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Recent Advances in Transition-Metal Catalyzed Oxidative Annulations to Benzazepines and Benzodiazepines

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Abstract. Benzazepines and benzodiazepines, benzofused seven-membered *N*-heterocycles, compose an important family of natural products and pharmaceuticals. Although certainly important and effectives, classical synthetic methods of these cyclic compounds involve methodologies that often require multistep procedures, with generation of waste materials and lack of sustainability. By contrast, cycloadditions based on transition metal catalyzed C-H bond activations (oxidative annulations) have emerged as appealing strategies for more sustainable synthetic processes. In this review, we focus our attention to describe the state-of-the-art transition-metal catalyzed annulations *via* C-H activations to benzazepines and benzodiazepines.

Keywords: Benzazepine, Benzodiazepine, C-H activation, Oxidative annulation, Transition-metal catalyst

1 Introduction

Seven-membered *N*-heterocycles, azepines, are important skeletal motifs found in numerous natural products and pharmaceuticals.[1] Due to their interesting biological properties, a large number of synthetic methods have been developed to access the azepine nuclei throughout the years.[2] Moreover, the benzofused analogs, benzazepines and benzodiazepines,[3] which compose a wide family of natural products and pharmaceuticals with unique biological activity, have also received considerable attention.[4] The azepine unit can be benzofused from three different sides of the ring (b, c or d) and, therefore, 1-benzazepine, 2-benzazepine or 3-benzazepine integrate the whole benzazepine family (Figure 1). The remarkable biological activity of this family arises from their interaction with specific human receptors in the Central Nervous System (CNS), such as D_1-receptor (dopamine)[5] or 5-HT_{1A} receptor (serotonine),[6] where benzazepines can act either as agonist or antagonist. For instance, Alsterpaullone has been described as a potent antitumoral agent,[7] Galantamine is used to treat Alzheimer' disease[8] and Lorcaserin was approved by FDA to treat obesity.[9]

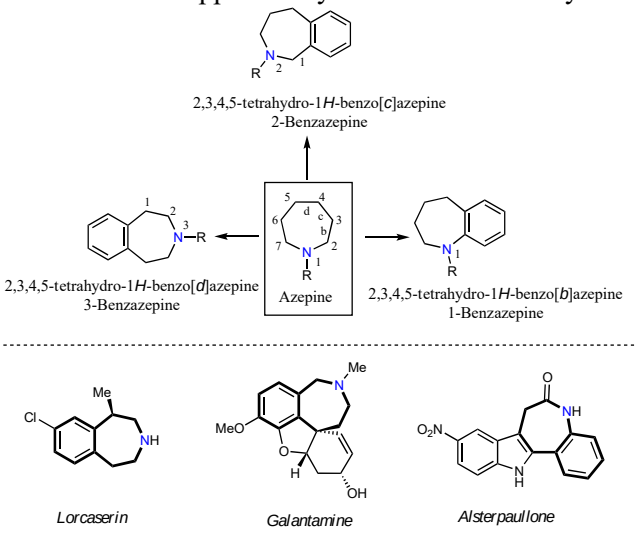


Figure 1. Representative benzazepines

Benzodiazepines, dinitrogenated benzofused members, are classified depending on the relative

position of both nitrogens in the azepine ring as 1,2-, 1,3-, 1,4- 1,5- and 2,3-benzodiazepines (Figure 2).[10] They are suitable drugs to affect the binding to human receptors such as $GABA_A$,[11] AMPA (e.g., Nerisopam)[12], even DNA (e.g., Anthramycin)[13] as well as inhibitors of bromodomains.[14] For instance, 1,4-benzodiazepines are one of the most common drugs owing to their extensive use to treat anxiety,[15] insomnia,[16] or cancer,[17] 1,2-benzodiazepines are highlighted as cancer inhibitors (e.g., CB-6644),[18] and 1,5-benzodiazepines are potent CNS active agents (e.g., Clobazam).[19]

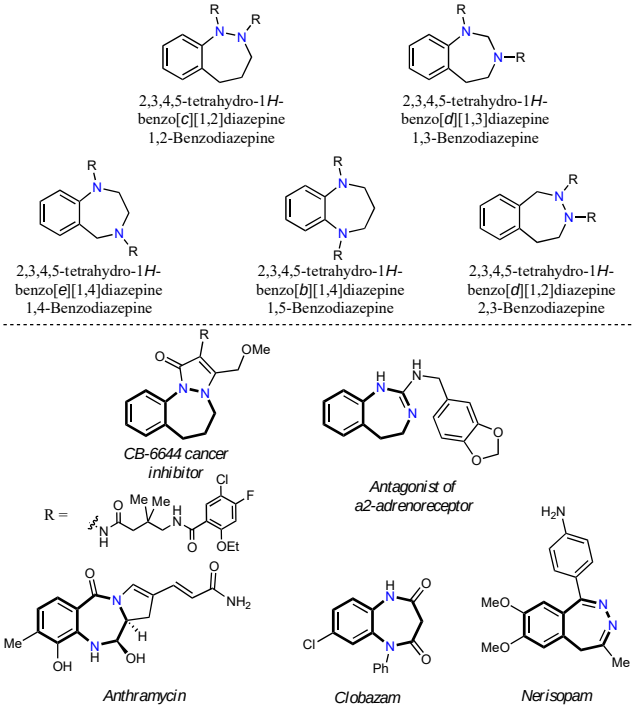


Figure 2. Representative benzodiazepines

A large number of synthetic routes to benzazepines and benzodiazepines have been described throughout the last decade,[20] the most used are those based on condensations,[21] cyclizations,[22] cycloadditions[23] and ring expansions.[24] All these classical strategies might be considered useful although they usually lack sustainability in their transformations.

In a step further toward more sustainable approaches, catalytic methods have been successfully employed to synthesize both benzazepines and benzodiazepines. Thus, transition-metal-catalyzed Heck type reactions,[25] cycloadditions,[26] metathesis,[27] oxidative couplings,[28] intramolecular C- and *N*-aryl(alkyl)ations,[29] tandem processes[30] or hydroamin(d)ation of alkynes[31] has been successfully employed.

Álvaro Velasco-Rubio, born in Salamanca (Spain), received his BSc in chemistry at the University of Salamanca, Spain, in 2015. He completed his MSc in Organic Chemistry in 2016 for research about transition-metal catalyzed heteroannulations via C-H bond activation under the supervision of Profs. Carlos Saá and Jesús A. Varela at Universidad de Santiago de Compostela, Spain. He spent a short research stay at Caltech working on synthetic methodology to access fully substituted α-amino ketones under the supervision of Prof. Brian Stoltz. He is currently a fourth year Ph D candidate working on "Sustainable Synthesis of Benzazepines and Benzodiazepines" under the supervision of Profs. Carlos Saá and Jesús A. Varela.

Jesús A. Varela was born in 1971 in Lugo, Spain and studied chemistry at the Universidad de Santiago de Compostela, Spain. He completed his MSc in 1994 and his Ph D thesis in 1999 (excellent award) under the supervision of Prof. Dr. Carlos Saá. After a predoctoral research training period in Harvad University under supervision of Prof. Dr. Matthew Shair and a postdoctoral period from 1999 to 2001 as an Alexander von Humboldt and Marie Curie Fellow with Prof. Dr. Paul Knochel at LMU in Munich (Germany), he joined the faculty at the Universidad de Santiago de Compostela as Ramón y Cajal researcher, and since 2008 as Associate Professor. His research interests are focused on organometallic catalysis towards the synthesis of bioactive compounds and molecular materials.

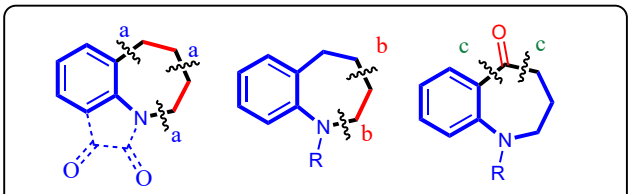
Carlos Saá born in Lugo (Spain), studied chemistry at the Universidad de Santiago de Compostela (Spain) where he received his PhD in 1985 under the supervision of Profs. L. Castedo, R. Suau and J. M. Saá. After postdoctoral studies with Prof. Vollhardt at the University of California, Berkeley, he was appointed as Associate Professor In 1990 at the University of Santiago de Compostela, and since 2004 as a full Professor. His research interest centers on the development of new methodology of organometallic catalysis and their applications to the synthesis of bioactive compounds and organic conductive materials.

The current challenges in transition-metal-catalysis lies in developing more ecofriendly strategies to access highly valuable benzofused seven-membered azaheterocycles. In this sense, annulation reactions, in which two bonds are formed in a single step, are among the most efficient methods for the synthesis of cyclic compounds.[32] Particularly, dehydrogenative

annulation reactions *via* metal-catalyzed C-H activation provide straightforward access to common cyclic scaffolds from easily available substrates.[33] Several strategies have been reported to obtain five- and six-membered benzofused azaheterocycles *via* transition-metal catalyzed C-H bond activation,[34] but few are known for the medium sized seven-membered analogs. In this review, the state-of-the-art metal-catalyzed annulations to synthesize benzofused seven-membered azaheterocycles are highlighted. Synthetic strategies, directing groups (DGs) and coupling partners used to obtain benzazepines and benzodiazepines, as well as the mechanism of these transformations, will be conveniently discussed. We have organized the sections according to the type of heterocycle and number of atoms involved in the annulation.

2 Benzazepines *via* Transition-Metal Catalyzed Oxidative Annulations

2.1 1-Benzazepines

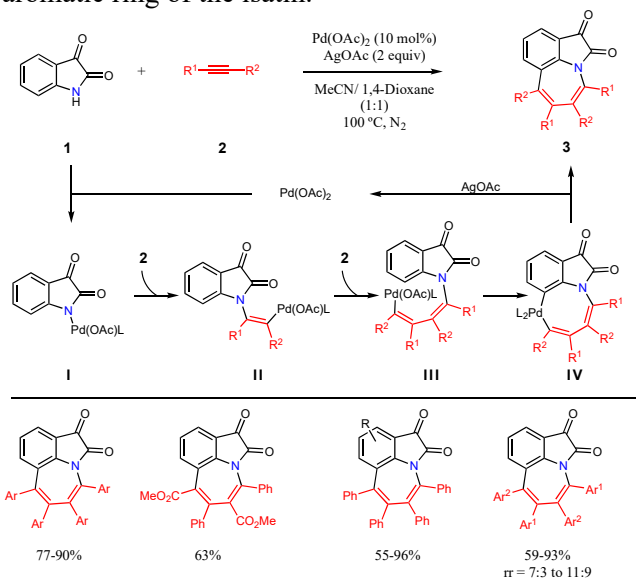


Key	Annulation	Metal	DG	Unsaturated partner
a	(3+2+2)	Pd	X-Type	Alkynes
b	(5+2)	Pd	L-Type	Alkynes
			X-Type	1,3-dienes
			X-Type	Allenes
		Ir	L-Type	Allyl carbonates
c	(6+1)	Rh		CO

Figure 3. 1-Benzazepine disconnections

1-Benzazepines have been synthesized under Pd catalysis using nitrogenated substrates bearing L-Type (amines) and X-Type (amides) DGs *via* multicomponent and standard annulations.[35-40] They have been also synthesized under Ir catalysis in a (5+2) annulation of *o*-alkenylanilines and allyl carbonates.[41] In addition, a Rh-catalyzed (6+1) carbonylation of *N*-cyclopropylanilides (carbonylative C-C activation) rendered benzazepin-5-ones (Figure 3).[42]

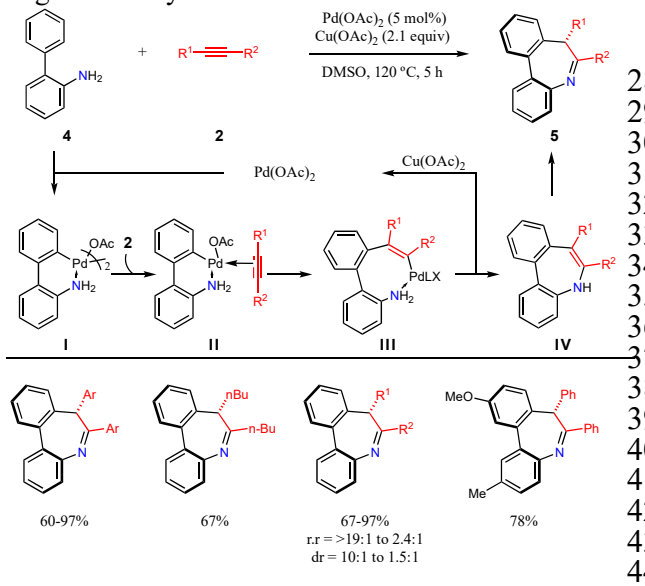
One of the pioneering examples of multicomponent annulations was reported by Wang and co-workers in 2013.[35] They probed that isatins **1**, a cyclic anilide type substrate, can react with two equivalents of alkynes **2** to give 1-benzazepines **3** in a formal (3+2+2) cycloaddition (Scheme 1).[36] The authors suggested a mechanism which starts with the ligand exchange to give **I**.[35] This is followed by two consecutive 1,2-insertions of alkynes to generate the butadienylpalladium intermediate **III**. Finally, C-H activation (*via* Concerted Metalation Deprotonation, CMD) led to the eight-membered palladacycle **IV**, which subsequently underwent reductive elimination to yield the 1-benzazepine **3**. The reaction afforded excellent yields with aromatic alkynes. However, when non-symmetrical alkynes were used, moderate to high yields of a mixture of regioisomers were obtained. The reaction tolerated all types of electron-donating and electron-withdrawing substituents in the aromatic ring of the isatin.



Scheme 1. Pd-catalyzed (3+2+2) annulation of isatins and alkynes to 1-benzazepines.

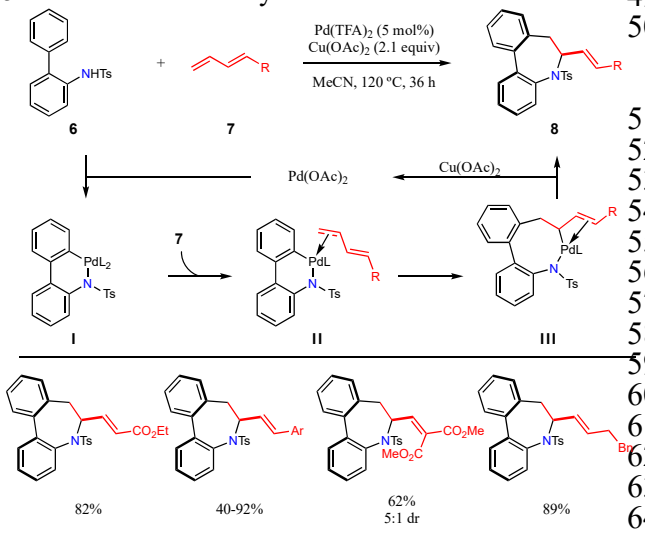
In 2015, Luan and co-workers reported a Pd-catalyzed (5+2) heteroannulation between *o*-arylanilines **4** and alkynes **2** to produce dibenzo[*b*,*d*]azepines **5** (Scheme 2).[37] The authors proposed a mechanism that is initiated with an aniline-assisted (L-type DG) C-H bond activation (*via* CMD) to form the dimeric six-membered palladacycle **I**. This dimeric complex is broken in the presence of the alkyne to form the coordinated species **II** that undergo 1,2-migratory insertion into the C-Pd bond to give an eight-membered palladacycle **III**. Subsequent C-N reductive elimination delivers the enamine dibenzo[*b*,*d*]azepine **IV** and concomitantly regenerate the Pd(II) catalyst to restart the cycle. Finally, tautomerization of the enamine to the thermodynamically more stable imine leads to the final dibenzo[*b*,*d*]azepine **5**. Both aromatic and aliphatic alkynes afforded good to high yields and excellent diastereoselectivities (>19:1). In the case of non-symmetrical alkynes, moderate to excellent yields of both regioisomers in modest to good diastereoselectivies were obtained. Furthermore, many

electron-rich and electron-poor substituents in both rings of the arylaniline were well tolerated.



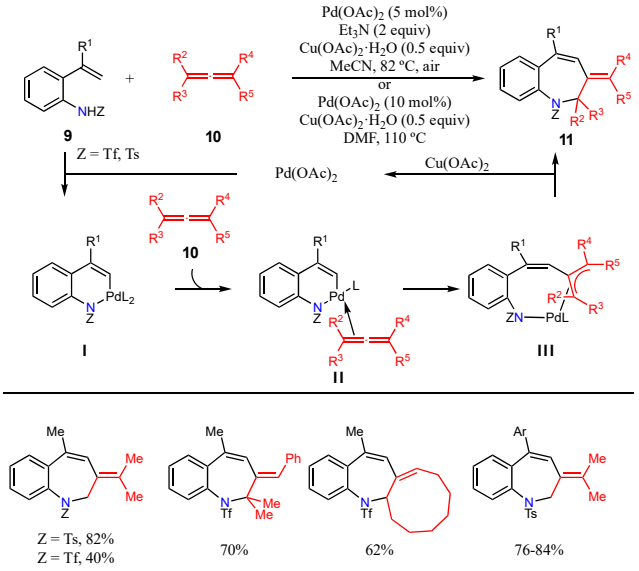
Scheme 2. Pd-catalyzed (5+2) annulation of *o*-arylanilines and alkynes to dibenzo[*b*,*d*]azepines.

In 2017, the same group also reported the access to the same core, dibenzo[*b*,*d*]azepines **8**, via Pd-catalyzed (5+2) heteroannulation between tosyl anilides **6** and 1,3-dienes (Scheme 3).[38] The mechanism suggested for this transformation involves the initial formation of the six-membered palladacycle **I** (*cis*-PdX_2L_2) *via* electrophilic palladation. Then, coordination (**II**) and migratory insertion of the 1,3-diene forms an eight-membered palladacycle **III**, which is further stabilized with the second double bond of the diene (Pd σ-allyl complex). Finally, C-N reductive elimination delivers the dibenzo[*b*,*d*]azepine **8** with concomitant regeneration of the active Pd(II) species to reinitiate the catalytic cycle. Monosubstituted 1,3-dienes gave good to excellent yields of the corresponding 1- dibenzo[*b*,*d*]azepines as a single diastereoisomer. However, 1,1-disubstituted 1,3-dienes also worked in good yields, but in a lower 5:1 diastereoselectivity.



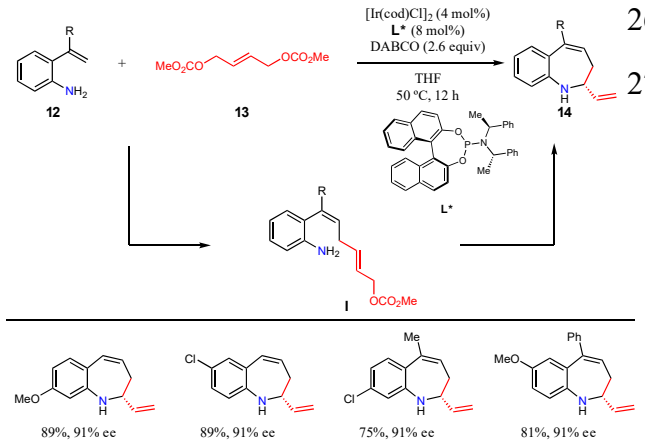
Scheme 3. Pd-catalyzed (5+2) annulation of aryl tosylanilides and 1,3-dienes to dibenzo[*b*,*d*]azepines.

Simultaneously, the groups of Mascareñas/Gulías[39] and Zeng[40] reported a Pd-catalyzed (5+2) annulation of *ortho*-alkenylanilides **9** (triflamides or tosylamides) and allenes **10** to give 3-alkylidene 1-benzazepines **11** (Scheme 4). Mechanistic studies supported by DFT calculations suggested the initial formation of a six-membered palladacycle **I** through a C-H bond activation (*via* CMD). Then, allene coordination (**II**) and regioselective migratory insertion into the C-Pd bond forms a π-allylic palladacycle **III**, which undergoes reductive elimination to the 1-benzazepine **11**. Oxidation of the resulting Pd(0) with $Cu(OAc)_2$ and air regenerates the active catalytic Pd(II) species. Either mono-, di- or tri-substituted allenes give the corresponding 1-benzazepines in good to excellent yields and usually as single isomers. Electron-withdrawing and electron-donating substituents in the aryl ring of the anilide were also well accepted.



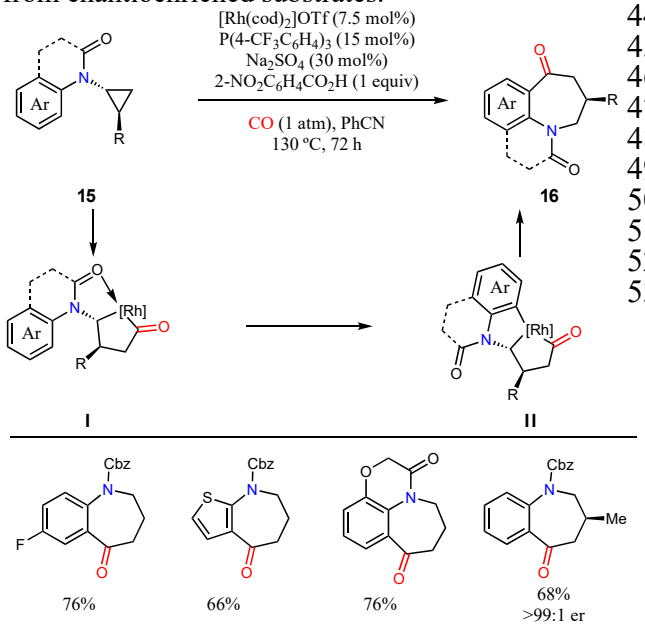
Scheme 4. Pd-catalyzed (5+2) annulation of *o*-alkenylanilides and allenes to 1-benzazepines.

In 2010, You and co-workers described an Ir-catalyzed (5+2) heteroannulation of *o*-alkenylanilines **12** and allyl carbonates **13** to 1-benzazepines **14** in a tandem allylic vinylation/allylic amination reaction (Scheme 5).[41] Furthermore, the allyl-vinyl intermediate **I** (*via* C-H activation) could be isolated and readily cyclized into the seven-membered azaheterocycle. The tandem reaction afforded α-vinyl 1-benzazepines in fairly good yields and excellent enantioselectivities upon employment of phosphoramidites (**L***) as chiral ligands. Either electron-withdrawing or electron-donating groups were well-tolerated in the 4 and 5 position of the aryl ring. 1,1- Disubstituted styrenes were also efficiently cyclized.



Scheme 5. Ir-catalyzed (5+2) annulation of *o*-alkenylanilines and allyl carbonates to 1-benzazepines.

In 2018, Bower and co-workers reported a Rh-catalyzed (6+1) annulation of *N*-cyclopropylanilides **15** and CO (carbonylative C-C activation) to benzazepine-5-ones **16** (Scheme 6).[42] The carbonylative cyclization involves a tandem C-C (carbonylation) / C-H bond activation (Friedel-Crafts type cyclization) process. The proposed mechanism begins with the C-C bond activation of the cyclopropane assisted by the carbonyl group of the amide to form the rhodacyclopentanone **I** upon CO insertion. This intermediate subsequently undergoes an aryl C(sp^2)-H bond activation to form the bicyclic rhodacycle **II** that, after C(sp^2)-C(sp^2) reductive elimination and protodemetalation, releases the 1-benzazepin-5-one **16**. Electron-poor and electron-rich aryl and heteroaromatic rings were well tolerated. Enantioenriched 1-benzazepinones were accessed from enantioenriched substrates.



Scheme 6. Rh-catalyzed (6+1) annulation of *N*-cyclopropylanilides and CO (carbonylative C-C activation) to 1-benzazepine-5-ones.

2.2 2-Benzazepines

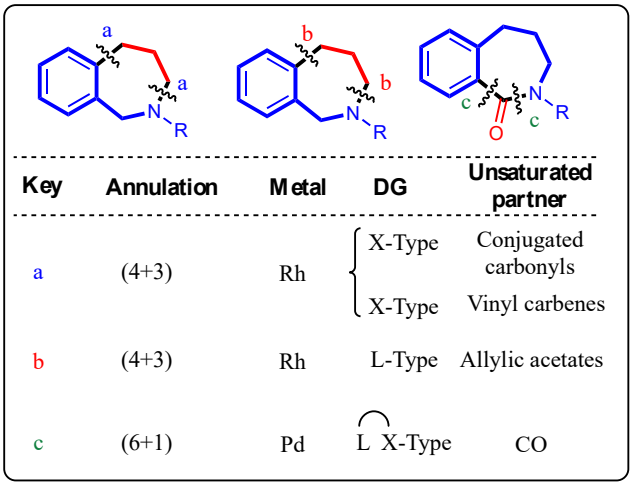
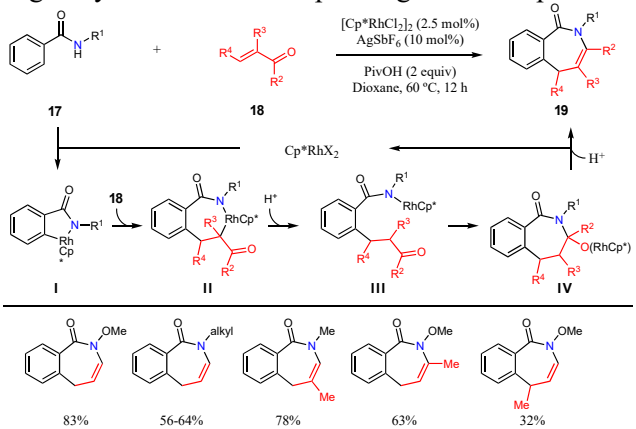


Figure 4. 2-Benzazepine disconnections

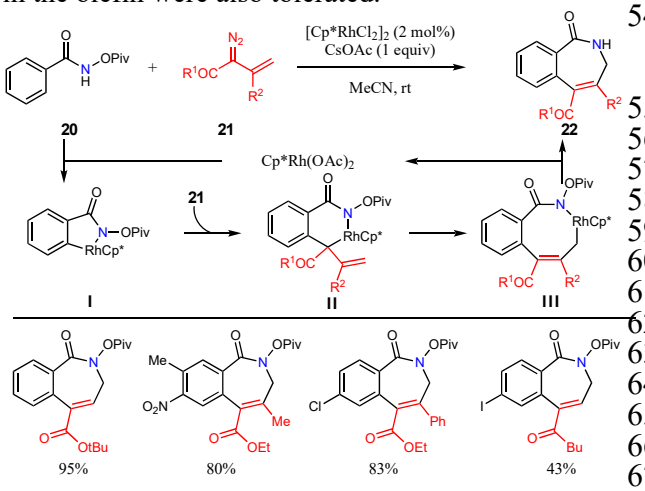
2-Benzazepines have been synthesized under Rh catalysis using nitrogenated substrates bearing either X-Type (amides) DGs *via* (4+3) annulations or L-type (amines) *via* intramolecular cyclizations.[43-45] A Pd-catalyzed (6+1) carbonylation assisted by a bidentate LX-type DG rendered 2-benzazepinones (Figure 4).[46]

In 2013, Glorius and co-workers reported a formal Rh-catalyzed (4+3) annulation of benzamides **17** and α,β-unsaturated aldehydes or ketones **18** to produce 2-benzazepinones **19** (Scheme 7).[43] The proposed mechanism involves an initial formation of the five-membered rhodacycle **I** through the coordination of the benzamide to a Rh(III) species to activate the *o*-C-H bond (*via* CMD). Then, coordination and 1,2-migratory insertion of the α,β-unsaturated compound gives the seven-membered rhodacycle **II**. After protonation (**III**) and addition of the N-Rh bond across the carbonyl group, the Rh-alkoxide intermediate **IV** was obtained. Protonolysis to give the seven-membered hemiaminal and final dehydration delivers the 2-benzazepinone. Electron-rich and electron-poor benzamides were well tolerated, as well as substituted aldehydes and methyl vinyl ketone, to give moderate to good yields of the corresponding 2-benzazepinones.



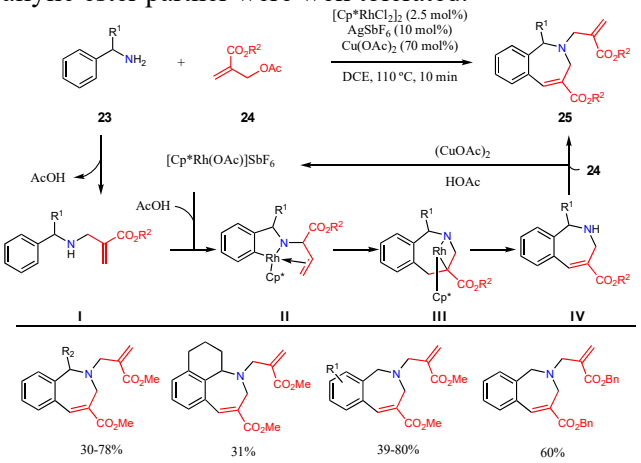
Scheme 7. Rh-catalyzed (4+3) annulation of benzamides and α,β-unsaturated aldehydes or ketones to benzazepinones.

In 2013, Cui and co-workers reported the Rh-catalyzed (4+3) annulation of benzamides **20** and vinylcarbenoids **21** (Scheme 8).[44] The proposed mechanism involves the initial formation of the five-membered rhodacycle **I** through the coordination of the benzamide to activate the *o*-C-H bond (*via* CMD). Then, coordination of the vinylcarbenoid followed by N_2 extrusion affords a Rh-carbene that undergoes a 1,1-migratory insertion to afford the six-membered rhodacycle **II**. A subsequent 1,3-allylic migratory insertion generates the eight-membered rhodacycle **III** that evolves *via* reductive elimination followed by N-O bond cleavage to the observed 2-benzazepinone **22** with regeneration of the active catalyst. Several electron-rich and electron-poor substituents in the aryl ring of the benzamide were well tolerated. Regarding the vinylcarbenoid, electron-withdrawing groups are necessary to stabilize the carbene and promote the reaction (esters or ketones); alkyl and aryl substituents in the olefin were also tolerated.



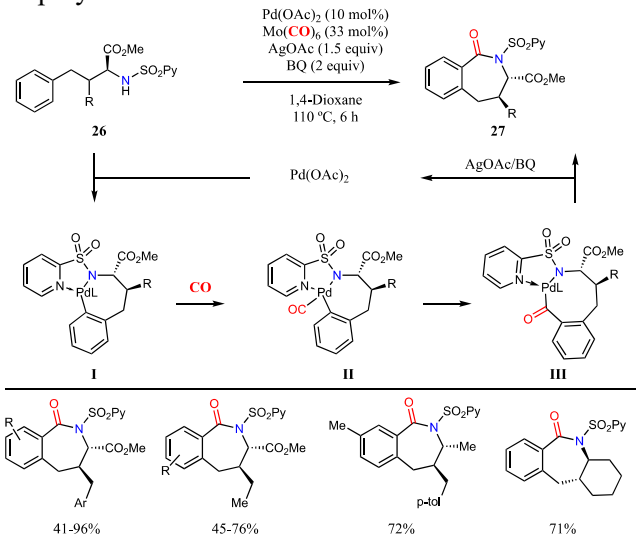
Scheme 8. Rh-catalyzed (4+3) annulation of benzamides and vinylcarbenoids to 2-benzazepinones.

In 2018, Kim and co-workers reported the Rh-catalyzed cyclization of 2-(benzylamino)methacrylates **I** to form 2-benzazepines **25** (Scheme 9).[45] The starting substrates were prepared *in situ* from addition of primary benzylamines **23** to allylic acetates **24** derived from methyl methacrylates. As a result, the whole process could be considered as a Rh-catalyzed (4+3) heteroannulation. The proposed catalytic cycle was supported by DFT calculations and mechanistic experiments. The secondary benzylamine coordinates to the Rh catalyst and undergo C-H bond activation **II** (*via* CMD). Then, the pending olefin becomes coordinated and subsequently undergoes a migratory 1,2-insertion to afford the seven-membered rhodacycle **III**. Finally, β-hydride elimination releases the secondary 2-benzazepine **IV** (after reductive elimination) with concomitant recovery of the active catalyst in the presence of oxidants to reinitiate the catalytic cycle. A final *N*-allylation gives rise to the observed tertiary 2-benzazepine **25**. A variety of substituents on the aryl ring and at the benzylic position of the starting benzylamine as well as in the allylic ester partner were well tolerated.



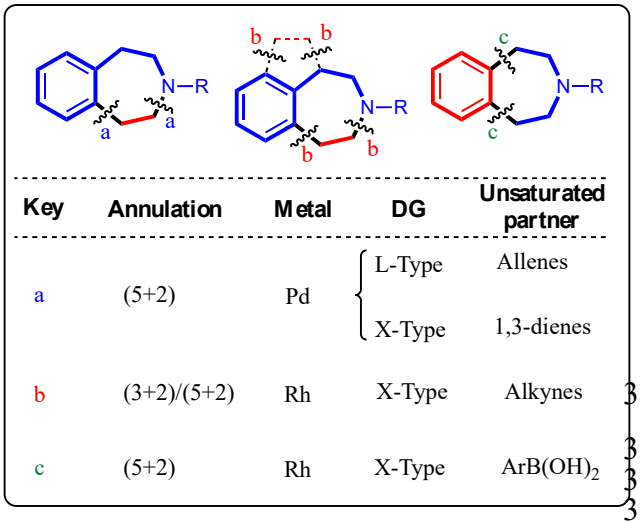
Scheme 9. Rh-catalyzed (4+3) heteroannulation of benzylamines and allylic acetates (from methylacrylates) to 2-benzazepines.

In 2019, Carretero and co-workers reported the Pd-catalyzed (6+1) heteroannulation of γ-arylpropylamine derivatives **26** and CO (Scheme 10).[46] The mechanism of the carbonylation, supported by DFT calculations and deuterium-labeling experiments, begins with the formation of the seven-membered palladacycle **I** assisted by the chelation of the pyridine (bidentate LX-type ligand). Then, CO ligand exchange takes place (**II**) to further undergo a 1,1-migratory insertion (**III**) and reductive elimination to the 2-benzazepinone **27**[47] with the regeneration of the Pd-active catalyst in the presence of the silver salt and BQ. The reaction tolerated a range of substituted aminoacid derivatives both on the activated aryl ring and on the alkyl chain; simple amines could also be employed instead of aminoacid derivatives.



Scheme 10. Pd-catalyzed (6+1) annulation of γ-arylpropylamine derivatives and CO to 2-benzazepinones.

2.3 3-Benzazepines

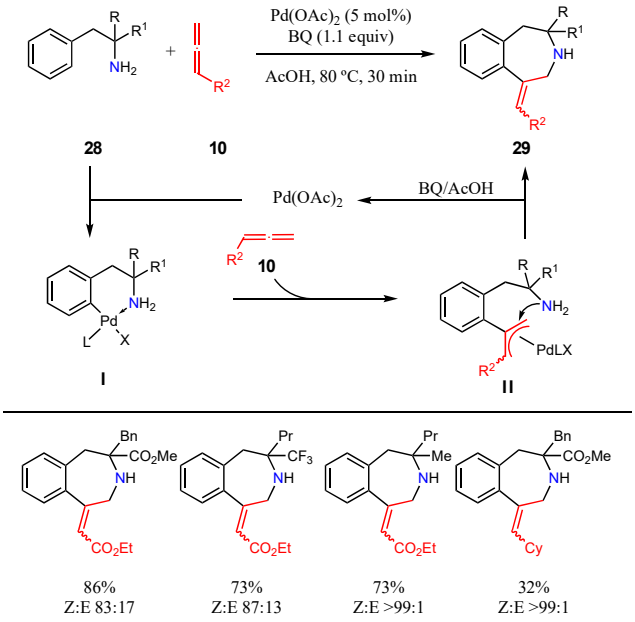


Key	Annulation	Metal	DG	Unsaturated partner
a	(5+2)	Pd	L-Type	Allenes
			X-Type	1,3-dienes
b	(3+2)/(5+2)	Rh	X-Type	Alkynes
c	(5+2)	Rh	X-Type	$ArB(OH)_2$

Figure 5. 3-Benzazepine disconnections

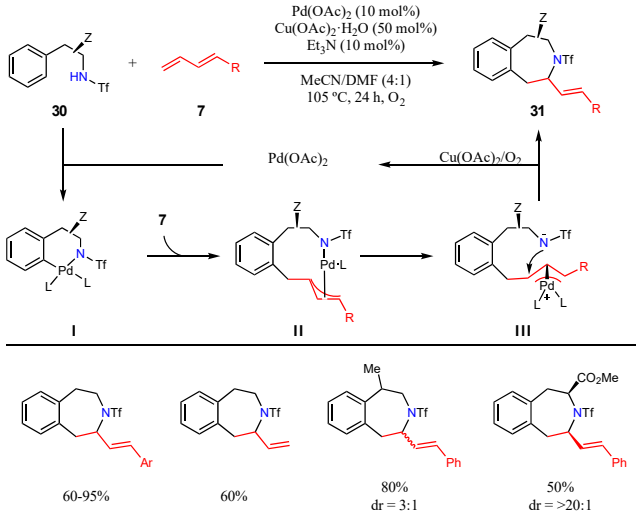
3-Benzazepines have been synthesized under Pd catalysis using nitrogenated substrates bearing L-Type (amines) and X-Type (triflamides) DGs *via* (5+2) annulations.[48,49] In addition, they have been also synthesized under Rh catalysis in a tandem (3+2)/(5+2) annulation of vinyl iminocarbenes and alkynes,[50] and in a formal (5+2) annulation of ynenoates and boronic acids (Figure 5).[51]

In 2014, Ariza and co-workers reported the Pd-catalyzed (5+2) annulation of α,α-disubstituted phenethylamines **28** with allenes **10** to give 3-benzazepines **29** (Scheme 11).[48] The use of α,α-disubstituted phenethylamines is mandatory for a successful annulation. The proposed mechanism for this transformation involves the coordination of the amine to promote the *o*-C-H activation (*via* CMD) with the generation of the six-membered palladacycle **I** (*trans*-PdX_2L_2). Then, the regioselective insertion of the allene into the Pd-C bond affords the π-allylic species **II**. Finally, an outer-sphere S_N2 attack by the nitrogen delivers the 3-benzazepine **29** with the concomitant regeneration of the Pd(II) active catalyst in the presence of a mixture of BQ/AcOH. The α,α-disubstitution on the phenethylamines was necessary for a favorable Thorpe-Ingold effect for cyclization. Furthermore, polarized allenes were needed to undergo a regioselective Tsuji-Trost allylic alkylation in moderate to very good yields.



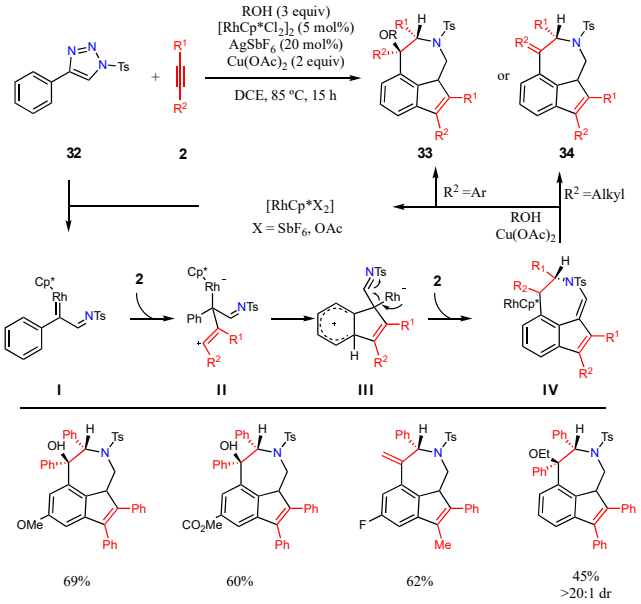
Scheme 11. Pd-catalyzed (5+2) annulation of α,α-disubstituted phenethylamines and allenes to 3-benzazepines.

Very recently, Saá and co-workers reported the Pd-catalyzed (5+2) heteroannulation of phenethyltriflamides **30** and 1,3-dienes **7** to yield 3-benzazepines **31** (Scheme 12).[49] The proposed mechanism for this transformation was supported by DFT calculations and involves an initial *o*-C-H activation (*via* CMD) with the generation of the six-membered palladacycle **I** (*cis*-PdX_2L_2). Then, coordination of the less substituted olefin of the 1,3-diene followed by a 1,2-migratory insertion yields the π-allylic intermediate **II**. The most favored pathway involves the decoordination of the DG from the Pd to form a zwitterionic species **III**, that subsequently undergoes an outer-sphere S_N2 attack to render the observed 3-benzazepine **31**. Notably, the typical reductive elimination from **II** was higher in energy and did not account for the observed diastereoselectivity. Reoxidation of the Pd(0) to the active Pd(II) catalyst was carried out in the presence of $Cu(OAc)_2$ and O_2. Several monosubstituted 1,3-dienes and electron-rich and electron-poor aromatic rings of phenethyltriflamides were tolerated. Interestingly, the reaction of α-substituted phenethyltriflamides was completely diastereoselective as compared to β-substituted with only a 3:1 ratio of diastereomers.



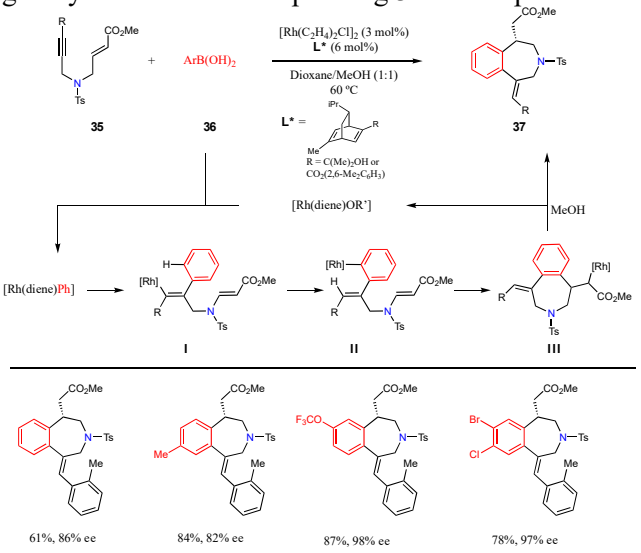
Scheme 12. Pd-catalyzed (5+2) annulation of phenethyl triflamides and 1,3-dienes to 3-benzazepines.

In 2015, Li and co-workers reported a tandem Rh-catalyzed (3+2)/(5+2) heteroannulation of 4-aryl tosyltriazoles **32** with alkynes **2** to yield 3-benzazepines **33** (Scheme 13).[50] The authors proposed a mechanism that starts with the generation of the Rh-carbenoid intermediate **I**. The addition of an alkyne affords a zwitterionic species **II** which undergoes an electrophilic cyclization to give the five-membered ring intermediate **III** ([3+2] annulation). Then, a second (5+2) annulation with the alkyne leads to the 3-benzazepine intermediate **IV** (*via* a transient Rh-H species) that evolves in two different pathways depending on the substituents of the alkyne. When aromatic alkynes are used, cleavage of the C-Rh bond with the aid of $Cu(OAc)_2$ through hydration with H_2O (or ROH) affords the benzylic alcohol and regenerate the active Rh(III) catalyst. On the other hand, when aliphatic alkynes are used, C-Rh bond is cleaved by $Cu(OAc)_2$ followed by a β-hydride elimination to give the *exo*-methylene 3-benzazepine **34**. A variety of substituents on the aryl ring and symmetrically and asymmetrically substituted alkyl/aryl alkynes were well tolerated to give fairly good yields of the corresponding 3-benzazepines.



Scheme 13. Tandem Rh-catalyzed (3+2)/(5+2) annulation of 4-aryl tosyltriazoles and alkynes to 3-benzazepines.

In 2017, Darses and co-workers reported an intriguing enantioselective Rh-catalyzed (5+2) annulation of yne-enoate derivatives **35** with arylboronic acids **36** to yield 3-benzazepines **37** (Scheme 14).[51] The authors suggested a mechanistic pathway that involves transmetallation of the arylboron reagent to the hydroxo Rh(I) complex followed by regioselective alkyne insertion to give a vinylrhodium intermediate **I**. Then, 1,4-rearrangement (C-H activation) occurs to give an arylrhodium species **II** that undergo a conjugated addition to the enoate to deliver, after hydrolysis, the 3-benzazepine **37** with the concomitant regeneration of the active Rh(I) catalyst. Halogenated, electron-rich and electron-poor arylboronic acids were well tolerated giving fairly good yields of the corresponding 3-benzazepines.



Scheme 14. Rh-catalyzed (5+2) annulation of yne-enoate derivatives and arylboronic acids to 3-benzazepines.

3 Benzodiazepines *via* Transition-Metal Catalyzed Oxidative Annulations

3.1 1,2-Benzodiazepines

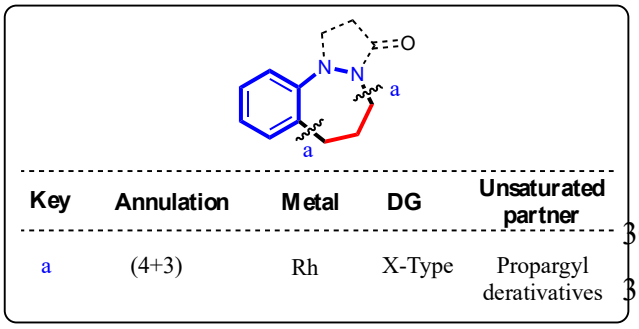
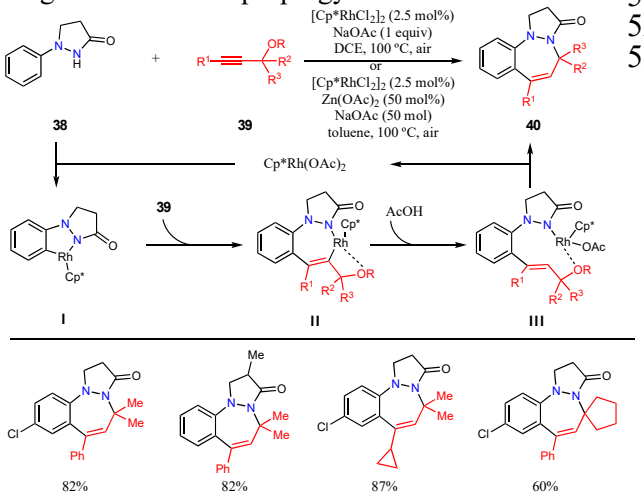


Figure 6. 1,2-Benzodiazepine disconnection

Very recently, the groups of Chauvin/Cui[52] and Zhang/Fan[53] reported the Rh-catalyzed (4+3) heteroannulation of *N*-arylpyrazolidinones **38** and propargyl derivatives **39** to 1,2-benzodiazepines **40** (Scheme 15). The proposed mechanism involves the initial formation of the five- membered rhodacycle **I** through the coordination of the pyrazolidinone to activate the *o*-C-H bond (*via* CMD). Then coordination of the alkyne followed by regioselective 1,2-insertion (attributed to the oxygen coordination) affords the seven-membered rhodacycle **II**. Finally protonolysis of the C-Rh bond (**III**) followed by nucleophilic substitution delivers the 1,2-benzazepine **40** with regeneration of the active catalyst. Electron-rich and electron-poor substituents on the aryl ring of the pyrazolidinone were well-tolerated as well a wide range of substituted propargylic derivatives.



Scheme 15. Rh-catalyzed (4+3) annulation of *N*-aryl pyrazolidinones and propargyl derivatives to 1,2-benzodiazepines.

3.2 1,3-Benzodiazepines

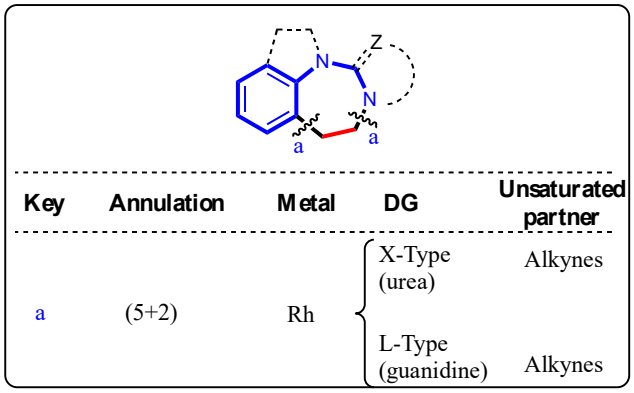
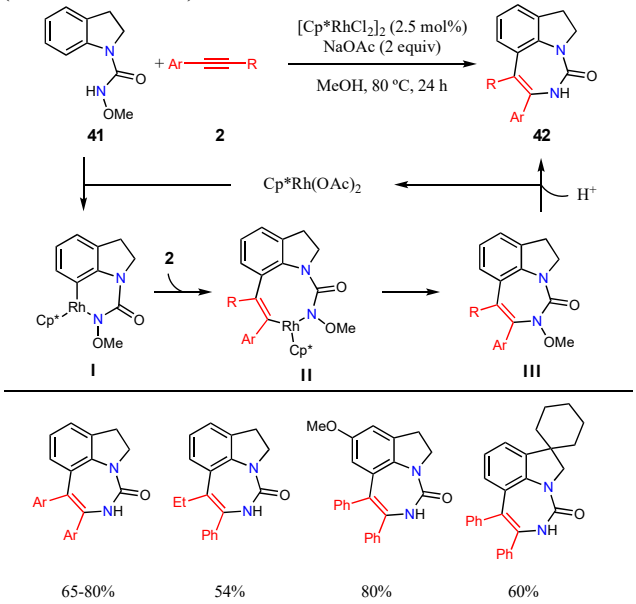


Figure 7. 1,3-Benzodiazepine disconnections

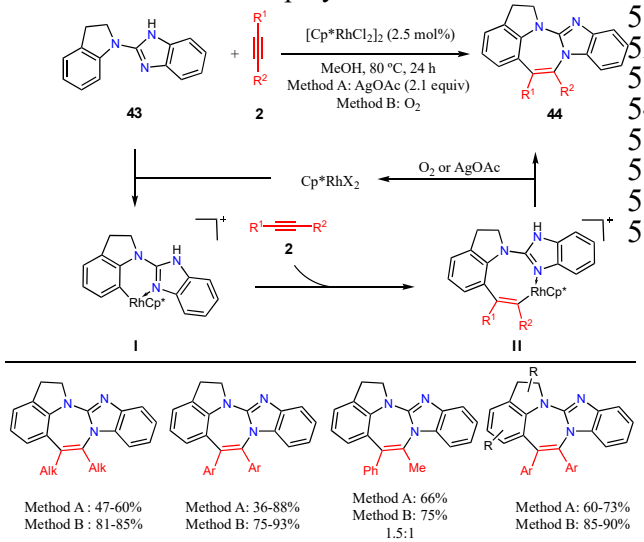
1,3-Benzodiazepines have been synthesized under Rh catalysis using nitrogenated substrates bearing X-Type (ureas)[54] and L-Type (guanidines)[55] DGs *via* (5+2) annulations (Figure 7).

In 2015, Zhou, Yang and co-workers reported a Rh-catalyzed (5+2) heteroannulation of *N*-methoxycarbamoyl indolines **41** and aryl alkynes **2** to give 1,3-benzodiazepines **42** (Scheme 16).[54] The proposed mechanism for this transformation involves the coordination of the *N*-methoxy urea DG to promote the *o*-C-H activation (*via* CMD) with the generation of the six-membered rhodacycle **I**. Coordination and insertion of alkyne into Rh-C bond affords the eight-membered rhodacycle **II** that, after reductive elimination, renders the *N*-methoxy 1,3-benzodiazepine **III**. Oxidative addition of Rh(I) species to this *N*-methoxy derivative regenerates the Rh(III) active catalyst and releases the final 1,3-benzodiazepine **42**. A variety of indolines and aryl alkynes were well tolerated whereas aliphatic alkynes failed, providing isoquinolones as the major product (4+2 annulation).



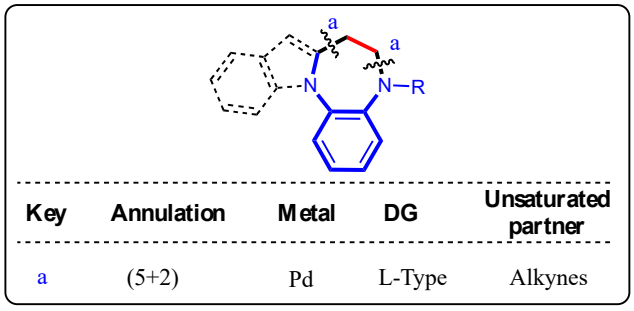
Scheme 16. Rh-catalyzed (5+2) annulation of *N*-methoxycarbamoyl indolines and aryl alkynes to 1,3-benzodiazepines.

Recently, Saá and co-workers reported the Rh-catalyzed (5+2) heteroannulation of cyclic arylguanidines **43** and alkynes **2** to give 1,3-benzodiazepines **44** (Scheme 17).[55] The use of O_2 (method B) as the sole oxidant in place of typical metal oxidants, like AgOAc (method A), clearly improves the efficiency of the oxidative annulation. The striking mechanism for this (5+2) annulation was supported by DFT calculations. When AgOAc was used, the C-H bond activation follows a classic CMD path (energetically favored) to give the six-membered rhodacycle **I** whereas, in the case of O_2, a S_EAr path is favored. Coordination and 1,2- migratory insertion of alkyne into Rh-C bond affords the eight-membered rhodacycle **II**. Curiously, the typical reductive elimination step was higher in energy than the decoordination of the benzimidazole moiety and subsequent S_N2 attack to the cationic Rh species that releases the 1,3-benzodiazepine **44**. Exergonic deprotonation and reoxidation of Rh(I) to Rh(III) was more favorable for O_2 as compared to AgOAc. A variety of electronically substituted indolines as well as both aromatic and aliphatic alkynes gave good to excellent yields of 1,3-benzodiazepines under the two oxidative conditions employed.



Scheme 17. Rh-catalyzed (5+2) annulation of cyclic arylguanidines and alkynes to 1,3-benzodiazepines.

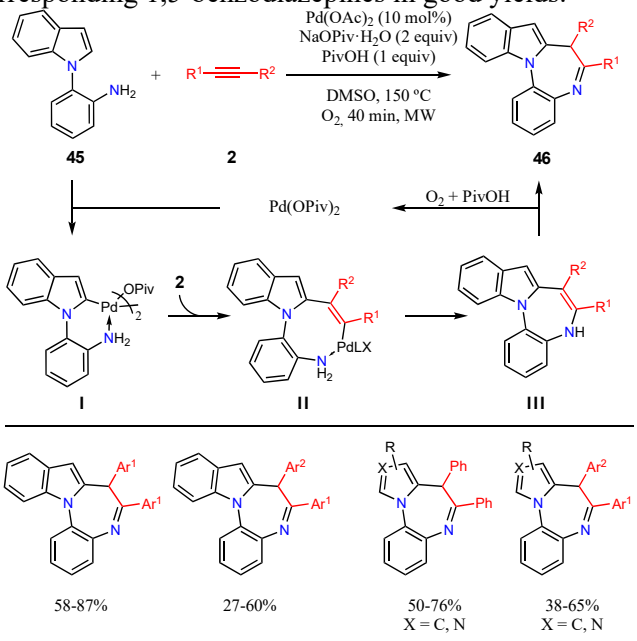
3.3 1,5-Benzodiazepines



Key	Annulation	Metal	DG	Unsaturated partner
a	(5+2)	Pd	L-Type	Alkynes

Figure 8. 1,5-Benzodiazepine disconnection

In 2017, Sun and co-workers reported the Pd-catalyzed (5+2) annulation of *o*-indoloanilines **45** and alkynes **2** to yield 1,5-benzodiazepines **46** (Scheme 18).[56] The authors propose a mechanism for this annulation similar to the one made by Luan for the case of *o*-arylanilines.[37] It is initiated with an aniline-assisted (L-type DG) C-H bond activation (*via* CMD) of the 2H-indole to form the dimeric six-membered palladacycle **I**. This dimeric complex is broken in the presence of the alkyne to form the coordinated species that undergoes 1,2-migratory insertion into the C-Pd bond to give an eight-membered palladacycle **II**. Subsequent C-N reductive elimination delivers the enamine 1,5-benzodiazepine **III** and concomitantly regenerates the Pd(II) to restart the catalytic cycle. Finally, tautomerization of the enamine to the thermodynamically more stable imine leads to the final 1,5-benzodiazepine **46**. Other *o*-heteroarylanilines like *o*-pyrroloanilines and *o*-imidazoloanilines led to the corresponding 1,5-benzodiazepines in moderate to good yields. Both electron-rich and electron-poor indole rings and aromatic alkynes afford the corresponding 1,5-benzodiazepines in good yields.



Scheme 18. Pd-catalyzed (5+2) annulation of *o*-indoloanilines and alkynes to 1,5-benzodiazepines.

3.4 2,3-Benzodiazepines

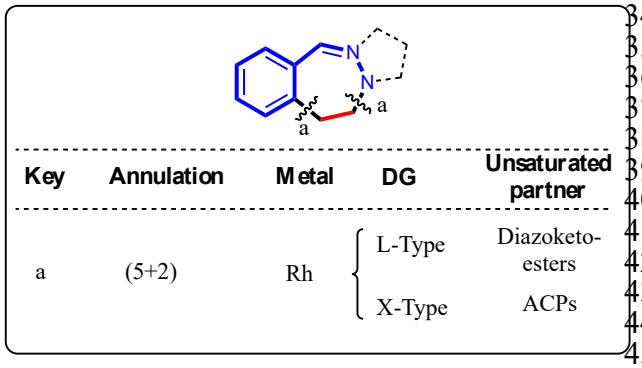
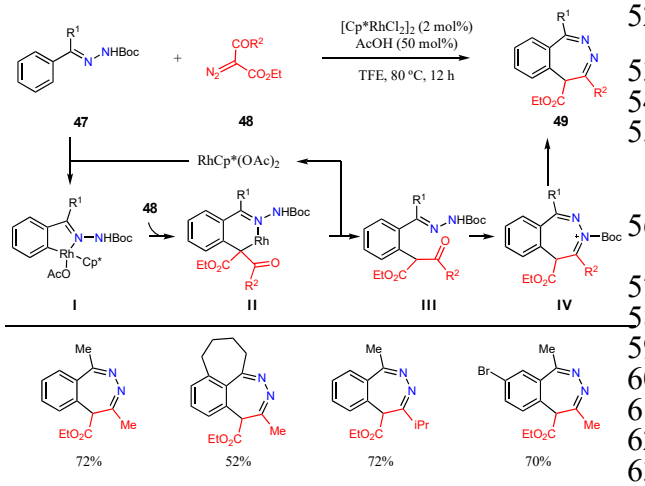


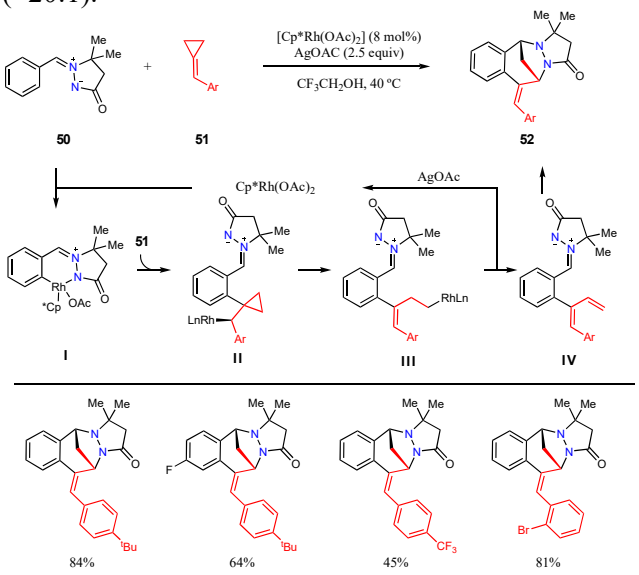
Figure 9. 2,3-Benzodiazepines disconnection

In 2017, Zhu and co-workers reported the Rh-catalyzed (5+2) heteroannulation between *N*-Boc hydrazones **47** and diazoketoesters **48** to 2,3-benzadiazepines **49** (Scheme 19).[57] As related antecedents, the proposed mechanism involves the initial formation of the five-membered rhodacycle **I** through the coordination of the *N*-Boc hydrazone to activate the *o*-C-H bond (*via* CMD). Then, coordination of the carbene would afford a Rh-carbene that undergoes a 1,1-migratory insertion to afford the six-membered rhodacycle **II**. Subsequent protonolysis of the C-Rh bond releases the transient ketone **III** and regenerates the active catalyst. Finally, a sequence involving intramolecular C-N cyclization, N-H deprotonation leading to the C=N double bond (**IV**) and *N*-Boc cleavage delivers the final product **49**. The reaction tolerated electron-rich and electron-poor substituents on the aryl ring of the *N*-Boc hydrazone, as well as alkyl substituents both on the benzaldimine and on the diazoketoester.



Scheme 19. Rh-catalyzed (5+2) annulation of *N*-Boc hydrazones and diazoketoesters to 2,3-benzodiazepines.

In 2018, Bai, Li and co-workers reported the Rh-catalyzed (5+2) heteroannulation of azomethine imines **50** and alkylidenecyclopropanes **51** (ACPs) to bicyclic 2,3-benzodiazepines **52** (Scheme 20).[58] The proposed mechanism involves the initial formation of the six-membered rhodacycle **I** through the coordination of the azomethine imines to activate the *o*-C-H bond (*via* CMD). [58] The proposed mechanism involves the initial formation of the six-membered rhodacycle **I** through the coordination of the azomethine imines to activate the *o*-C-H bond (*via* CMD). Then, coordination of the ACP and subsequent regioselective 1,2-migratory insertion of the Rh-aryl bond provides the cyclopropyl Rh intermediate **II**, which undergoes a β-C elimination to afford the Rh-alkyl species **III**. Subsequent β-H elimination followed by reductive elimination affords the transient 1,3-diene **IV** with the concomitant recovery of the active Rh(III) catalyst after oxidation with AgOAc. Finally, an intramolecular (3+2) cycloaddition delivers the bicyclic 2,3-benzodiazepine **52**. Electron-rich and electron-poor substituents either on the aryl ring of the azomethine imine or on the ACP were well tolerated giving fairly good yields and diastereoselectivities (>20:1).



Scheme 20. Rh-catalyzed (5+2) heteroannulation of azomethine imines and ACP to bicyclic 2,3-benzodiazepines.

4 Summary and Outlook

Transition-metal catalyzed annulation reactions that involve the direct activation of aromatic C-H bonds are among the most elegant and environmentally friendly methods to construct azaheterocyclic compounds. Regioselectivity (ortho activation) is commonly addressed by using substrates that bear L-type and X-type DGs capable of precoordinating the metal catalyst. In this review we have described the state-of-the-art advances in the transition-metal catalyzed annulations *via* C-H bond activation to synthesize benzofused seven-membered azaheterocycles, benzazepines and benzodiazepines, whose members typically show potent and useful biological/pharmacological properties.

The difficulty to obtain seven-membered azaheterocycles using this sustainable methodology

compared to five- or six-membered analogs, and the large synthetic application of this type of compounds makes their synthetic exploration an emerging field. Indeed, it is necessary to increase the availability of seven-membered azaheterocycles in the pharma pipeline. These new synthetic methodologies open access to valuable drug-like scaffolds with many potential therapeutic targets. Future work should provide new DGs, coupling partners and mechanistic insights to expand the synthetic toolbox toward bioactive azaheterocycles. In addition, total synthesis and industrial application of selected members, e. g. 1,4-benzodiazepines, and the use of more-abundant metals than Pd and Rh as catalysts should be increasingly explored in the near future.

Acknowledgements

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