257.
- [77] P. Binger, P. Bentz, *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 622-623; *Angew. Chem.* **1984**, *94*, 636.
- [78] K. Chen, M. Jiang, Z. Zhang, Y. Wei, M. Shi, *Eur. J. Org. Chem.* **2011**, 7189-7193.
- [79] A. I. Sirwardana, I. Nakamura, Y. Yamamoto, *J. Org. Chem.* **2004**, *69*, 3202-3204.
- [80] P. Binger, P. Wedemann, S. I. Kozhushkov, A. de Meijere, *Eur. J. Org. Chem.* **1998**, 113-119.
- [81] A. Delgado, J. R. Rodríguez, L. Castedo, J. L. Mascareñas, *J. Am. Chem. Soc.* **2003**, *125*, 9282-9283.
- [82] a) A. Stolle, J. Ollivier, P. P. Piras, J. Salaün, A. de Meijere, *J. Am. Chem. Soc.* **1992**, *114*, 4051-4067; b) A. Stolle, H. Becker, J. Salaün, A. de Meijere, *Tetrahedron Lett.* **1994**, *35*, 3517-3520; c) G. Delogu, J. Salaün, C. de Candia, D. Fabbri, P. P. Piras, J. Ollivier, *Synthesis*, **2002**, 2271-2279.
- [83] F. Verdugo, L. Villarino, J. Durán, M. Gulías, J. L. Mascareñas, F. López, *ACS Catal.* **2018**, *8*, 6100-6105.
- [84] A. Khan, L. Yang, J. Xu, L. Y. Jin, Y. J. Zhang, *Angew. Chem. Int. Ed.* **2014**, *53*, 11257-11260; *Angew. Chem.* **2014**, *126*, 11439-11442.
- [85] K. Ohmatsu, N. Imagawa, T. Ooi, *Nat. Chem.* **2013**, *6*, 47-51.
- [86] I. Shimizu, Y. Ohashi, J. Tsuji, *Tetrahedron Lett.* **1985**, *26*, 3825-3828.
- [87] For a selection of recent articles, see: a) B. M. Trost, P. J. Morris, *Angew. Chem. Int. Ed.* **2011**, *50*, 6167-6170; *Angew. Chem.* **2011**, *123*, 6291-6294; b) L.-Y. Mei, Y. Wei, Q. Xu, M. Shi, *Organometallics*, **2012**, *31*, 7591-7599; c) B. M. Tost, P. J. Morris, S. J. Sprague, *J. Am. Chem. Soc.* **2012**, *134*, 17823-17831; d) M.-S. Xie, Y. Wang, J.-P. Li, C. Du, Y.-Y. Zhang, E.-J. Hao, Y.-M. Zhang, G.-R. Qu, H.-M. Guo, *Chem. Commun.* **2015**, *51*, 12451-12454; e) S.-C. Zhang, X.-X. Lei, Y.-J. Yang, Y.-C. Luo, H.-H. Zhang, P.-F. Xu, *Org. Chem. Front.* **2019**, *6*, 2415-2419.
- [88] K. Aoyagi, H. Nakamura, Y. Yamamoto, *J. Org. Chem.* **2002**, *67*, 5977-5980.
- [89] M. A. Lowe, M. Ostovar, S. Ferrini, C. C. Chen, P. G. Lawrence, F. Fontana, A. A. Calabrese, V. K. Aggarwal, *Angew. Chem. Int. Ed.* **2011**, *50*, 6370-6374; *Angew. Chem.* **2015**, *127*, 1624-1627.
- [90] C.-F. Xu, B.-H. Zheng, J.-J. Suo, C.-H. Ding, X.-L. Hou, *Angew. Chem. Int. Ed.* **2015**, *54*, 1604-1607; *Angew. Chem.* **2011**, *123*, 6494-6498.
- [91] J.-J. Guo, J. Du, Q.-R. Liu, D. Chen, C.-H. Ding, Q. Peng, X.-L. Hou, *Org. Lett.* **2017**, *19*, 6658-6661.
- [92] J. Du, Y.-J. Jiang, J.-J. Suo, W.-Q. Wu, X.-Y. Liu, D. Chen, C.-H. Ding, Y. Wei, X.-L. Hou, *Chem. Commun.* **2018**, *54*, 13143-13146.
- [93] M. Laugeois, S. Ponra, V. Ratovelomanana-Vidal, V. Michelet, M. Vitale, *Chem. Commun.* **2016**, *52*, 5332-5335.
- [94] K. S. Halskov, L. Næsborg, F. Tur, K. A. Jørgensen, *Org. Lett.* **2016**, *18*, 2220-2223.
- [95] M. Meazza, R. Rios, *Chem. Eur. J.* **2016**, *22*, 9923-9928.
- [96] a) M. Suzuki, S. Sawada, T. Saegusa, *Macromolecules*, **1989**, *22*, 1505-1507; b) M. Suzuki, S. Sawada, S. Yoshida, A. Eberhardt, T. Saegusa, *Macromolecules*, **1993**, *26*, 4748-4750.
- [97] K. Zhang, M. Meazza, A. Izaga, C. Contamine, M. C. Gimeno, R. P. Herrera, R. Rios, *Synthesis* **2017**, *49*, 167-174.
- [98] a) M. Laugeois, J. Ling, C. Féraud, V. Michelet, V. Ratovelomanana-Vidal, M. R. Vitale, *Org. Lett.* **2017**, *19*, 2266-2269; b) Y. S. Gee, D. J. Rivinoja, S. M. Wales, M. R. Gardiner, J. H. Ryan, C. J. T. Hyland, *J. Org. Chem.* **2017**, *82*, 13517-13529.
- [99] a) M. Sun, Z.-Q. Zhu, L. Gu, X. Wan, G.-J. Mei, F. Shi, *J. Org. Chem.* **2018**, *83*, 2341-2348; b) J.-Q. Zhang, F. Tong, B.-B. Sun, W.-T. Fan, J.-B. Chen, D. Hu, X.-W. Wang, *J. Org. Chem.* **2018**, *83*, 2882-2891.
- [100] D. J. Rivinoja, Y. S. Gee, M. G. Gardiner, J. H. Ryan, C. J. T. Hyland, *ACS Catal.* **2017**, *7*, 1053-1056.
- [101] a) J.-J. Suo, W. Liu, J. Du, C.-H. Ding, X.-L. Hou, *Chem. Asian J.* **2018**, *13*, 959-963. For an additional example from nitrobenzofurans, see: (b) Q. Cheng, H.-J. Zhang, W.-J. Yue, S.-L. You, *Chem* **2017**, *3*, 428-436.
- [102] For an example, see: Y.-N. Wang, L.-C. Yang, Z.-Q. Rong, T.-L. Liu, R. Liu, Y. Zhao, *Angew. Chem. Int. Ed.* **2018**, *57*, 1596-1600; *Angew. Chem.* **2018**, *130*, 1612-1616.
- [103] For an example, see: C. Yuan, Y. Wu, D. Wang, Z. Zhang, C. Wang, L. Zhou, C. Zhang, B. Song, H. Guo, *Adv. Synth. Catal.* **2018**, *360*, 652-658.

## MINIREVIEW

Annulative  $\eta^3$ -allylpalladium chemistry has been a trending topic in catalysis since the 80's and is still a challenging area of research through the discovery of new reactivities, the development of enantioselective versions and their applications in total synthesis. The latest developments in this field are summarized here.

**Palladium-catalysis**

*Yang Liu, Julie Oble, Alexandre Pradal,\* and Giovanni Poli\**

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