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

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Abstract. Benzazepines and benzodiazepines, benzfused seven-membered N-heterocycles, compose an important family of natural products and pharmaceuticals. Although certainly important and effective, 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 annihilations) 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 annihilations via C-H activations to benzazepines and benzodiazepines.

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 benzfused 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 benzfused 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 D1-receptor (dopamine)[5] or 5-HT1A receptor[6] (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’s disease,[8] and Lorcaserin was approved by FDA to treat obesity.[9]

Figure 1. Representative benzazepines

Benzodiazepines, dinitrogenated benzfused 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]

3. 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 alkenes,[31] has been successfully employed.

The current challenges in transition-metal-catalysis lies in developing more ecofriendly strategies to access highly valuable benzo-fused 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
2 Benzazepines via Transition-Metal Catalyzed Oxidative Annulations

2.1 1-Benzazepines

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. The C-H bond activation provide straightforward access to common cyclic scaffolds from easily available substrates. Several strategies have been reported to obtain five- and six-membered benzofused azaheterocycles via transition-metal catalyzed C-H bond activation, 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 heterocycle and number of atoms involved in the heterocycle and number of atoms involved in the annulation reactions via metal-catalyzed C-H bond activation provide straightforward access to common cyclic scaffolds from easily available substrates.

In 2015, Luan and co-workers reported a Pd-catalyzed (5+2) heteroannulation between o-arylanilines and alkynes to give 1-benzazepines. 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. This dimeric complex is broken in the presence of the alkynyl to form the coordinated species II that undergo 1,2-migratory insertion into the C-Pd bond to give an eight-membered palladacycle IV. Subsequent C-N reductive elimination delivers the enamine dibenzo[b,d]azepine 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. 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 diastereoselectivities were obtained. Furthermore, many type substrate, can react with two equivalents of alkynes to give 1-benzazepines in a formal (3+2+2) cycloadition (Scheme 1). The authors suggested a mechanism which starts with the ligand exchange to give I. 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, which subsequently underwent reductive elimination to yield the 1-benzazepine. 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.

In 2013, they probed that isatins, a cyclic aniline, can react with two equivalents of alkynes to give 1-benzazepines in a formal (3+2+2) cycloadition (Scheme 1). The authors suggested a mechanism which starts with the ligand exchange to give I. 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, which subsequently underwent reductive elimination to yield the 1-benzazepine. 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.

Figure 3. 1-Benzazepine disconnections

<table>
<thead>
<tr>
<th>Key</th>
<th>Annulation</th>
<th>Metal</th>
<th>DG</th>
<th>Unsaturated partner</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>(3+2+2)</td>
<td>Pd</td>
<td>X-Type</td>
<td>Alkynes</td>
</tr>
<tr>
<td>b</td>
<td>(5+2)</td>
<td>Pd</td>
<td>X-Type</td>
<td>1,3-dienes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>X-Type</td>
<td>Allenes</td>
</tr>
<tr>
<td>c</td>
<td>(6+1)</td>
<td>Rh</td>
<td>L-Type</td>
<td>Allyl carbonates</td>
</tr>
</tbody>
</table>

Scheme 1. Pd-catalyzed (3+2+2) annulation of isatins and alkynes to 1-benzazepines.
Scheme 2. Pd-catalyzed (5+2) annulation of o-arylanilides and alkynes to dibenzo[b,d]azepines.

In 2010, You and co-workers described an Ir-catalyzed (5+2) heteroannulation of o-arylanilines and allyl carbonates 12 and allyl carbonates 13 to 1-benzazepines 14 in a tandem allylic vinylation/allylic amination reaction (Scheme 5). 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.
2-Benzazepines have been synthesized under Rh catalysis using nitrogenated substrates bearing either X-Type (amines) DGs via (4+3) annulations or L-type (aldehydes and ketones) DGs via intramolecular cyclizations. A Pd-catalyzed (6+1) carbonylation assisted by a bidentate LX-type DG rendered 2-benzazepinones (Figure 4).

In 2013, Glorius and co-workers reported a formal Rh-catalyzed (4+3) annulation of benzamides to benzazepinones (Scheme 7). 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 α-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.

2.2 2-Benzazepines

Scheme 6. Rh-catalyzed (6+1) annulation of N-cyclopropylanilides and CO (carbonylative C-C activation) to 1-benzazepine-5-ones. 25

In 2018, Bower and co-workers reported a Rh-catalyzed (6+1) annulation of N-cyclopropylanilides 15 and CO (carbonylative C-C activation) to benzazepin-5-ones 16 (Scheme 6). The carbonylative cyclization involves a tandem C-C 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 elimination and protodemetalation, releases the benzazepin-5-one. Electron-poor and electron-rich aryl and heteroaromatic rings were well tolerated.

Scheme 5. Ir-catalyzed (5+2) annulation of α-alkenylanilines and allyl carbonates to 1-benzazepines. 3

Figure 4. 2-Benzazepine disconnections
In 2013, Cui and co-workers reported the Rh-catalyzed (4+3) annulation of benzamides 20 and vinylcarbenoids 21 (Scheme 8). 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 N₂ 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.

\[
\begin{align*}
\text{C-H bond activation} & \rightarrow \text{N₂ extrusion} \\
& \rightarrow \text{Rh-carbene} \rightarrow \text{1,1-migratory insertion} \\
& \rightarrow \text{eight-membered rhodacycle III} \\
& \rightarrow \text{reductive elimination} \rightarrow \text{2-benzazepinone 22}
\end{align*}
\]

**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). 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). 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 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

Figure 5. 3-Benzazepine disconnections

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-PdX2L2). 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. The 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 O2. 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.
In 2015, Li and co-workers reported a tandem Rh-catalyzed (3+2)/(5+2) heteroaanulation 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 alkyn 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 alkyn 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 alkyn. When aromatic alkynes are used, cleavage of the C-Rh bond with the aid of Cu(OAc)₂ through hydration with H₂O (or ROH) affords the benzylic alcohol and regenerate the active Rh(II) 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.

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 following by regioselective alkyn insertion to give a vinylrhodium intermediate I. Then, 1,4-rearrangement (C-H activation) occurs to give an aryllrhodium species II that undergo a conjugated addition to the enoate to yield 3-benzazepine intermediate III. Halogenated, electron-rich and electron-poor arylboronic acids were well tolerated giving fairly good yields of the corresponding 3-benzazepines.

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

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

Scheme 14. Rh-catalyzed (5+2) annulation of yne-enoate derivatives and arylboronic acids to 3-benzazepines.
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 and Zhang/Fan reported the Rh-catalyzed (4+3) heteroannulation of N-arylpyrazolidinones and propargyl derivatives to 1,2-benzodiazepines (Scheme 15). The proposed mechanism involves the initial formation of the five-membered rhodacycle through the coordination of the pyrazolidinone to activate the $\sigma$-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. Finally, protonolysis of the C-Rh bond followed by nucleophilic substitution delivers the 1,2-benzazepine with regeneration of the active catalyst. Electron-rich and electron-poor substituents on the aryl ring of the pyrazolidinone were well-tolerated as well as 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.

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

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

**Figure 7.** 1,3-Benzodiazepine disconnections
Scheme 16. Rh-catalyzed (5+2) annulation of \(\text{N}^{-1}\) methoxy carbamoyl 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 SEAr 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 \(S_e,2\) 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

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 \(o\)-imidazoanilines 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.
3.4 2,3-Benzodiazepines

In 2017, Zhu and co-workers reported the Rh catalyzed (5+2) heteroannulation between N-Boc hydrazones 47 and diazoketoesters 48 to 2,3-benzodiazepines 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 benzalimine 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 alkylidene cyclopropanes 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...
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15. however simple anilide derivatives gave 87


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