



Review

Palladium-Catalyzed Benzodiazepines Synthesis

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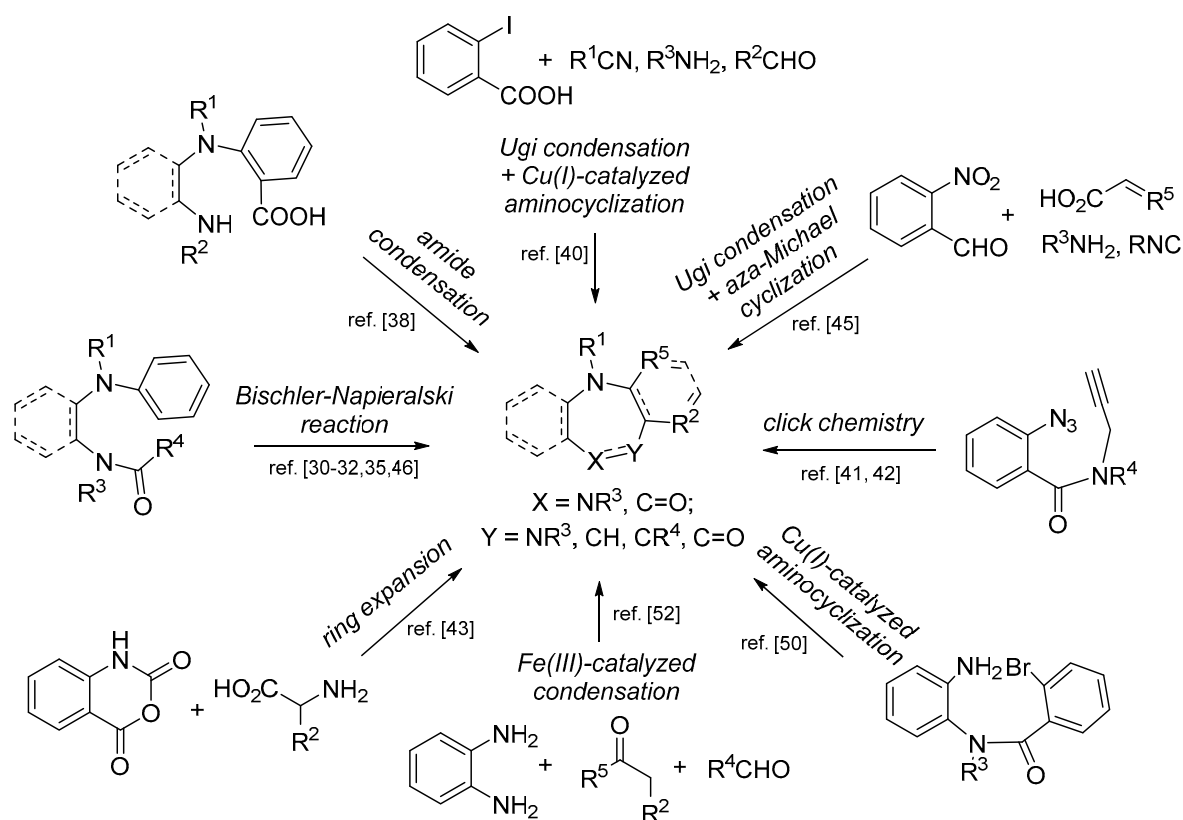
Abstract: This review is focused on palladium-catalyzed reactions as efficient strategies aimed at the synthesis of different classes of benzodiazepines. Several reaction typologies are reported including hydroamination, amination, C–H arylation, N-arylation, and the Buchwald–Hartwig reaction, depending on the different substrates identified as halogenated starting materials (activated substrates) or unactivated unsaturated systems, which then exploit Pd(0)- or Pd(II)-catalytic species. In particular, the use of the domino reactions, as intra- or intermolecular processes, are reported as an efficient and eco-compatible tool to obtain differently functionalized benzodiazepines. Different domino reaction typologies are the carboamination, aminoarylation, aminoacethoxylation, aminohalogenation, and aminoazidation.

Keywords: Pd-catalysis; benzodiazepine; cyclization; domino process; intramolecular Buchwald–Hartwig; N-arylation; C–H activation; C–H functionalization

1. Introduction

Benzodiazepines play an important role in medicinal chemistry due to a wide range of pharmaceutical applications [1–7]. Much of the biological activities are concerning the action in the central nervous system. This includes anxiolytic, anticonvulsant, antiepileptic, muscle relaxant, antidepressant, sedative, and hypnotic activities [8–16], mainly ascribed to the 1,4-benzodiazepines but also to the 1,5-benzodiazepines. Furthermore, the application of benzodiazepines has been extended to the treatment of bipolar disorder [17,18] and chronic back pain [19] and several studies make them potential candidates for use in anti-cancer [20–24], anti-infective [20,21], and anti-HIV [25,26] drugs. Moreover, particularly 1,4-benzodiazepines are present in many natural alkaloids [27–29]. Even though the most significant class of these structures is the 1,4-benzodiazepine, different isomers exist and the classification is dependent on the mutual position of the two nitrogen atoms characterizing the seven-membered ring.

Due to the significance of benzodiazepines, various methods for the synthesis of these classes of compounds have been reported. The existing routes rely on the preparation of amide [30–35] or lactam [36–39] intermediates providing the products through multi-step reactions. Further, Ugi condensation [40], Friedel–Crafts reaction [34], click chemistry [41,42], ring expansion reactions [43], and aza-Michael cyclization are reported [44,45]. The commonly employed methods for the 1,5-benzodiazepines involve the reactions of *o*-phenylenediamines with 1,3-dicarbonyl compounds or α,β unsaturated carbonyl compounds [46]. In recent years, the development of a new methodology, using transition metal catalysis, has broadened the range of synthetic pathways to obtain benzodiazepine derivatives (Scheme 1) [47–53]. The literature reports few reviews regarding the synthesis of benzodiazepines [54–58].



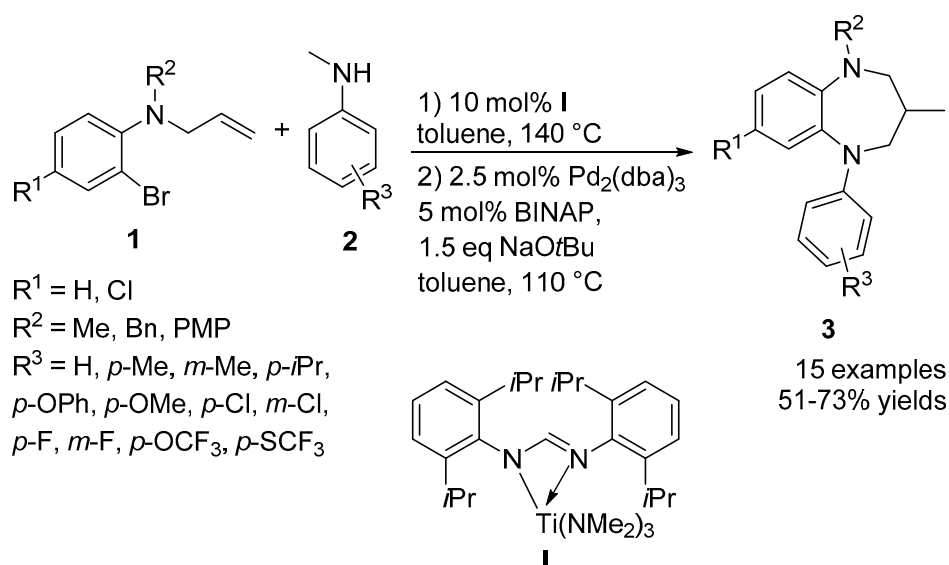
Scheme 1. An overview of the not-Pd-catalyzed synthetic routes to access benzodiazepines.

The present review collects the palladium-catalyzed synthetic strategies applied to the synthesis of benzodiazepine derivatives, exploiting innovative bond formation. The review is organized into subsections on the basis of the different types of benzodiazepines prepared: 1,5-benzodiazepines, 1,4-benzodiazepines, 1,3-benzodiazepines, 2,3-benzodiazepines, and 2,4-benzodiazepines.

2. Synthesis of Benzodiazepines

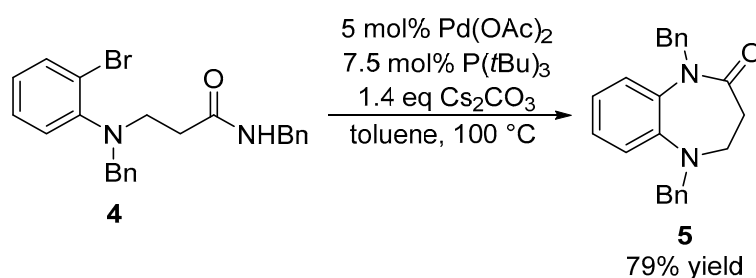
2.1. 1,5-Benzodiazepines

There are only few examples of Pd-catalyzed protocol for the synthesis of 1,5-benzodiazepines. The most recent publication reported a combined one-pot procedure involving hydroaminoalkylation of *N*-allyl-2-bromoanilines **1** and *N*-methyl anilines **2** followed by an intramolecular Buchwald–Hartwig reaction (Scheme 2) [59]. Indeed, the first step of hydroaminoalkylation was performed under the titanium catalyst **I**, taking place under selective C–H activation in the α -position to the nitrogen atom, and heating the reaction mixture in toluene, at 140 °C for 24 h. The subsequent cyclization was achieved by adding the reagents necessary for the Buchwald reaction and heating at 110 °C for an additional 24 h, providing the 1,5-benzodiazepines **3**. The sensitivity of the titanium catalyst against the alcohols and carbonyl compounds hampered the addition of the two catalysts at the same time.



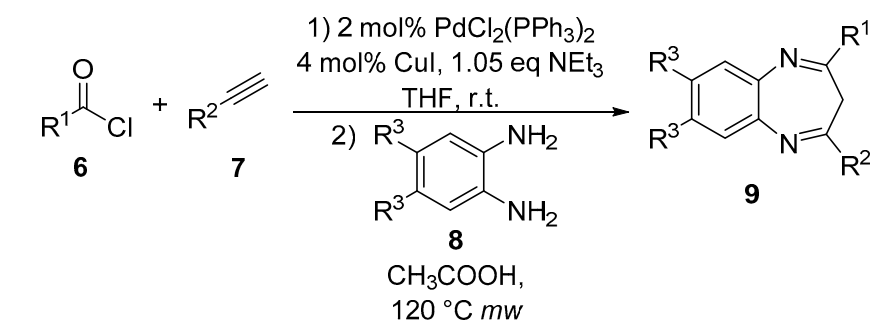
Scheme 2. One-pot synthesis of 1,5-Benzodiazepines **3**.

Buchwald–Hartwig strategy was applied also in a study related to the effect of Pd-ligand on the intramolecular amidation, for the formation of a medium-sized ring. 1,5-Dibenzyl-tetrahydro-1,5-benzodiazepin-2-one **5** was achieved in a satisfying yield, starting from the corresponding benzylamide **4** and by using $\text{P}(t\text{Bu})_3$ as the ligand. Compared with other ligands, the steric hindrance of the $\text{P}(t\text{Bu})_3$ was the critical factor to improve the formation of the palladacycle able to provide the product **5** in 79% yield. (Scheme 3) [60].



Scheme 3. Synthesis of 1,5-dibenzyl-1,3,4,5-tetrahydro-1,5-benzodiazepin-2-one **5** in the presence of $\text{P}(t\text{Bu})_3$ as the ligand.

In 2008, 1,5-benzodiazepines **9** were obtained through a consecutive one-pot, three-component synthesis, starting from acyl chlorides and terminal alkynes through a Pd-catalyzed Sonogashira coupling (Scheme 4) [61]. For the first step, the choice of THF as the solvent was beneficial for reducing the amount of base employed. The obtained alkynones reacted with the binucleophilic benzene-1,2-diamines **8**, added to the reaction mixture in acetic acid. For the cyclocondensation step, the use of microwave heating decreased the reaction times from three days to one hour, affording substituted benzodiazepines **9**.



R¹ = 4-OMe(C₆H₄), 4-Me(C₆H₄), 4-NO₂(C₆H₄), 4-Cl(C₆H₄),

2-thienyl, CH(CH₂)₂

R² = Ph, 4-NO₂(C₆H₄), 4-CN(C₆H₄), 4-OMe(C₆H₄),

4-CO₂Me(C₆H₄), 4-*t*Bu(C₆H₄), 2-pyridyl, *n*Bu

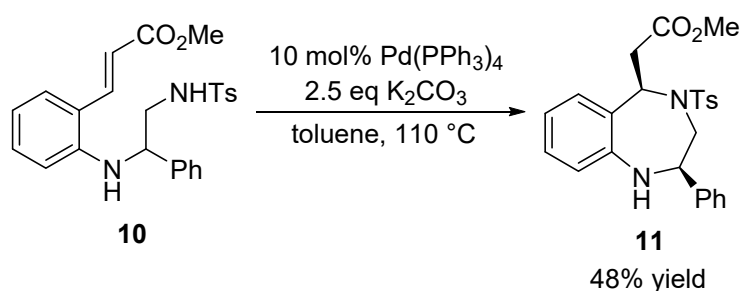
R³ = H, Cl

15 examples
40-88% yields

Scheme 4. One-pot Pd-catalyzed Sonogashira reaction, affording 1,5-benzodiazepines **9**.

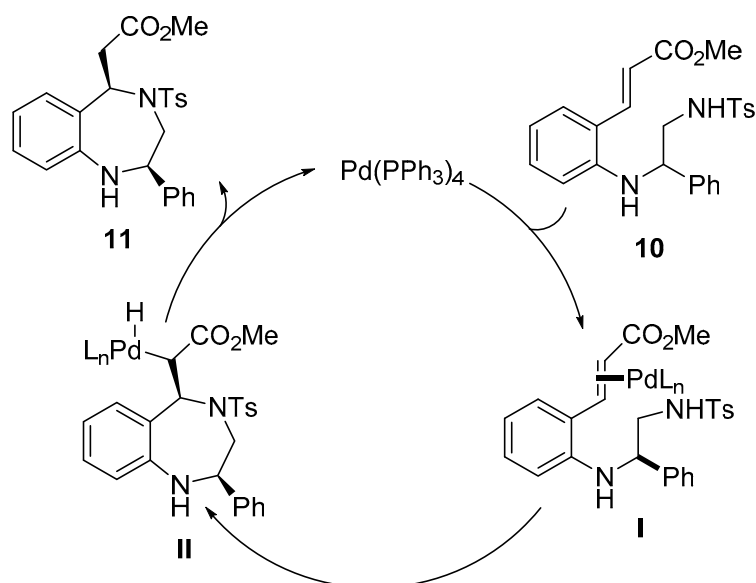
2.2. 1,4-Benzodiazepines

The most common class of these structures is the 1,4-benzodiazepines and several different types of palladium-catalyzed reaction typologies were applied. A simple and efficient synthetic route to 2,3,4,5-tetrahydrobenzodiazepine bearing easily functionalizable appendages was developed by Ghorai et al. through a palladium-catalyzed aza-Michael reaction (Scheme 5) [62]. The reaction was performed in the presence of 10 mol% of Pd(PPh₃)₄ as the catalyst and 2.5 Equivalents of K₂CO₃ in toluene at 110 °C, providing the desired tetrahydrobenzodiazepine **11** as a single diastereomer. The relative *cis*-stereochemistry was unambiguously confirmed by spectroscopic analysis.



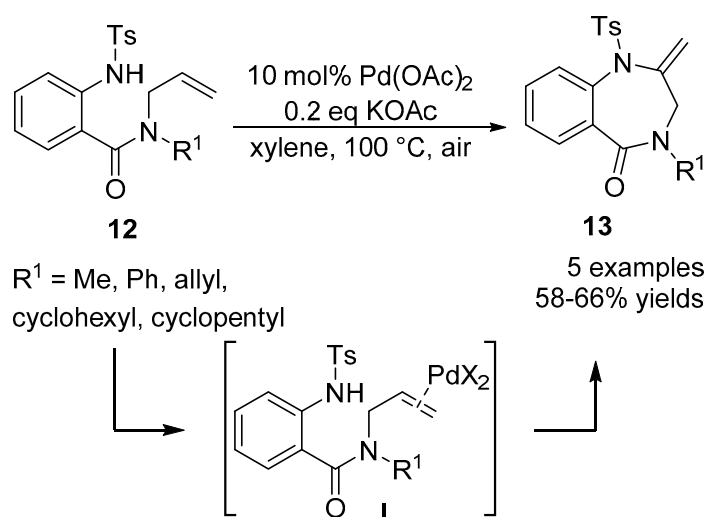
Scheme 5. Synthesis of tetrahydrobenzodiazepine **11** via aza-Michael addition.

A proposed mechanism included the addition of the *N*-tosyl group to the Pd-coordinated olefinic moiety to generate the intermediate **II**, which on subsequent reductive elimination provided the tetrahydrobenzodiazepine **11** and the regeneration of the Pd(0) catalyst (Scheme 6).



Scheme 6. Proposed mechanism for the synthesis of tetrahydrobenzodiazepine **11**.

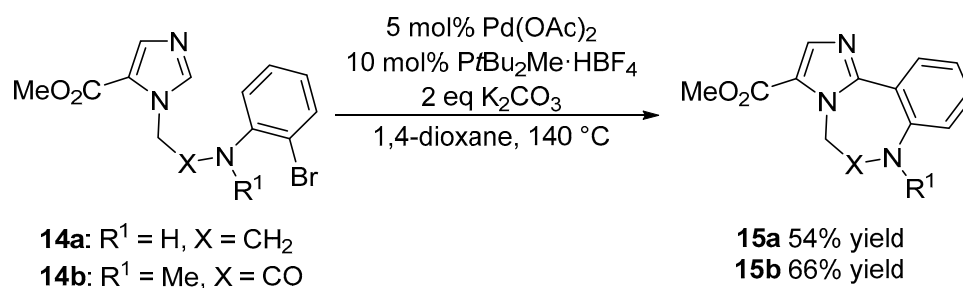
Exploiting as the catalyst the Pd(II) species, the intramolecular amination of tosylated *N*-allyl-anthranilamides **12** was reported for the synthesis of 1,4-benzodiazepin-5-ones **13** (Scheme 7) [63]. The seven-membered ring was obtained through a 7-*exo*-dig cyclization in a complete regioselective pathway by choosing carefully the appropriate reaction conditions. In particular, the presence of the base was essential to obtain the result as well as the presence of the tosyl substituent on the amino group, no product was obtained with a different protecting group. Notably, the presence of air was enough for the reoxidation of the Pd(0) species to the active Pd(II). A plausible mechanism indicated the formation of the common π -olefin-Pd intermediate **I**, which after C–N bond formation and reductive elimination provided the 1,4-benzodiazepin-5-ones **13**.



Scheme 7. Regioselective synthesis of 1,4-benzodiazepin-5-ones **13**.

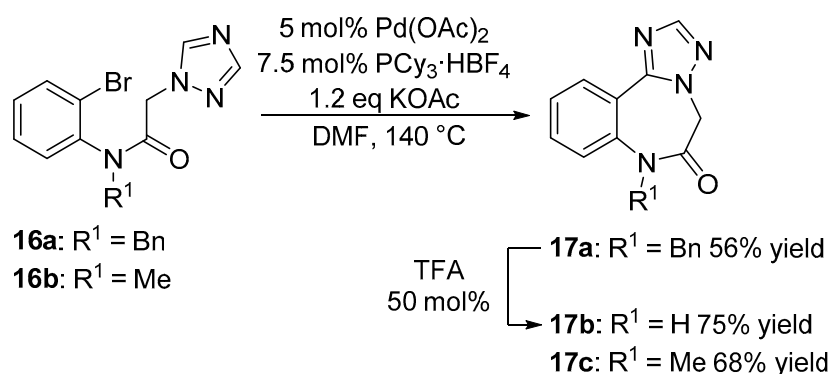
The intramolecular direct C–H arylation reaction was applied for the synthesis of tricyclic benzoimidazodiazepine derivatives **15**, starting from the imidazole derivatives **14** (Scheme 8) [64]. The reaction was performed in the presence of 5 mol % of Pd(OAc)_2 , and the yield was improved by utilizing K_2CO_3 as the base. After scanning a range of phosphine ligands, the electron-rich

$PtBu_2Me \cdot HBF_4$ ligand was optimal, whereas the sterically hindered $PtBu_3 \cdot HBF_4$ and the mono- and diphosphines $P(4-FC_6H_4)$ and 1,4-bis(diphenylphosphino) butane (dppb) gave poorer results.



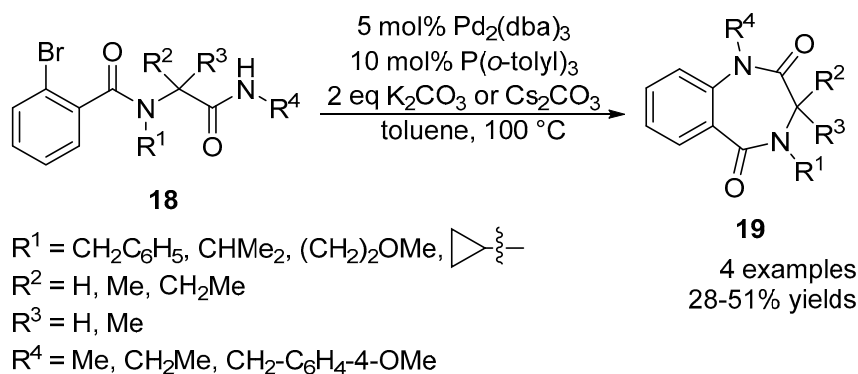
Scheme 8. Synthesis of benzoimidazodiazepines **15** through C–H arylation.

The same intramolecular direct C–H arylation of a heterocycle was exploited as an unprecedented strategy and step economy to access the polycyclic benzotriazolodiazepinones **17**, starting from the *o*-bromo-anilide derivatives **16** (Scheme 9) [65]. The reaction proceeded with 5 mol % of catalyst, 7.5 mol % of the $PCy_3 \cdot HBF_4$ ligand, and the use of a mild base, and in contrast to cross-coupling-based strategies, involved the direct activation of the otherwise inert C–H bonds. These new compounds were identified as a low molecular weight new heat shock protein 90 (Hsp90), inhibitors with nanomolar inhibitory activity.



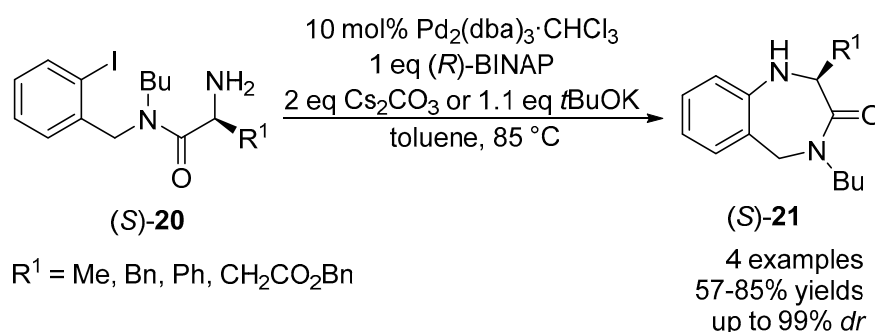
Scheme 9. Synthesis of benzotriazolodiazepinones **17** through C–H arylation.

The most applied strategy to obtain 1,4-benzodiazepines through Pd-catalyzed reactions rely on the intramolecular Buchwald–Hartwig reaction. The synthesis of substituted 1,4-benzodiazepin-2,5-diones **19** was developed as a general procedure for the synthesis of heterocycle compounds from the easily prepared precursors **18**, obtained in turn by the Ugi four-component reaction (Scheme 10) [66]. For the formation of the precursors **18**, different substituents on isocyanides as well as aldehydes or ketones were tolerated. The ring-closing reaction was performed by a classical intramolecular *N*-aryl amidation of secondary amides catalyzed by a 5 mol % $Pd_2(dba)_3$ and 10 mol % $P(o-tolyl)_3$ ligand system, under basic conditions.



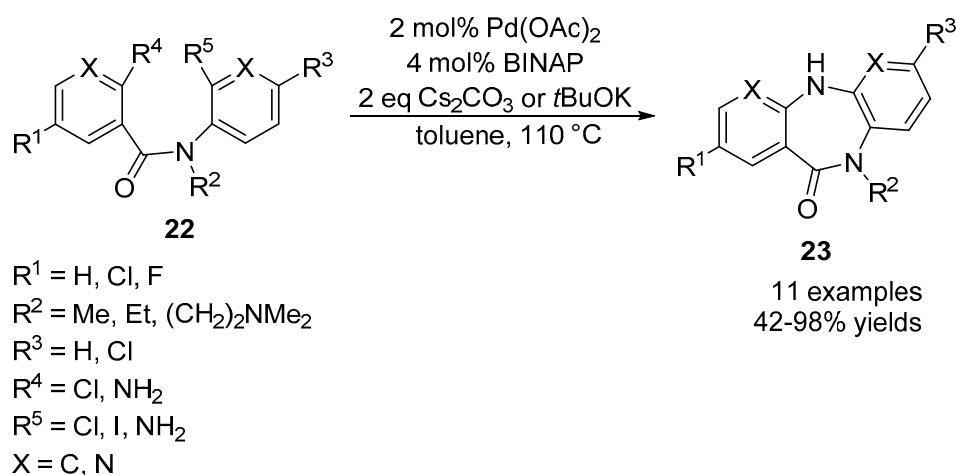
Scheme 10. Buchwald–Hartwig reaction for the synthesis of substituted benzodiazepin-2,5-diones **19**.

Stereospecific intramolecular palladium-catalyzed *N*-arylation of the (*S*)-amides **20** led to the formation of the optically active 1,2,4,5-tetrahydro-1,4-benzodiazepin-3(*3H*)-ones **21** (Scheme 11) [67]. Screening different ligands and bases, the product formation was succeeded using BINAP as the bidentate phosphine ligand and *t*BuOK or Cs₂CO₃ as a base, dependent on the substrate used, with fair yields and excellent *ee*. The use of the chelating bis(phosphine) minimized or entirely suppressed the carbon-2 racemization which occurred when a mono(phosphine) ligand was used.



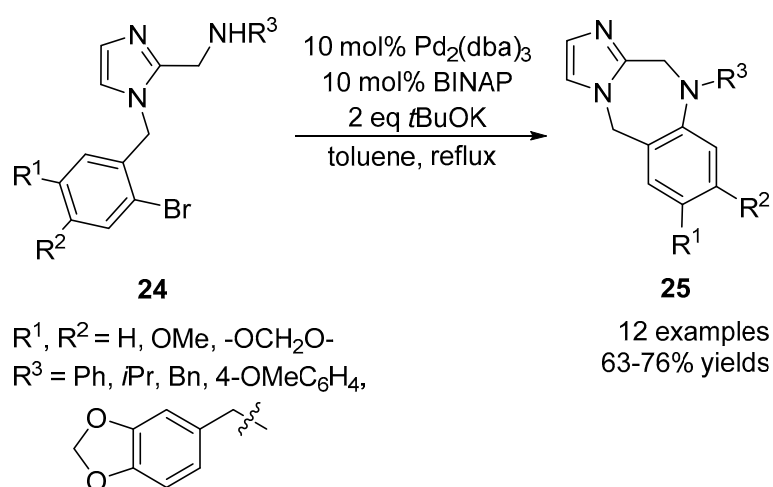
Scheme 11. Enantiopure synthesis of 1,2,4,5-tetrahydro-1,4-benzodiazepin-3-(*3H*)-ones **21**.

A novel approach to tricyclic dibenzo[*b,e*][1,4]diazepinones and pyridobenzodiazepinones **23** was achieved in 2005 by an intramolecular Buchwald–Hartwig reaction between an (hetero)aryl halide and an aromatic amino group on the substrates **22** (Scheme 12) [68]. The catalytic system consisted of 2 mol % Pd(OAc)₂ and 4 mol % BINAP in the presence of 2 Equations of Cs₂CO₃ in toluene at 100 °C for the synthesis of dibenzo[*b,e*][1,4]diazepinones, whereas in the case of pyridobenzodiazepinones, the use of 2 Equations of *t*BuOK was fundamental for the cyclization. The presence of halogen atoms on the dibenzo[*b,e*][1,4]diazepinones could be important for a potential biological activity. The same intramolecular C–N bond formation was applied as the key step for the synthesis of the natural dibenzodiazepinone BU-4664L [69].



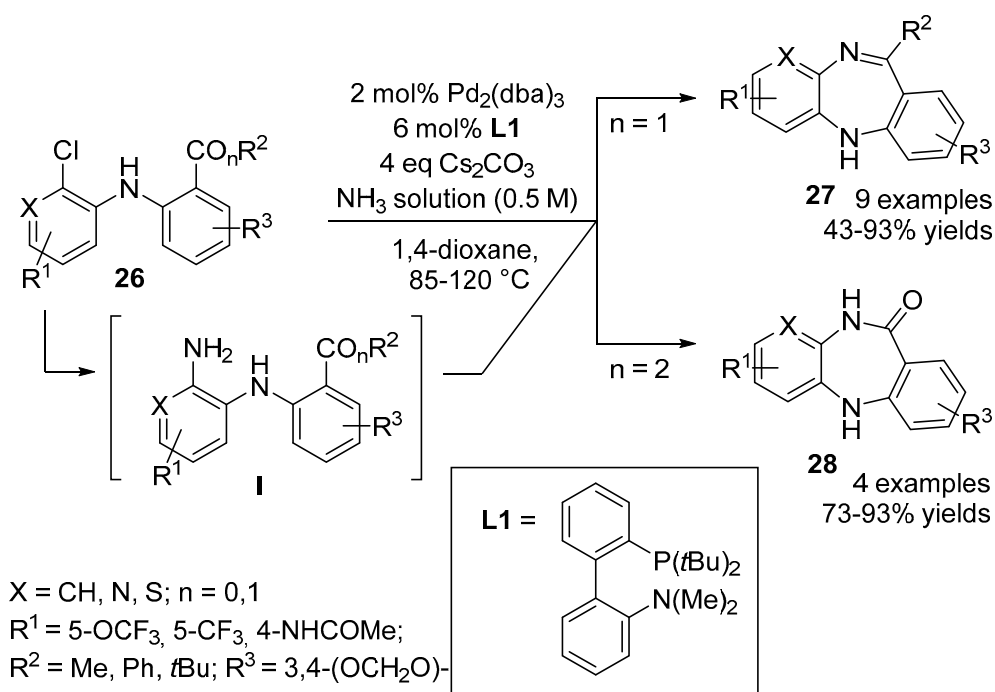
Scheme 12. Intramolecular Buchwald–Hartwig reaction to obtain dibenzodiazepines **23**.

The synthesis of imidazobenzodiazepines **25** were realized from easily available imidazo *N*-alkylated amines **24** through an intramolecular Buchwald–Hartwig cycloamination reaction (Scheme 13) [70]. For the progress of the reaction, the 10 mol % of the catalyst was optimal and the presence of a ligand (10 mol %) was mandatory. Various amines and different substituents on the substrates **24** were tolerated, providing the products in good yields. This strategy was suitable for the synthesis of imidazole-fused benzodiazepines but it could not be extended to the synthesis of pyrrole-fused benzodiazepines.



Scheme 13. Intramolecular Buchwald–Hartwig reaction for the formation of imidazobenzodiazepines **25**.

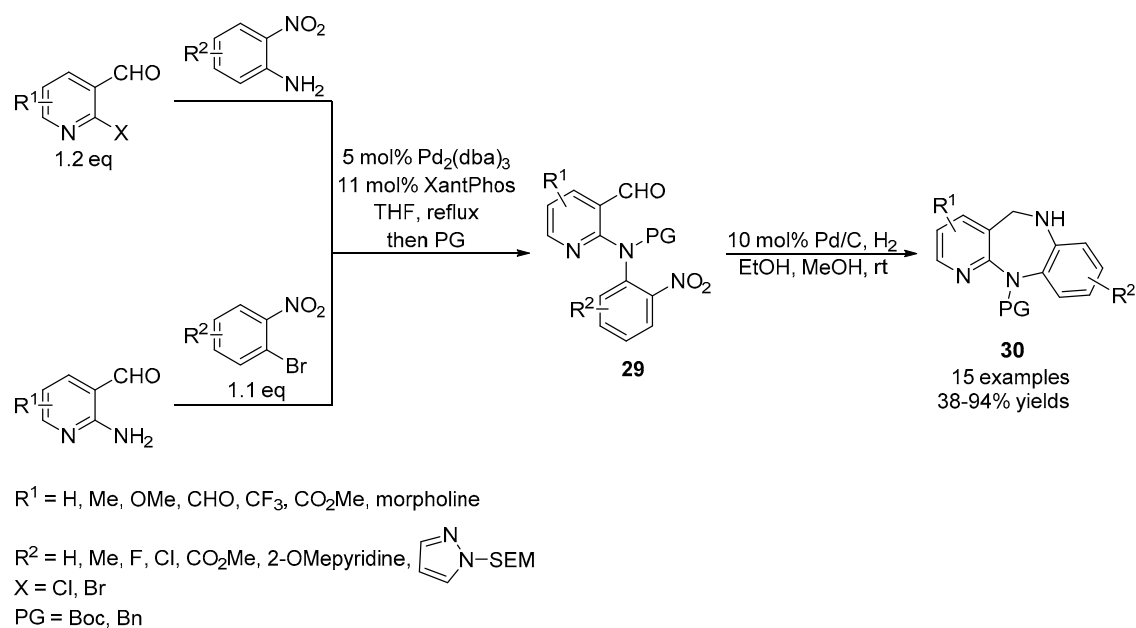
In 2011, Buchwald et al. reported a straightforward method for the synthesis of dibenzodiazepine analogues via a Pd-catalyzed *Csp*²amination between compounds **26** and ammonia, furnishing the intermediate **I**, which underwent an intramolecular condensation to form the corresponding dibenzodiazepine **27** and dibenzodiazepinone **28** in one step (Scheme 14) [71]. This was the first time that a Pd-catalyzed coupling of ammonia was described in the synthesis of complex heterocycles. The reaction proceeded in the presence of Pd₂(dba)₃ as the catalyst, **L1** as the ligand, a commercially available solution of ammonia (0.5 M in 1,4-dioxane), and Cs₂CO₃ as the base. In these reaction conditions, both electron-rich and electron-deficient substrates, such as thiols and pyridines as well as various functional groups, were well-tolerated, providing derivatives **27** and **28** in good to excellent yields.



Scheme 14. Inter-intramolecular reaction to obtain dibenzodiazepines **27** and **28**.

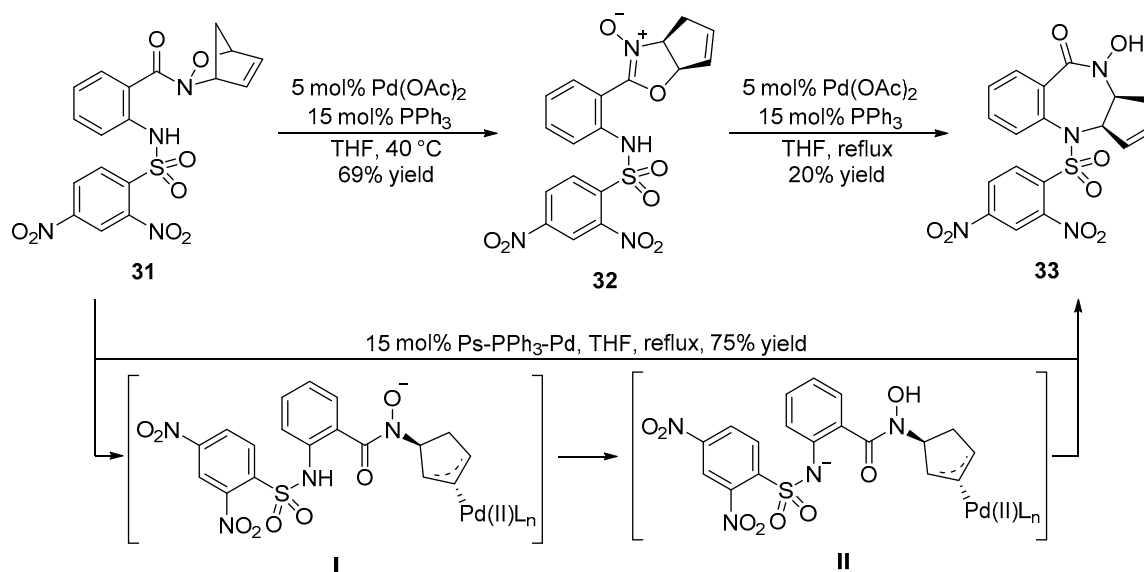
A scalable synthesis of dihydropyridobenzodiazepines **30** via a palladium-catalyzed C–N coupling and catalytic hydrogenation cascade from versatile starting materials was developed from Maddess et al. (Scheme 15) [72]. This approach overcame important drawbacks such as moderate yields associated with lactam reduction, low solubility, and potential regiochemical issues related to selective functionalization at either nitrogens of the central diazepine.

Starting from aryl- or heteroaryl-halides and anilines or heteroarylamines, through a Pd-catalyzed coupling reaction, the intermediate 2-anilino-nicotinaldehydes **29** were isolated, from which the hydrogenation and intramolecular reaction afforded the products **30**. The sequence tolerated a high degree of functional groups including electronic and steric perturbations. For substrates that contained halides, the use of platinum doped with vanadium was employed in place of Pd/C to minimize unwanted C–X reduction, which was notably more prevalent with bromides than chlorides.



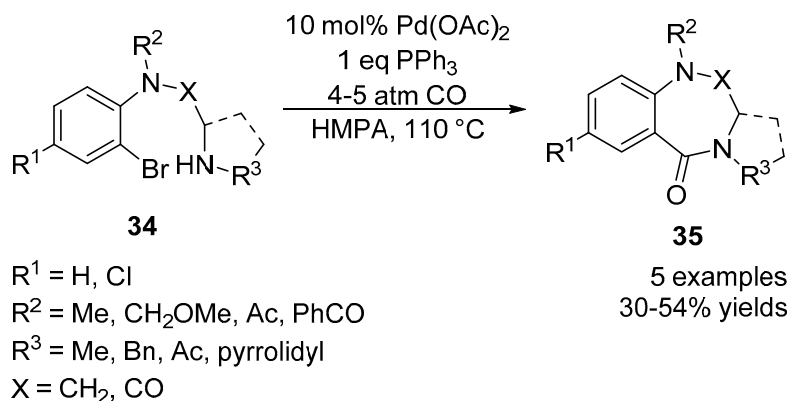
Scheme 15. Synthesis of dihydropyridobenzodiazepines **30**.

A particular synthetic strategy to provide the benzodiazepine **33** was reported exploiting an intramolecular Pd(0)-mediated ring opening of the acyl nitroso-derived cycloadduct **31** (Scheme 16) [73,74]. Initial treatment of the cycloadduct **31** with 5 mol % of Pd(OAc)₂ in the presence of 15 mol % of PPh₃ in THF at 40 °C gave the nitron **32**, which after purification and resubmission to the same catalytic system, but this time in refluxing THF, afforded the benzodiazepine **33**. Oxazoline *N*-oxides are versatile synthons and have been used in [3 + 2] cycloadditions. Different palladium systems were examined, however, the polymer-bound triphenylphosphine-Pd(0) appeared the most practical due to the ease of product isolation and increased yield. The intermediate π -allyl complex **I**, which after intramolecular proton transfer to the intermediate **II** followed by an irreversible nucleophilic attack of the sulfonamide nitrogen, was considered as a plausible mechanism for the formation of the benzodiazepine **33**, the structure of which was confirmed by X-ray analysis. Further modifications on the benzodiazepine scaffold provided compounds with antiproliferative activity.



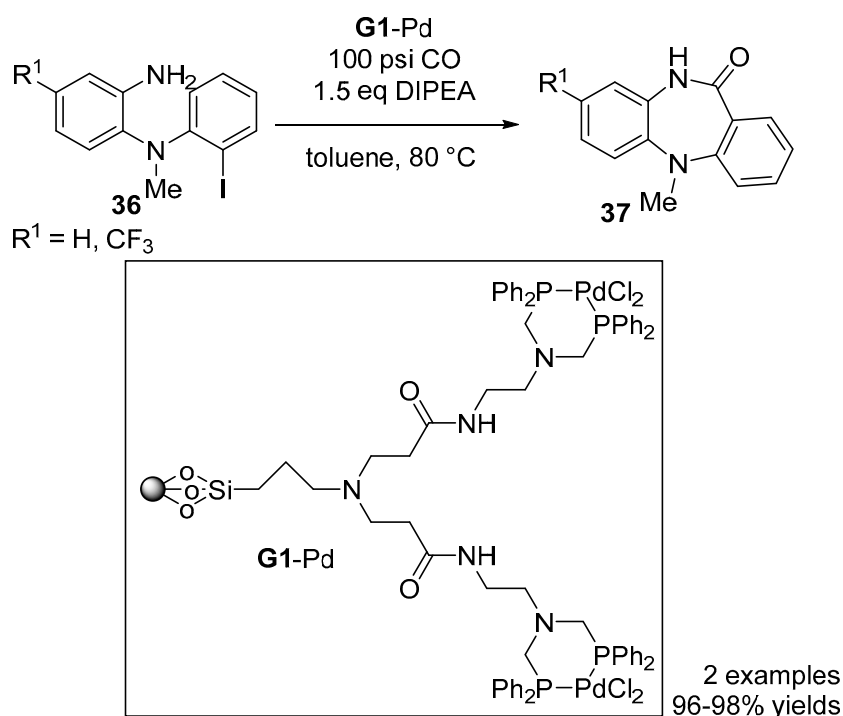
Scheme 16. Intramolecular Pd(0)-mediated ring opening of the acylnitroso-derived cycloadduct **31** to obtain benzodiazepine **33**.

The first palladium-catalyzed synthesis of diazepam, cyclopeptine, cyclophenin, and cyclophenol precursors was reported in 1982, exploiting a carbonylation reaction of *o*-bromoaniline derivatives **34**, with the formation of the 1,4-benzodiazepin-5-one skeleton **35** (Scheme 17) [75]. The reaction occurred with 10 mol % Pd(OAc)₂ and 1 mol of PPh₃ in HMPA (hexamethylphosphoramide) at 100 °C under 4–5 atm of CO. This synthetic process was applied also on the preparation of the pyrrolo[2,1-*c*][1,4]benzodiazepines [76] and the total synthesis of neothramycin, [77,78] prothracarcin, and tomaymycin [79].



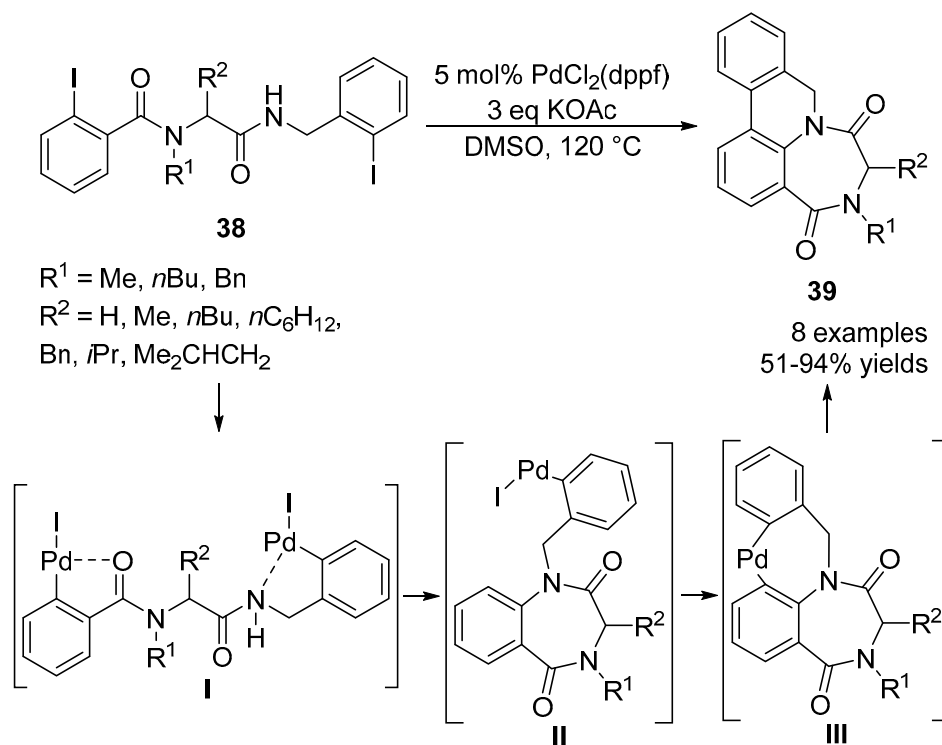
Scheme 17. Carbonylation reaction of *o*-bromoaniline derivatives **35**.

The synthesis of dibenzo[*b,e*][1,4]diazepinones **37** was also achieved via a carbonylation reaction with the recyclable palladium-complexed dendrimers on silica **G1**-Pd as the catalyst [80]. After screening different solvents and bases, toluene and DIPEA were chosen as the optimal reaction conditions. Starting from benzenediamine derivatives **36**, the carbonylation reaction was performed in the presence of a dendritic catalyst, affording the desired products in excellent yields (Scheme 18). An advantage of this method, which was also applied to the synthesis of other medium-ring heterocycles, was the recyclability of the **G1**-Pd catalyst, which was reused up to eight times with only a slight loss of activity.



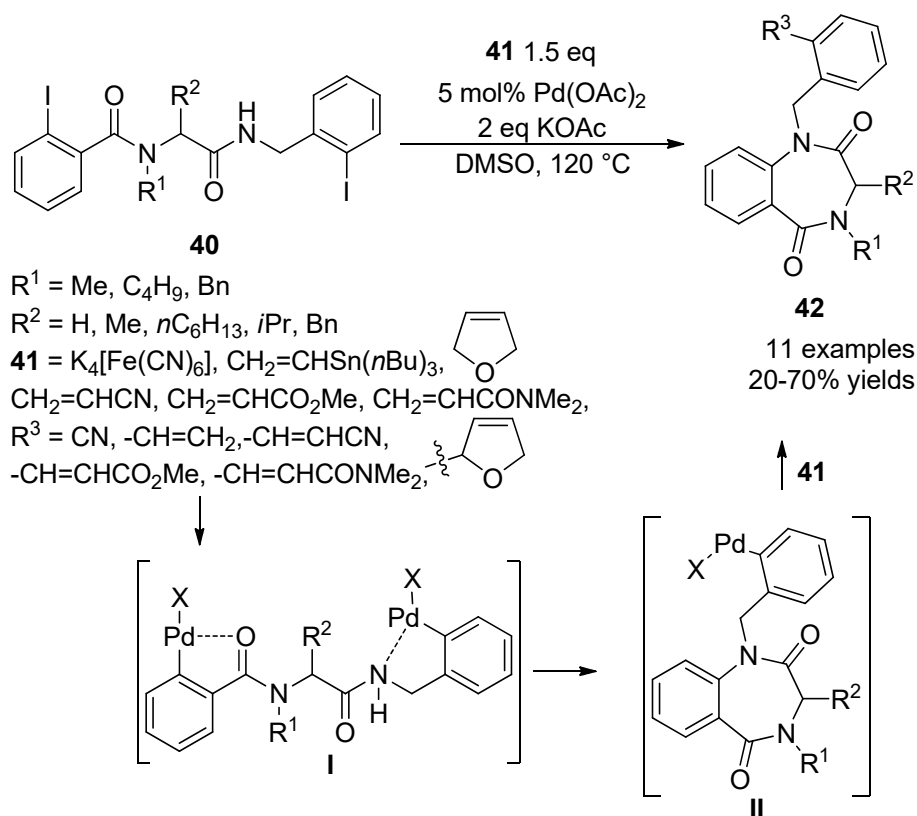
Scheme 18. Carbonylation reaction of benzendiamines **36**.

In 2003, Zhu et al. showed the first examples where an intramolecular Buchwald–Hartwig amidation was successfully applied to the synthesis of polycyclic systems containing medium-sized rings and macrocycles [81,82]. The synthetic pathway consisted on the catalytic domino process, involving an intramolecular *N*-Arylation, C–H activation, and aryl–aryl bond formation, as shown in the intermediates **I–III**. After a screening of catalysts, PdCl₂(dppf) was chosen for the simplicity of manipulation and product purification. In this way, differently substituted amides **38** provided the 1,4-benzodiazepine-2,5-dione derivatives **39** in good to excellent yields (Scheme 19). Control experiments indicated the crucial role of the bis-iodide function in the cyclization of amides **38**. The accessibility of the starting materials indicated their potentiality in the diversity-oriented synthesis of this family of compounds.



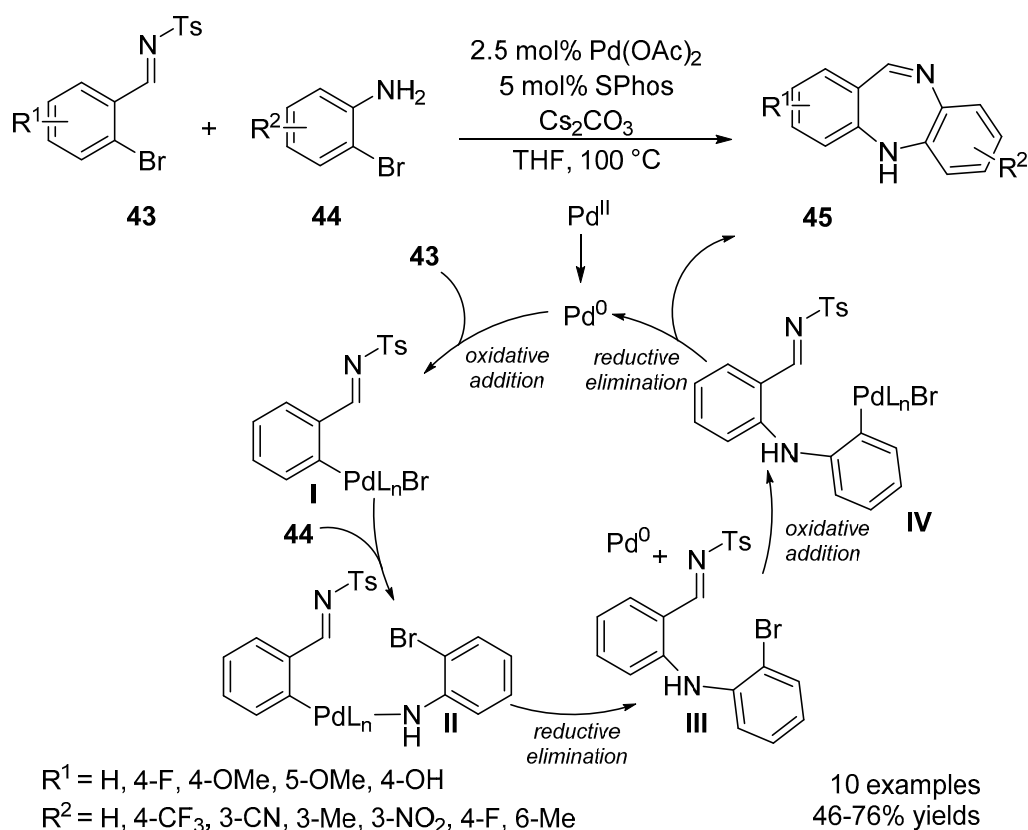
Scheme 19. N-arylation/C–H activation of amides **38**.

Later, the same group outlined that the C–H arylation could be effectively interrupted in the presence of a suitable trapping agent [83]. In this scenario, the intramolecular N-arylation should precede any intermolecular bond-forming process to avoid the formation of linear adducts. At the same time, after the formation of the benzodiazepinedione (intermediate **II**), the subsequent intermolecular bond formation with **41** must be kinetically faster than the alternative intramolecular C–H functionalization. Thus, the absence of a ligand was essential for the domino process. As a result, starting from the precursors **40**, prepared by an Ugi four-component reaction, a domino sequence involving an intramolecular N-arylation followed by an intermolecular Heck reaction with the appropriate compound containing a double bond as a functional group (**41**) provided the functionalized benzodiazepinediones **42** (Scheme 20).



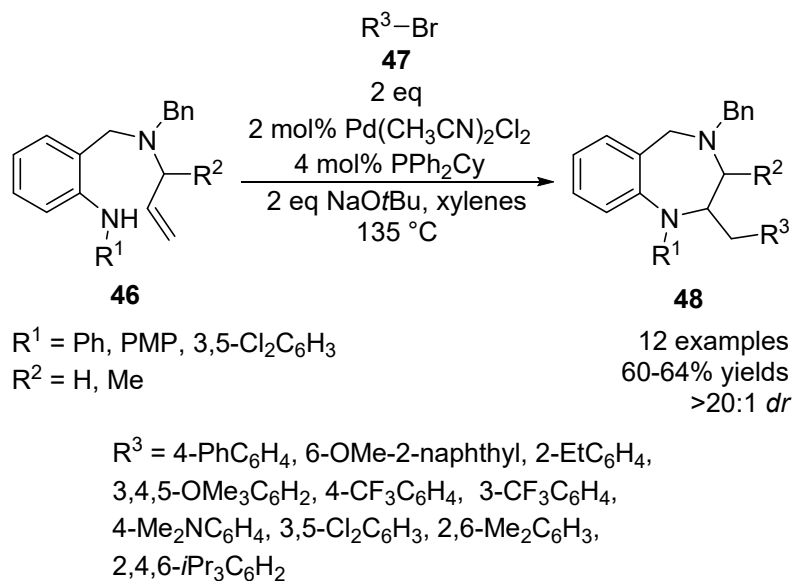
Scheme 20. Domino sequence for the synthesis of benzodiazepinediones **42**.

In 2015, Burke and Locati's group reported an alternative pathway for the synthesis of a family of dibenzodiazepines **45**, characterized by the unsubstituted diazepine ring, employing Pd-catalyzed C–N coupling of *o*-bromoaldimines **43** with *o*-bromoanilines **44** (Scheme 21) [84]. The optimized reaction conditions gave the best results in THF when Pd(OAc)₂ was used as the catalyst, SPhos as the ligand, and the inorganic base Cs₂CO₃ instead of alkoxides. Generally, the substitution pattern did not influence the reaction's outcome, except when strong electron-withdrawing groups were present on the aniline ring, resulting in a slightly lower yield. Due to the ambiguity of the mechanism in hand, DFT calculations were carried out. Firstly, the oxidative addition between the aldimine and the Pd(0) catalyst occurred, and intermediate **I** was calculated to be more stable than the one formed with the amine. The Buchwald–Hartwig amination afforded intermediate **III** through the reductive elimination of the metal. A second oxidative addition took place on the aniline ring, giving the intermediate **IV**, and the intramolecular coupling involving the imine nitrogen afforded the product **45** with the final N–S bond cleavage.



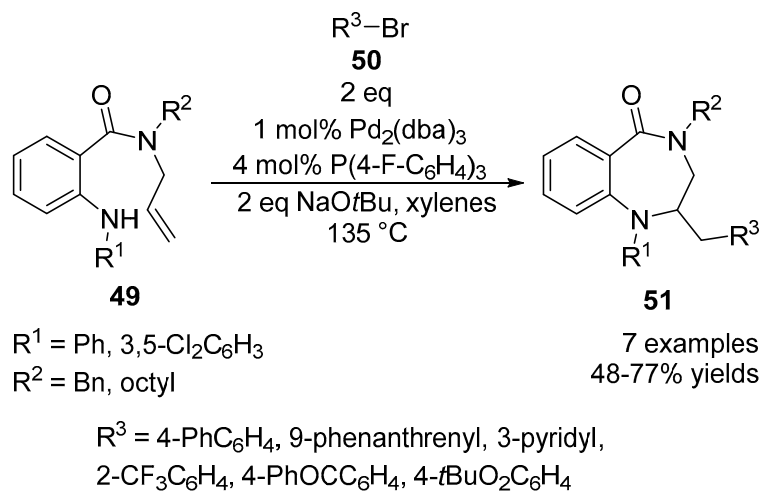
Scheme 21. Domino sequence for the synthesis of dibenzodiazepines **45**.

The carboamination domino process was exploited by Wolfe et al. for the synthesis of saturated 1,4-benzodiazepines **48** from easily prepared *N*-allyl-2-aminobenzylamine derivatives **46** and various aryl bromides **47** (Scheme 22) [85]. The optimal conditions were 2 mol % Pd(CH₃CN)₂Cl₂ in the presence of 4 mol % PPh₂Cy as the ligand and 2 Equation of NaOtBu as the base in xylenes at 135 °C, and various aryl bromides, bearing electron-donating or electron-withdrawing groups or bulky groups, were coupled in good yields, although highly electron-poor aryl bromides did not react. Substrates containing an allylic-methyl group were transformed to *cis*-2,3-disubstituted products with >20:1 stereoselectivity but larger substituents at the allylic position, or 1,1-disubstituted alkenes, failed to react. Although the use of a benzyl group on the cyclizing nitrogen atom resulted as unsuccessful, the electronic properties of the *N*-aryl group did not influence the chemical yield.



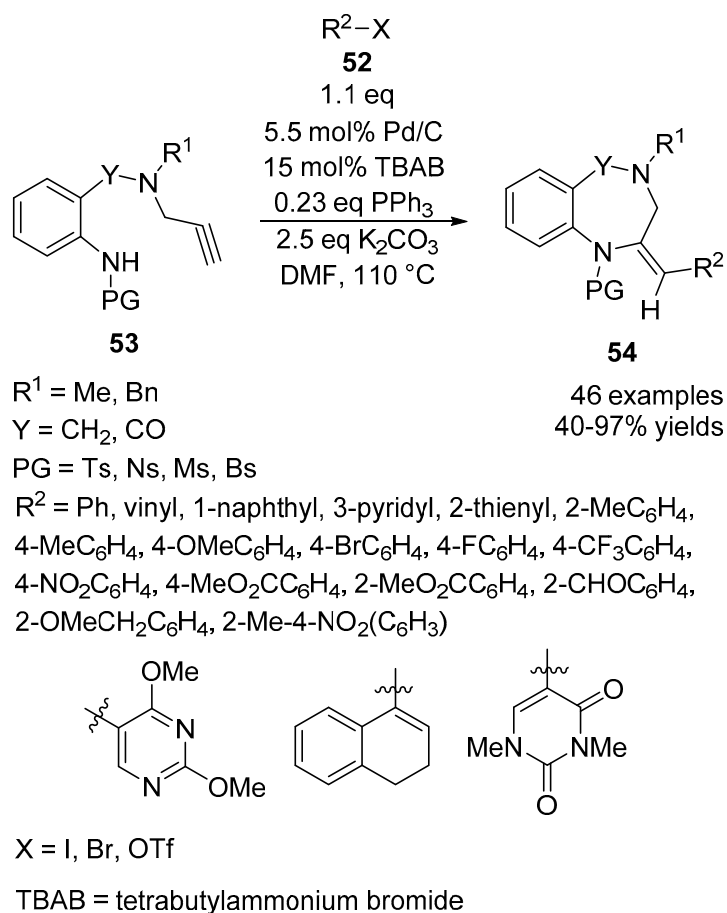
Scheme 22. Carboamination synthesis of saturated 1,4-benzodiazepines **48**.

Applying the same strategy to amides **49**, but in this case changing the catalyst to 1 mol % $\text{Pd}_2(\text{dba})_3$ and the ligand to 4 mol % $\text{P}(4\text{-F-C}_6\text{H}_4)_3$, the coupling with various aryl bromides **50** provided the desired 1,4-benzodiazepin-5-ones **51** in good yields (Scheme 23) [85]. However, in this case, the use of amide substrates bearing a 2-methylallyl group did not afford the corresponding products.



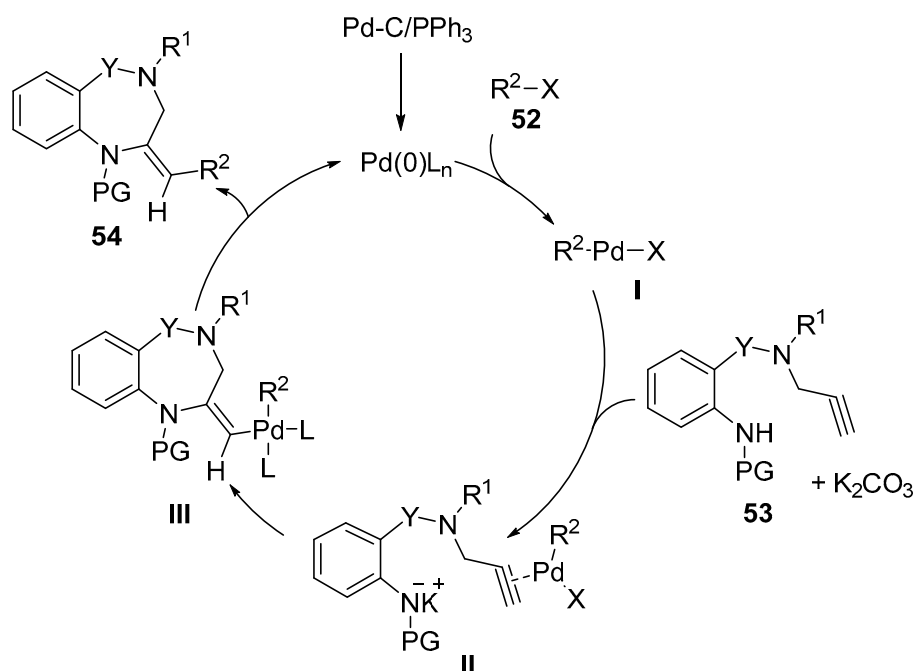
Scheme 23. Carboamination synthesis of 1,4-benzodiazepin-5-ones **51**.

The same synthetic strategy was applied for the stereoselective synthesis of (*E*)-2-aryl- (or vinyl)methylidene-1,4-benzodiazepin-5-ones and (*E*)-2-aryl- (or vinyl)methylidene-1,4-benzodiazepines **54**, starting from aryl(or vinyl) halides/triflates **52** with various 2-amino-benzamide or 2-amino-benzylamine derivatives **53**, utilizing the inexpensive Pd/C as the catalyst (Scheme 24) [86]. The reaction tolerated both electron-donating and electron-withdrawing groups on the aryl and heteroaryl halides and on the aryl triflates. The presence of the sulfonamide group on the substrate **53** was found to be essential for the conversion, since the use of the free amine or other protecting groups (Boc, COCF_3 , Me) did not provide the desired products. Moreover, the internal alkynes pendant did not furnish the desired products. Isomerization of the exocyclic double bond was observed in the presence of KOH but only for the obtained 1,4-benzodiazepin-5-ones.



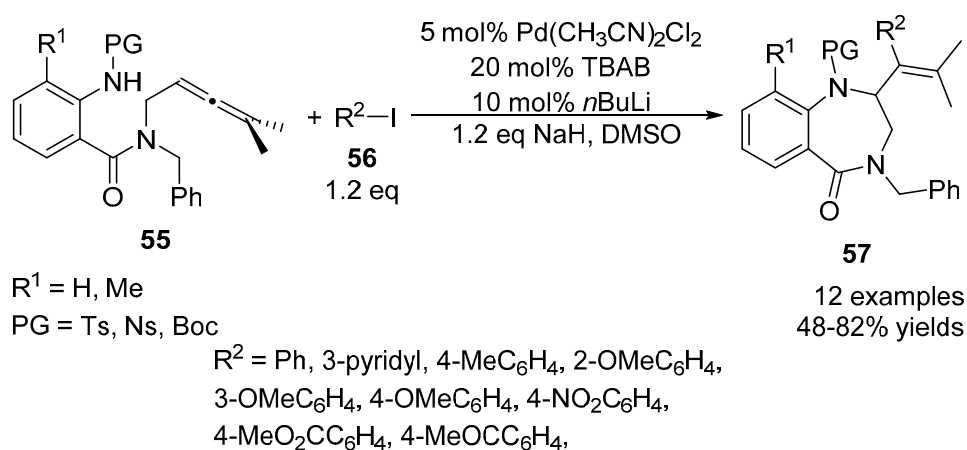
Scheme 24. Stereoselective carboamination synthesis of 1,4-benzodiazepin-5-ones and 1,4-benzodiazepines **54**.

A plausible reaction mechanism started with the oxidative addition of the aryl (or vinyl) halide/triflate **52** to the active Pd(0)L_n complex, formed through leaching of palladium from the Pd/C surface into the solution where it underwent interaction with phosphine ligands, providing the intermediate **I** (Scheme 25). Subsequently, activation of the triple bond of the substrate **53** and intramolecular nucleophilic attack by the nitrogen of the sulfonamide moiety, via a trans-aminopalladation pathway, led to the formation of the (*E*)-intermediate **III**. The final reductive elimination furnished the products **54** and regenerated the Pd(0) species, ensuring the *E*-stereochemistry.



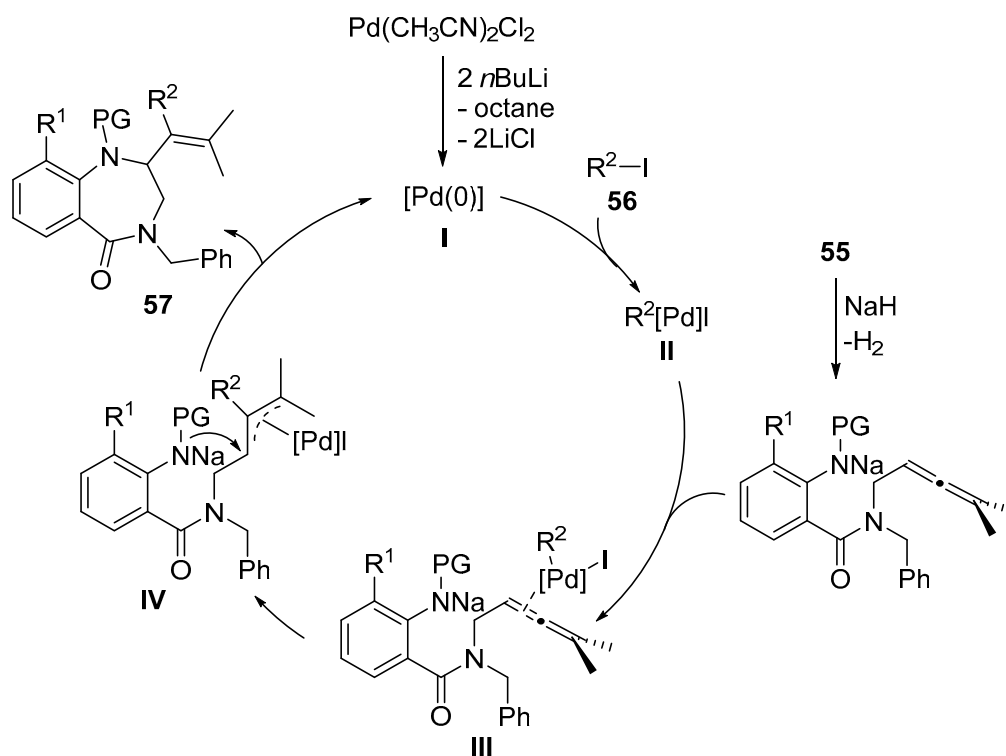
Scheme 25. Plausible mechanism for the stereoselective formation of the products **54**.

An original domino sequence starting from *N*-allenamides of the anthranilic acid **55** and aryl halides **56** was developed for the synthesis of 1,4-benzodiazepinones **57** [87]. The synthetic pathway was based on a Pd(0)-catalyzed carbopalladation/allylic amination process and the reaction was fruitful with electron-rich or electron-poor aryl halides and with the heteroaryl compound 3-iodopyridine. A methyl group on the aromatic ring of the substrates and Boc or nosyl protecting groups were also tolerable in the optimal reaction conditions (Scheme 26).



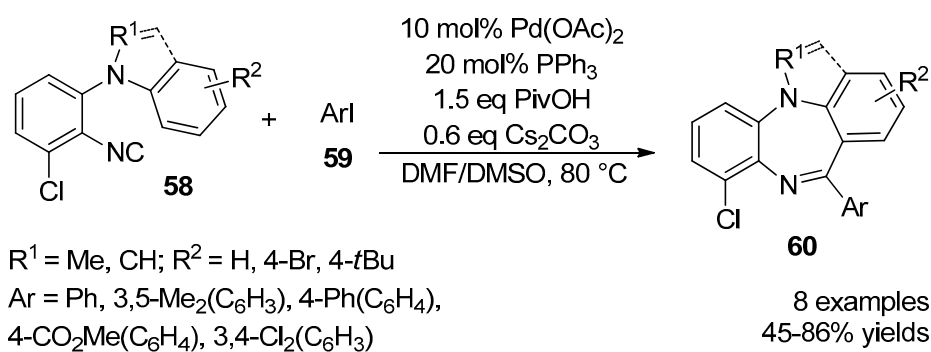
Scheme 26. Allene carbopalladation/amination domino sequence for the synthesis of 1,4-tetrahydrobenzodiazepinones **57**.

A rational mechanism was initiated with the generation of the Pd(0) complex **I** from Pd(CH₃CN)₂Cl₂ and *n*BuLi, which after oxidative addition of the aryl halide and carbopalladation, afforded the η³-allyl complex **IV** via the complex **III**. The final products were obtained after a 7-*exo* nucleophilic attack by the sodium salt of the sulfonamide (or the carbamate) nitrogen atom (Scheme 27).



Scheme 27. Proposed mechanism for the synthesis of tetrahydrobenzodiazepinones **57**.

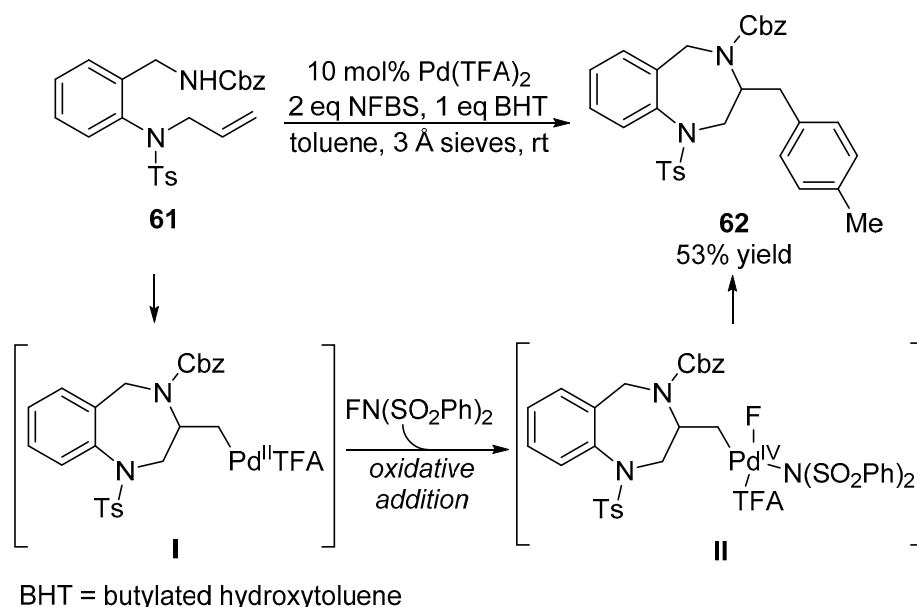
Recently, Lou and Zhu reported the first example of a seven-membered heterocycle formation by Pd-catalyzed C–H imidoylative annulation [88]. The likely formation of an eight-membered palladacycle intermediate, characterized by a high energy barrier, could enhance the contribution of this work. The improvement of the reaction conditions was given by using Cs_2CO_3 as the base and a mixture of DMF/DMSO in a 1:1 ratio. Further, the employment of PivOH as the additive provided an increase in the products **60** (Scheme 28). The presence of a substituent in the *o*-position (–Cl) to the functionalized isocyanides on substrates **58** was necessary for the outcome of the reaction and to avoid undesired dimerization by-products. Thus, the requirement of an *o*-substituent was an obvious limitation of this method, but the compatibility of the chloride substituent in the reaction conditions paved the way for further transformations. Starting from an indole derivative, even a unique tetra-fused analogue was achieved in 78% yield.



Scheme 28. Arylisocyanides substrates **58** for the synthesis of dibenzodiazepines **60**.

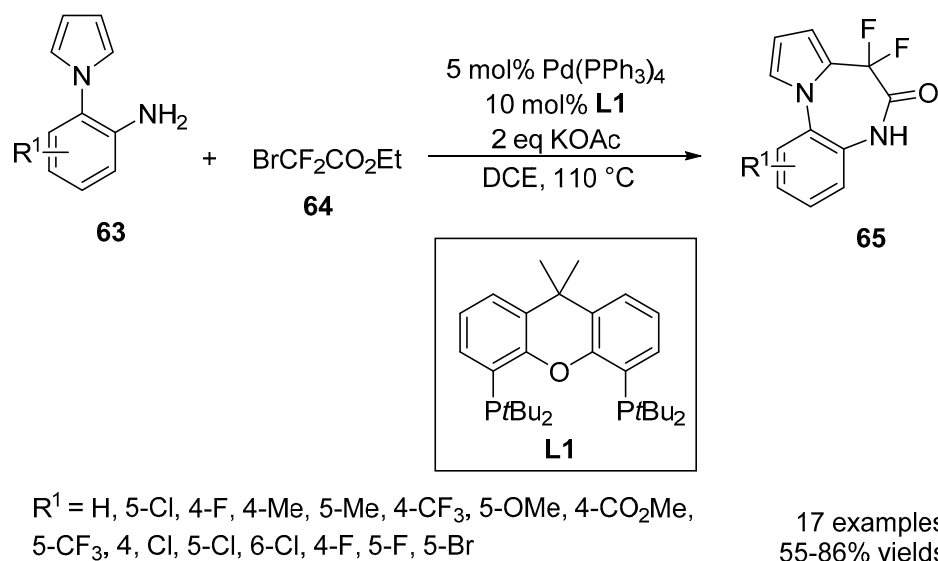
Michael et al. described a novel method for Pd-catalyzed carboamination of alkenes using NFBS (*N*-fluorobenzenesulfonimide) as an oxidant to incorporate weakly nucleophilic arenes for a variety of synthetically useful nitrogen heterocycles [89]. In this scope, and starting from the benzyl

carbamate derivative **61**, the 1,4-benzodiazepine **62** was synthesized in good yield (Scheme 29). Initial aminopalladation of the benzyl carbamate derivative **61** gave the Pd(II)-alkyl intermediate **I**, which after the subsequent oxidative addition of NFBS generated the key Pd(IV) intermediate **II**. Then, in the presence of toluene, or Pd(IV), the center is intercepted and displaced in an electrophilic aromatic substitution reaction, forming the final product **62** and regenerating the Pd(II) catalyst, or, alternatively, C–H activation of toluene by the Pd(IV) species followed by reductive elimination is also a plausible route to the observed product. The use of a radical scavenger eliminates the possibility of a radical mechanism.



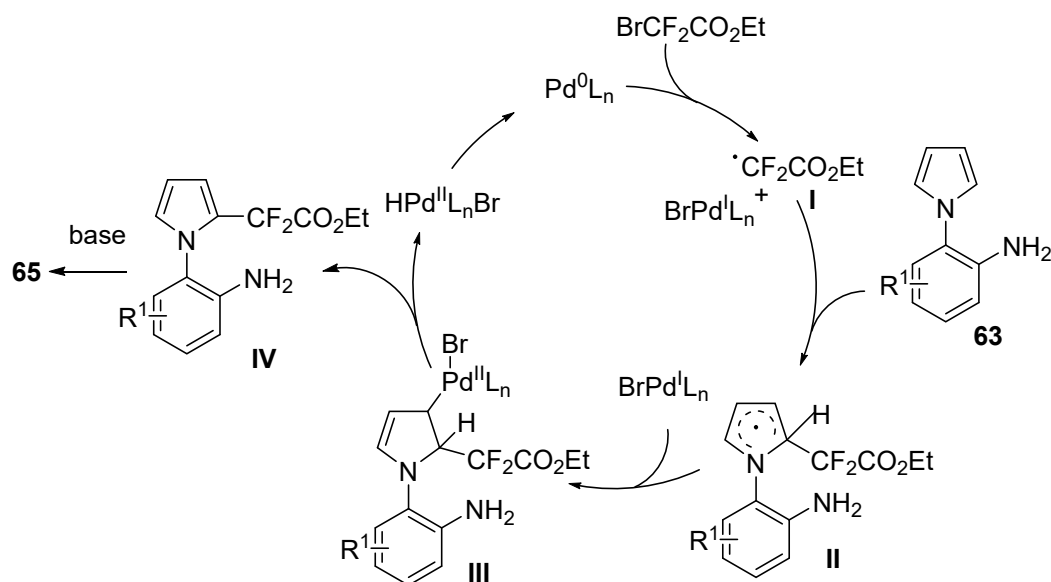
Scheme 29. Carboamination promoted by *N*-fluorobenzenesulfonimide.

A protocol for the synthesis of difluoroalkylated pyrrolbenzodiazepines **65** was developed by using a Pd-catalyzed two-component C–H difluoroalkylation/cyclization cascade reaction (Scheme 30) [90]. The direct installation of difluoroalkyl groups using reagents containing difluoromethylene groups enabled to access difluoroalkylated pyrrolbenzodiazepines, avoiding the use of highly toxic and corrosive fluorinating agents. Therefore, the employment of the cheap and available fluoroalkyl bromide **64** together with 1-(2-aminophenyl) pyrroles **63**, in the presence of Pd(PPh₃)₄ as the catalyst, the bulky and electron-rich bidentate ligand **L1**, and K₂CO₃ as the base in DCE, furnished the product **65** in good yields. The use of a bulky ligand, ought to promote the reductive elimination from the fluoroalkyl palladium(II) complex, and the use of a 4 Equation of **64** were essential to increase up to 86% the yields of products **65**. Regarding the substitution pattern, electron withdrawing (EWG) and electron donating group (EDG) were well-tolerated, but when substituted-pyrrole, indole, or imidazole derivatives were employed, the desired products were not obtained. The involvement of the pyrrole heterocycle in the radical pathway may be an explanation for the observed results.



Scheme 30. Cascade reaction for the synthesis of difluoroalkylated pyrrolobenzodiazepines **65**.

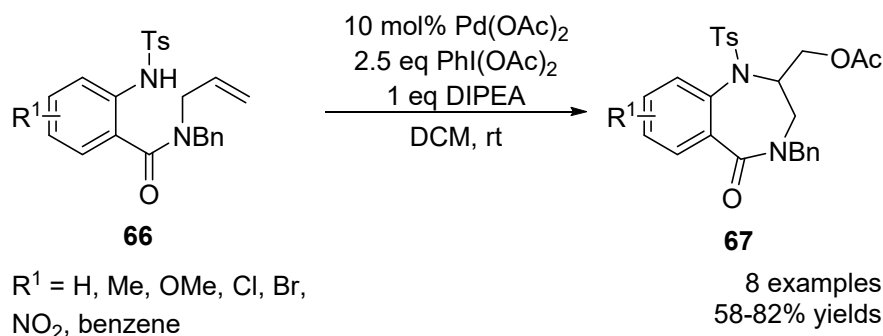
In fact, the described mechanism was likely to be initiated by a Pd(0)-promoted SET, generating the difluoroalkyl radical **I** and Pd(I) (Scheme 31). The subsequent reaction with **63** produced the intermediate radical **II**, whose electron was stabilized on the pyrrole ring. The oxidative addition of Pd(I) to the radical **II** provided the intermediate **III**, which through the β -elimination aromatized to intermediate **IV**. The subsequent intramolecular cyclization in the presence of the base furnished the desired products **65**.



Scheme 31. Proposed mechanism for the synthesis of difluoroalkylated pyrrolobenzodiazepines **65**.

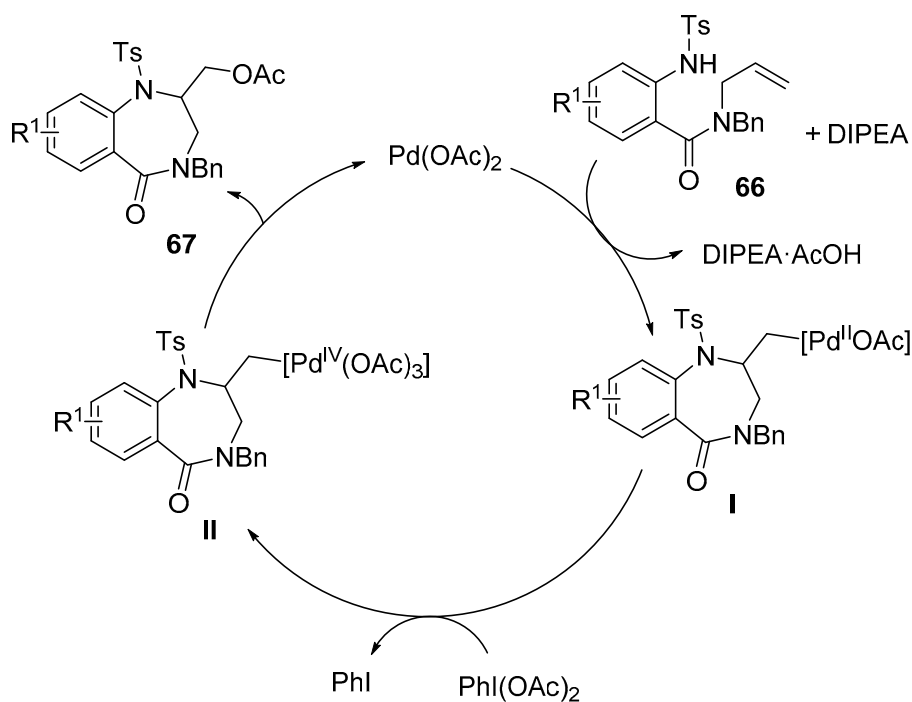
The first instance of a seven-membered ring-closure diheterofunctionalization for the synthesis of 1,4-benzodiazepin-5-ones **67** was reported from Prestat et al. via a palladium-catalyzed aminoacetoxylation of alkenes **66** (Scheme 32) [91]. With the use of Pd(OAc)₂ as the catalyst and DIPEA as the base, PhI(OAc)₂ was the oxidant of choice, given the fact that the replacement of PhI(OAc)₂ with PhI(OTFA)₂ or Cu(OAc)₂ completely inhibited the reaction. On the other hand, the use of 3-NO₂- and 4-MeO-(diacetoxyiodo)benzene provided the same result. Moreover, changing the tosyl group with a nosyl group slightly decreased the yield, whereas in the cases of the Boc or Ac

protecting groups, the starting material was recovered. The reaction tolerated electron-donating as well as electron-withdrawing substituents on the aryl ring.



Scheme 32. Aminoacetoxylation domino process to afford benzodiazepinones **67**.

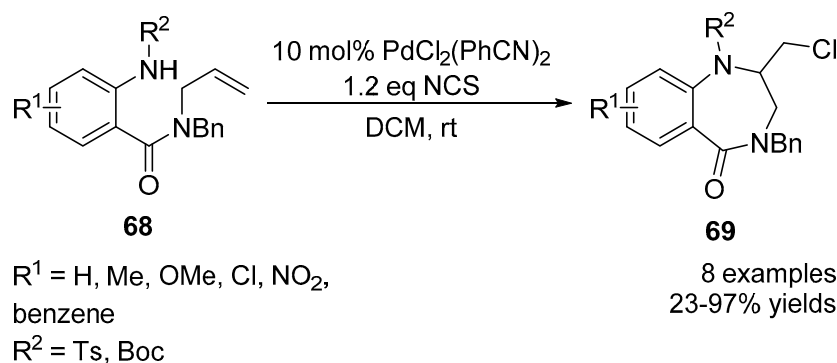
The proposed mechanism started with the aminopalladation of the alkene followed by a Pd(II) to Pd(IV) oxidation mediated by PhI(OAc)₂. The organopalladium(IV) complex **II** advanced via reductive elimination to form the C–OAc bond of the product **67** and regenerated the Pd(II) catalyst (Scheme 33).



Scheme 33. Proposed catalytic cycle for benzodiazepinones **67**.

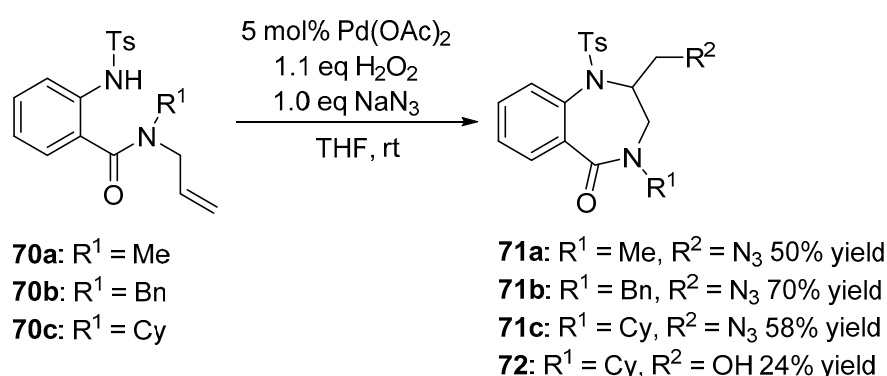
Later, the same group presented a mild and efficient domino synthesis of chloromethyl-substituted benzodiazepinones **69** via the aminochlorination of anthranilic acid derivatives **68**, using the NCS (*N*-chlorosuccinimide) and performing the reaction in DCM as the solvent (Scheme 34) [92]. The use of NBS (*N*-bromosuccinimide) and NIS (*N*-iodosuccinimide), on the contrary, did not promote the haloamination reaction as well as the Selectfluor, and DAST/NFBS as potential fluorine sources remained unsuccessful (DAST = diethylaminosulfur trifluoride). Polar solvents such as MeCN and DMF were found to completely inhibit the reaction. The reaction tolerated electron-withdrawing or electron-donating groups on the aryl ring, and also the *N*-Boc protective group was

proven to be compatible but providing lower yields. The introduction of the chloromethyl appendage should facilitate their post-functionalization towards more complex molecules.



Scheme 34. Aminochlorination domino process to afford benzodiazepinones **69**.

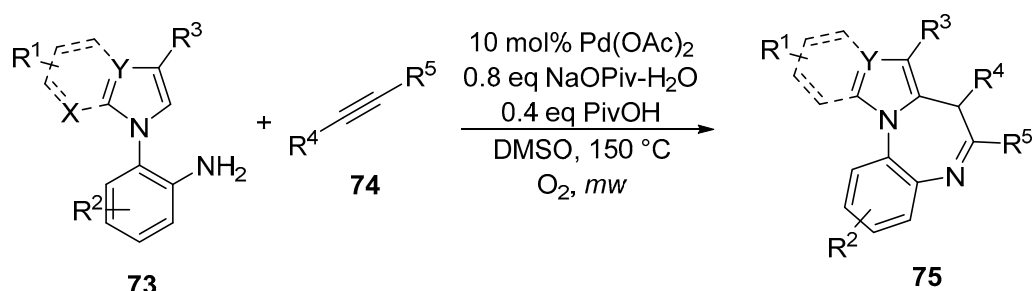
In 2020, the aminoazidation domino process was described for the synthesis of the 1,4-benzodiazepines **71a–c** starting from the unactivated *N*-allyl-anthranilamides **70a–c** through a selective 7-*exo*-cyclization (Scheme 35) [93]. The reaction proceeded under mild conditions with NaN_3 as the azide anion source and H_2O_2 as the inexpensive oxidant agent. The use of H_2O_2 was crucial to generate the Pd(IV) intermediate, which avoided competitive reactions such as the β -hydride elimination. Instead, when 1,4-benzoquinone or $\text{Cu}(\text{OAc})_2$ was used as the oxidant, no product was observed. In the case of compound **70c**, a small amount of the hydroxymethyl-substituted compound **72** was observed (Scheme 35).



Scheme 35. Aminoazidation domino process of the unactivated *N*-allyl-anthranilamides **70**.

A one-pot synthesis of the imine-containing 1,2-fused indole-diazepines **75** was described starting from inactivated substrates, in particular from accessible disubstituted acetylenes **74** and indoles **73** (Scheme 36) [94]. The regioselective functionalization of the indole at the C-2 or C-3 position has been the subject of many studies. Herein, a Pd-catalyzed regio- and chemoselective alkyne insertion/cyclization of the C(2)–H was obtained, starting from *o*-indoloanilines **73**. Despite the more favorable electrophilic attack of the metal catalyst at the C-3 position on the indole, in this case, the amino group-directed heteroannulation with the internal alkynes provided a regioselective C(2)–H bond functionalization, affording diazepines **75** by an unprecedented [5 + 2] annulation on these kind of substrates. The use of pivalic acid proved to be fundamental, thanks to the generation of highly activated electrophilic $[\text{Pd}(\text{PivO})]^+$ species in situ. Further, here, the use of microwave irradiation allowed a reduction in the reaction time. The presence of electron-rich and electron-deficient substituents on the indole ring and aniline ring did not particularly influence the outcome of the reaction, showing the strength of this protocol. In fact, it was effective towards the less reactive *o*-pyrrole- and *o*-imidazole-substituted anilines. When unsymmetrical alkynes containing electron-

donating groups (H, Me, OMe) and/or electron-withdrawing groups (F, Cl, NO₂) were tested, a mixture of the two separable regioisomers was obtained.

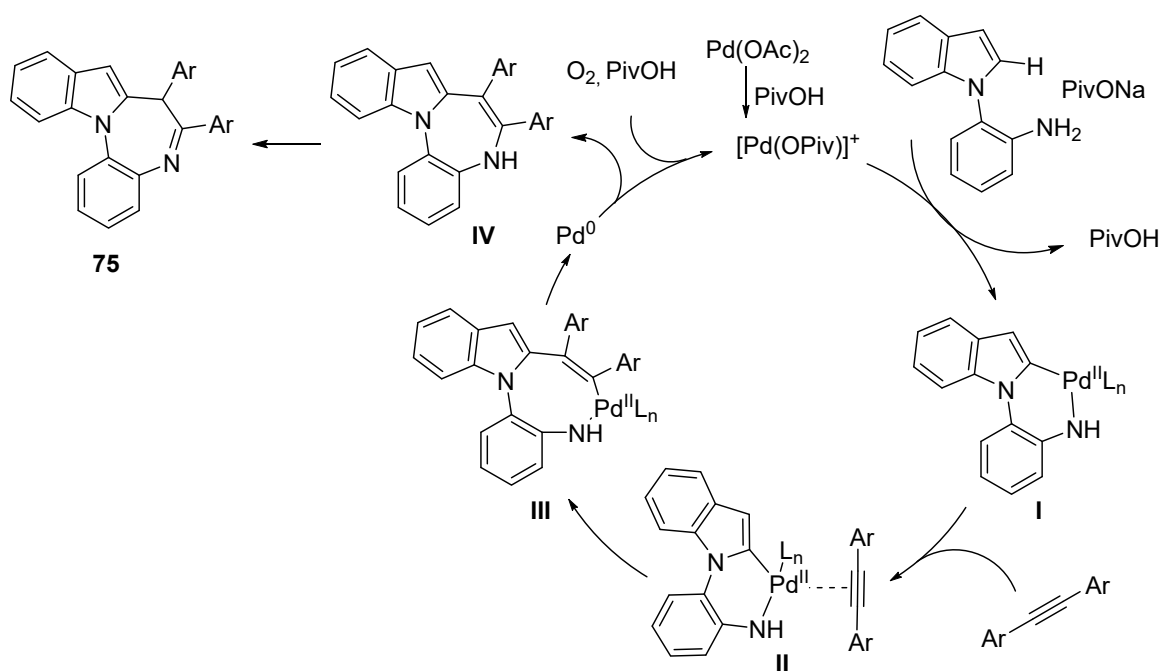


X = CH, N; Y = C, CH, N; R¹ = 4-OMe, 3-OMe, 4-CN
R² = 4-Me, 4-CO₂Me, 4-CF₃; R³ = H, Me
R⁴ = R⁵ = Ph, 4-Me(C₆H₄), 4-OMe(C₆H₄), 4-CF₃(C₆H₄)
If **74** is not symmetric a mixture has been obtained when:
R⁴ = 4-NO₂(C₆H₄), R⁵ = Ph; R⁴ = 4-NO₂(C₆H₄), R⁵ = 4-OMe(C₆H₄); R⁴ = 4-Cl(C₆H₄), R⁵ = 4-OMe(C₆H₄); R⁴ = 4-F(C₆H₄), R⁵ = 4-OMe(C₆H₄)
except when: R⁴ = 2-thienyl, R⁵ = 4-Me(C₆H₄); R⁴ = 4-Me(C₆H₄), R⁵ = 4-*i*-Pr(C₆H₄); R⁴ = Et, R⁵ = Ph

26 examples
23-87% yields

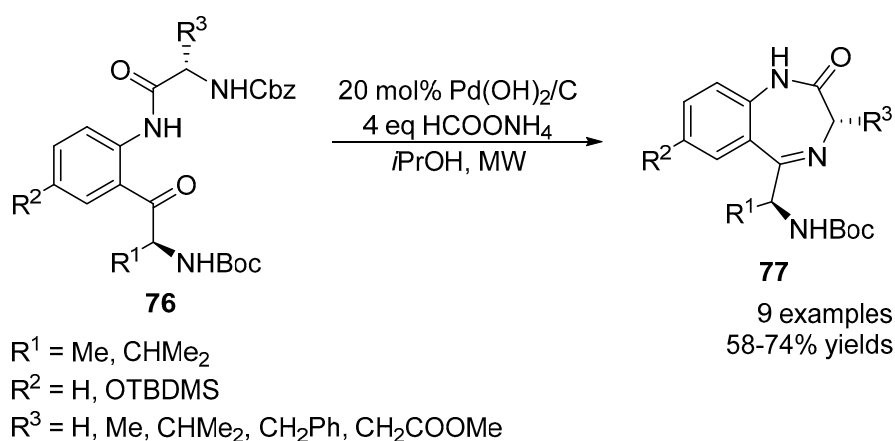
Scheme 36. One-pot synthesis of 1,2-fused indole-diazepines **75**.

The reaction proceeded through an initial activation of the Pd species to the more active [Pd(PivO)]⁺, followed by the formation of the palladacycle complex **I**, through a selective C(2)-H bond activation of the indole ring (Scheme 37). The consequent coordination of the alkyne with the Pd complex favored the formation of intermediate **III**, which underwent reductive elimination, providing compound **IV**. The consequent tautomerization of the enamine to the imine afforded the product **75**. The catalyst active species was restored by molecular oxygen and pivalic acid.



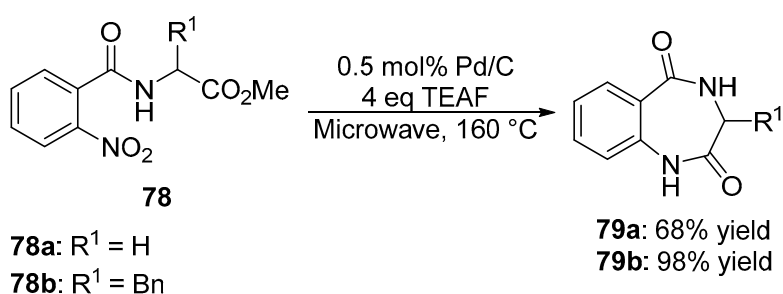
Scheme 37. Proposed mechanism for the synthesis of 1,2-fused indole-diazepines **75**.

In some syntheses of 1,4-benzodiazepines, the palladium played a minor role. The synthesis of 1,4-benzodiazepines **77** carrying different substituents at positions 3 and 5 were obtained from substrates **76** performing the reaction in *i*PrOH with ammonium formate in the presence of 20 mol% Pd-(OH)₂/C, under microwave irradiation (Scheme 38) [95]. The Cbz protective group was used as an orthogonal to Boc, as Boc should be maintained during the process of deprotection/cyclization. This method allowed the regiocontrolled formation of the diazepine ring with respect to a substituent on the aromatic ring and the formation of the enantiomerically pure 1,4-benzodiazepines **77** starting from naturally occurring amino acids.



Scheme 38. Synthesis of 3,5-disubstituted 1,4-benzodiazepines **77**.

An environmentally-benign cascade methodology for the efficient and diversified construction of 1,4-benzodiazepine-2,5-diones **79** was developed by Qin et al. (Scheme 39) [96]. This solvent-free and microwave-assisted method was established using a palladium-catalyzed transfer hydrogenation (CTH)/condensation cascade from 2-nitrobenzoyl- α -amino acid methyl esters **78** in an azeotropic mixture of triethylamine–formic acid (TEAF). In this TEAF medium, only 0.5 mol% of the Pd/C was sufficient to complete the reaction. Interestingly, after reduction, the substrates did not cyclize with TEAF in a Niementowski way to provide the quinazoline products but instead, intramolecular aminolysis of the methyl ester prevailed, affording the benzodiazepine compounds. Other common mono-carbon CTH reagents including formic acid, ammonium formate, and the mixture of formamide–ammonium formate failed or furnished the desired products in lower yields.



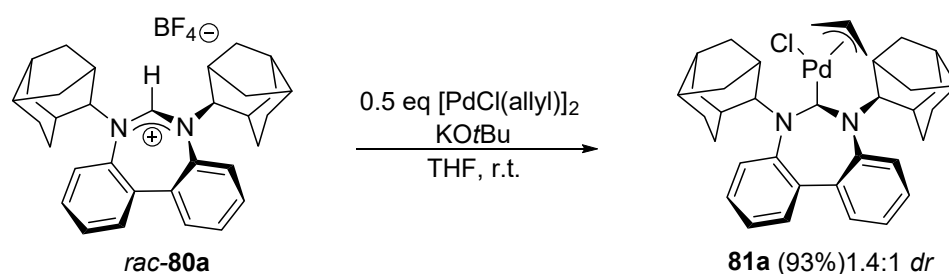
Scheme 39. Synthesis of 1,4-benzodiazepine-2,5-diones **79** via palladium-catalyzed transfer hydrogenation (CTH) reduction–cyclocondensation.

2.3. 1,3-Benzodiazepines

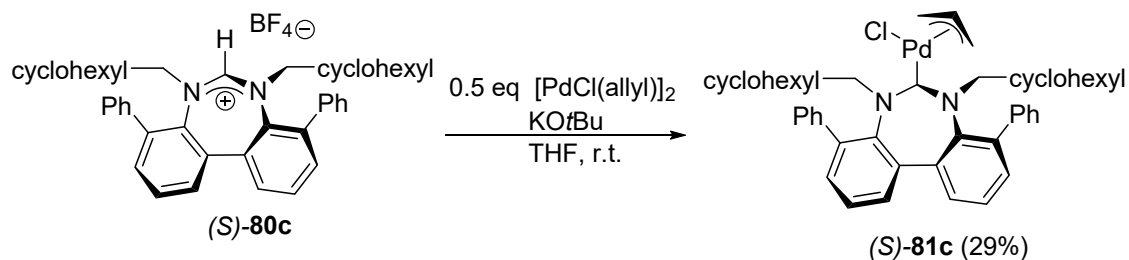
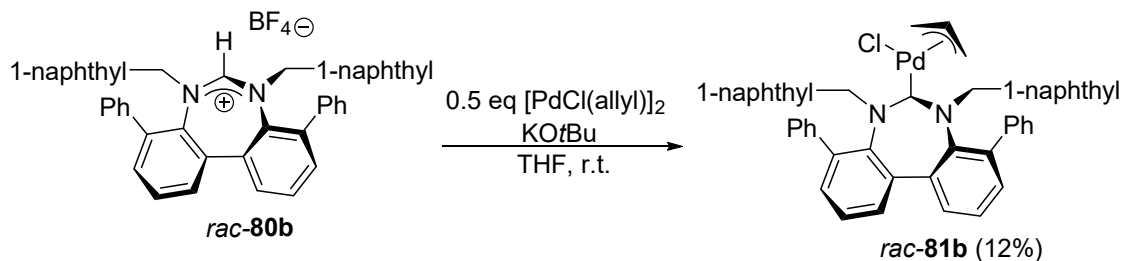
While the 1,4 benzodiazepines have been widely studied and investigated by virtue of their role in pharmaceuticals, some of the few examples of 1,3 benzodiazepines involving the palladium chemistry were related to the formation of a complex between the already formed 1,3 benzodiazepine

nuclei and the palladium (Scheme 40). In fact, the seven-membered ring in the dibenzo[1,3]diazepines **80a-c** and **82** contains a labile C–H at the position C-2, which can be removed in the presence of a quite strong base, such as KOtBu, generating a *N*-heterocyclic carbene. Stahl's pioneering work in 2005 paved the ways to this new class of carbene ligand, offering the possibilities for an enantioselective NHC catalysis, thanks to the two existing axially twisted conformations [97]. In this way, the free rotation of **81a** in the axial plane caused its racemization in the solution. Thus, for preventing this racemization, in 2009, Stahl developed a new generation of ligands, **80b-c**, with an aromatic substituent at the C-6 and C-6' positions of the two fused-phenyl rings, in order to create a stable complex through π -interaction with the *N*-naphthyl group (**81b**) or steric hindrance with the *N*-cyclohexyl group (**81c**). Therefore, starting from the chiral (*S*)-**80c**, a stable and enantiomeric pure Pd-carbene complex **81c** was achieved [98]. In 2014, Li and co-workers reported, instead, the use of a phosphine-based achiral ligand **82**, which through the complexation of palladium in situ, was extremely effective in catalyzing a Mizoroki–Heck reaction of aryl bromides and chlorides with olefins [99].

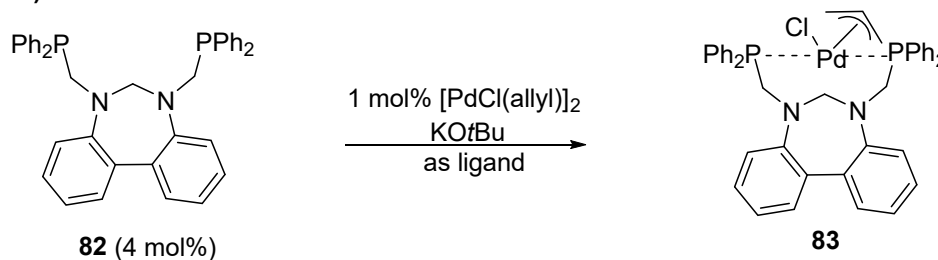
1) Stahl (2005)



2) Stahl (2009)

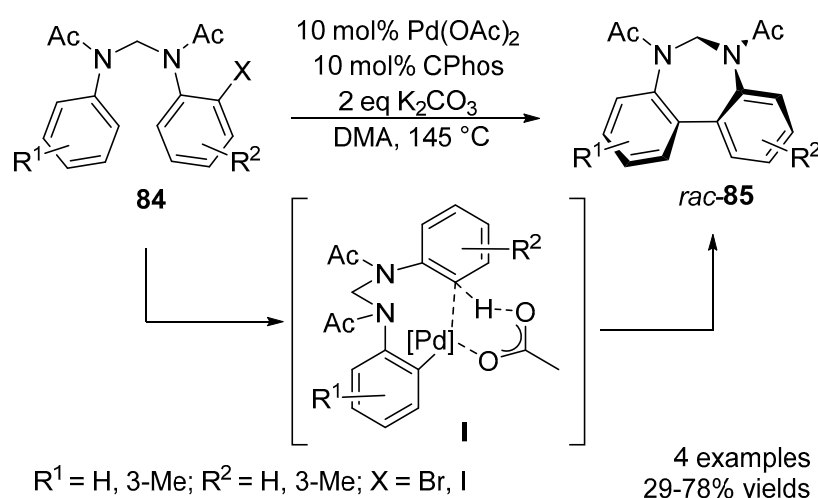


3) Li (2014)



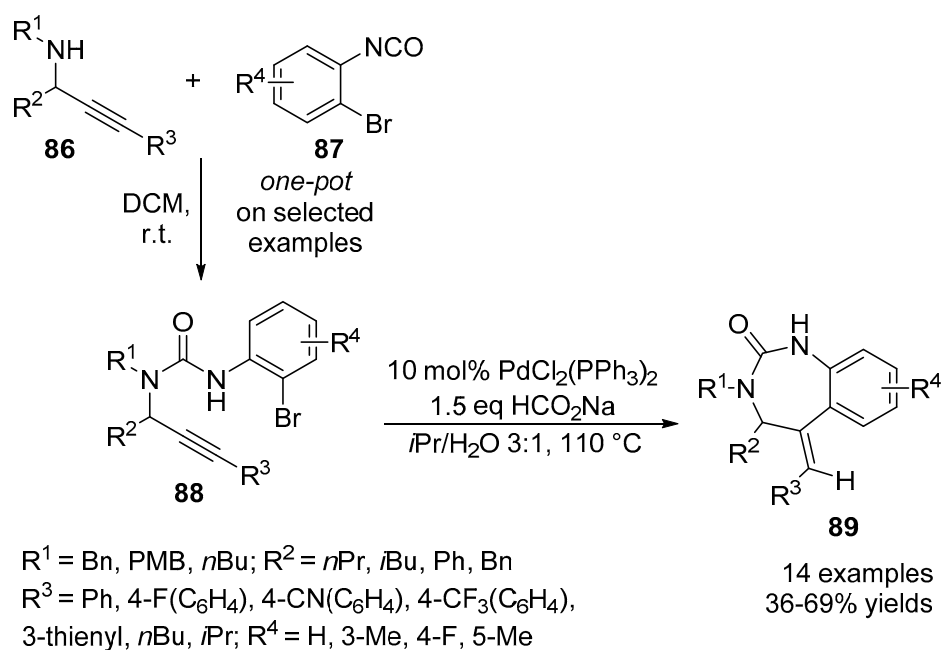
Scheme 40. 1,3-Benzodiazepines as carbene precursors for Pd complexes formation.

The use of dibenzo-1,3-diazepines as carbene ligands has been limited to the long-steps and old-fashioned protocol reported for their synthesis. Therefore, in order to overcome these synthetic limitations and to open up access to this class of compounds for futures applications, in 2015, Masters' group described a Pd-catalyzed direct C–H arylation to non-symmetrical, axially chiral dibenzodiazepines **85**, starting from halo-substituted 1,3-diaminomethylene biphenyls **84** (Scheme 41). [100] The methylene tether to the two heteroatoms contributed to the regiocontrol over the difficult biaryl bond formation, furnishing more flexibility for the formation of the key intermediate **I**. Only *N*-acetyl-protected substrates were tested in the presence of Pd(OAc)₂ as the catalyst and the CPhos ligand, affording dibenzodiazepines **85** as a racemic mixture in moderate to good yields. The axial chirality observed was due to the axial torsion, which constrains the rotation around the bond joining the two phenyl rings. In order to transform these substrates to their respective carbenes, according to Stahl's conditions (see Scheme 39), treatment with a metal complex, such as [Pd(allyl)Cl]₂, should deliver metal–NHC complexes.



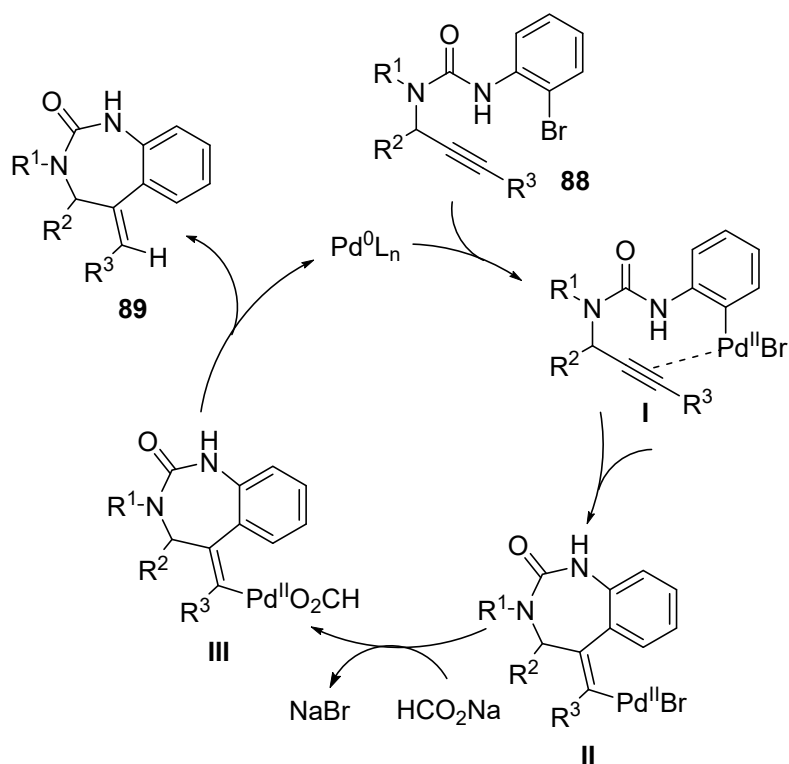
Scheme 41. Synthesis of carbene precursors **85**.

Moreover, examples related to the synthesis of 1,3-benzodiazepine nuclei, as important pharmaceutical cores, have been also reported. A synthetic sequence involving the addition of propargylamine to isocyanate and the subsequent Pd-catalyzed intramolecular alkyne hydroarylation has been developed both through stepwise and one-pot approaches (Scheme 42) [101]. 1,3-Benzodiazepinones **89** were achieved from bromophenyl propargylic ureas **88**, employing 10 mol% PdCl₂(PPh₃)₂ as the catalyst. To perform the reaction, the mixture *i*PrOH/H₂O in a 3:1 ratio was crucial to prevent the degradation of urea **88**, ensuring the formation of products **89** in moderate yields. The quantitative reaction between propargylamines **86** with *o*-bromophenyl isocyanates **87** encouraged the authors to test a one-pot procedure for the synthesis of 1,3-benzodiazepinones **89**, with satisfying results.



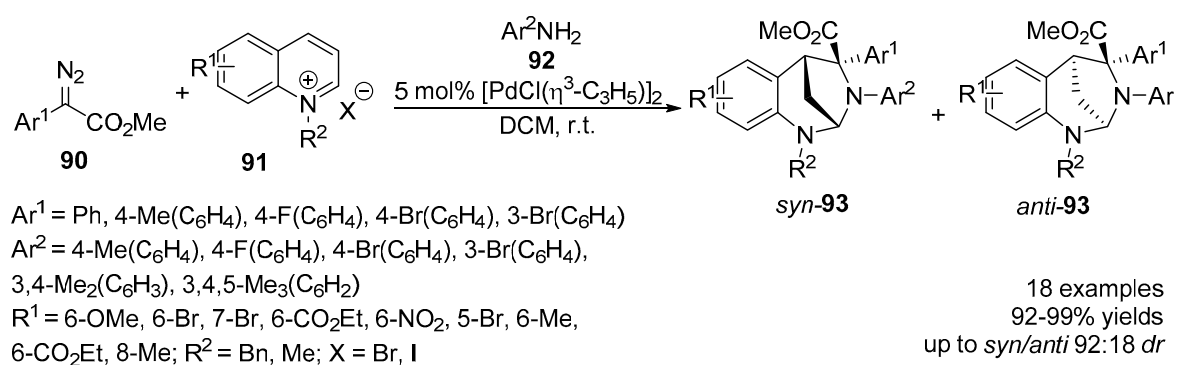
Scheme 42. Intramolecular alkyne hydroarylation affording 1,3-benzodiazepinones **89**.

The proposed hydroarylation process involved an oxidative addition of Pd(0) to the aryl bromides **88**, followed by a triple bond carbopalladation, a step accountable to the regioselectivity obtained. The subsequent trapping of the vinyl-palladium species **II** with sodium formate as the reducing agent furnished the intermediate **III** and the 1,3-benzodiazepinone products **89** were obtained after the reductive elimination of the catalyst (Scheme 43).



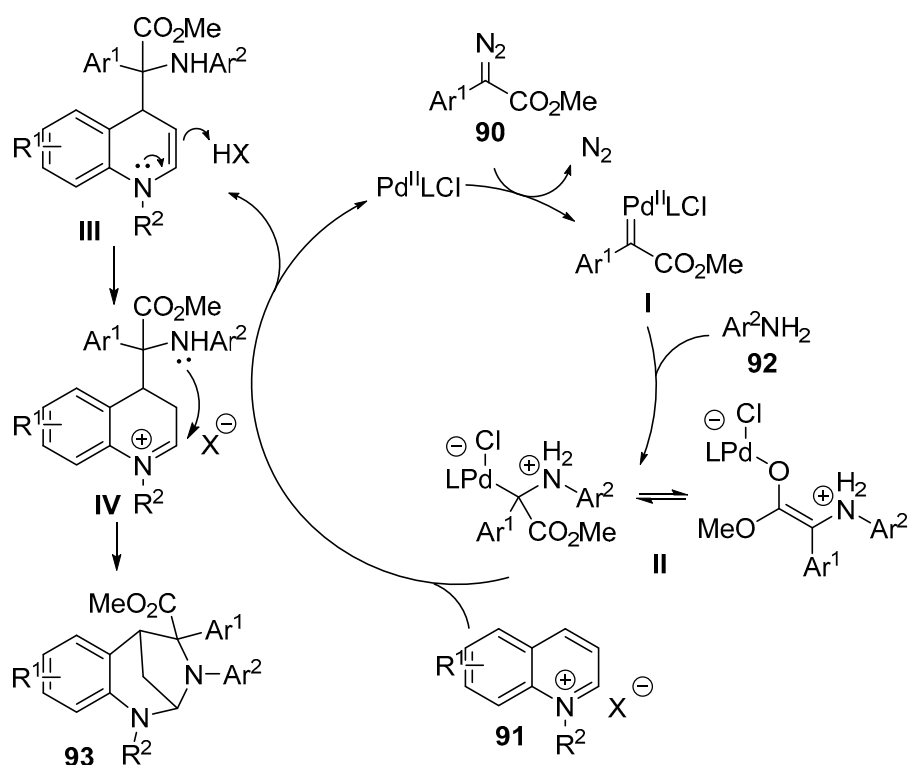
Scheme 43. Proposed mechanism for the hydroarylation process.

In 2017, Hu described a Pd(II)-catalyzed three-component reaction via the trapping of ammonium ylides with *N*-alkylquinolinium salts **91**, providing, under mild reaction conditions, the bridged 1,3-benzodiazepines **93** with high regioselectivity and moderate diastereoselectivity (Scheme 44) [102]. There are not many synthetic examples of bridgehead diazepine cores, even if this nucleus is occurring in nature in different biologically active heterocycles, including ecteinascidin. The use of nucleophilic intermediates with unique reactivity, such as ylides, generated in situ from the diazo compounds **90**, which can be trapped by nucleophilic species, was the key step to accomplish non-directed regioselective C-4 additions to the quinolinium salts **91**. In fact, usually the C-2 nucleophilic addition to the quinolinium salts is favored, due to the more electrondeficient C-2 position. Thus, the dearomatization of cationic quinolinium ions, affording bridged 1,3-benzodiazepines **93**, was obtained under mild conditions by using $[\text{PdCl}(\eta^3\text{-C}_3\text{H}_5)]_2$ as the catalyst and bench-stable *N*-alkylquinolinium salts, bearing a benzyl or a methyl group. The substrate scope showed high tolerability except when a substituent was present at the C-3 position of the quinolinium salt.



Scheme 44. A rare example of bridged 1,3 benzodiazepines **93**, though the formation of ylides species.

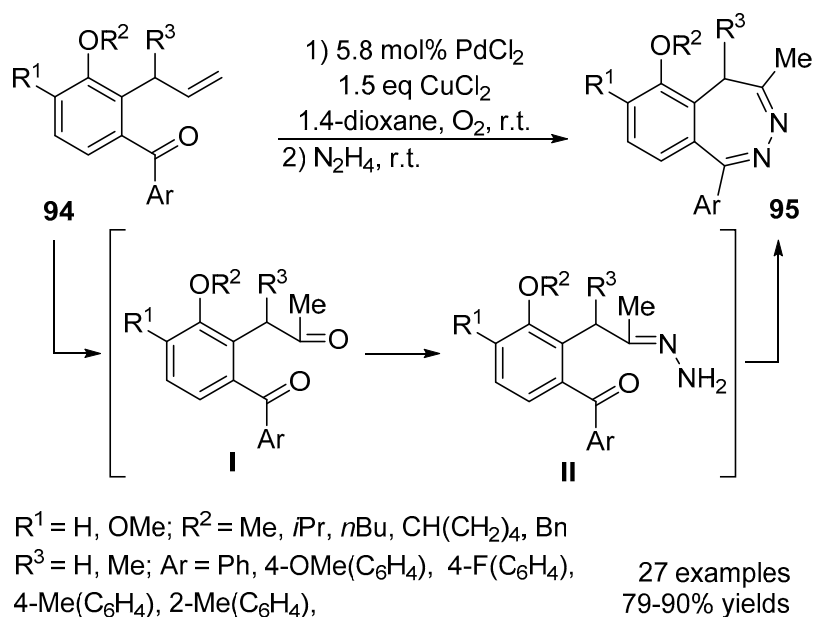
Regarding the mechanism, the Pd(II) decomposed the diazo substrate **90** to the carbene intermediate **I**, which reacted with anilines **92** to give ammonium ylide **II**, existing in the two isomers. Afterwards, the ylide intermediates **II** were trapped by the quinolinium salts **91** via the C-4 regioselective addition, providing 1,4-dihydroquinolines **III** and restoring the Pd(II)-catalyst. The following protonation gave the intermediate **IV**, and the intramolecular nucleophilic cyclization driven by the amino group afforded the products **93** (Scheme 45). The moderate and good stereocontrol observed was explained by the formation of a H-bond between the aniline NH group in ammonium ylides intermediates **II** and bromide of quinolinium salt, as well as the π - π stacking between the two aromatic moieties of intermediates **II** and substrates **91**, favoring the formation of the *syn*-isomers.



Scheme 45. Proposed mechanism for the formation of the bridged derivatives **93**.

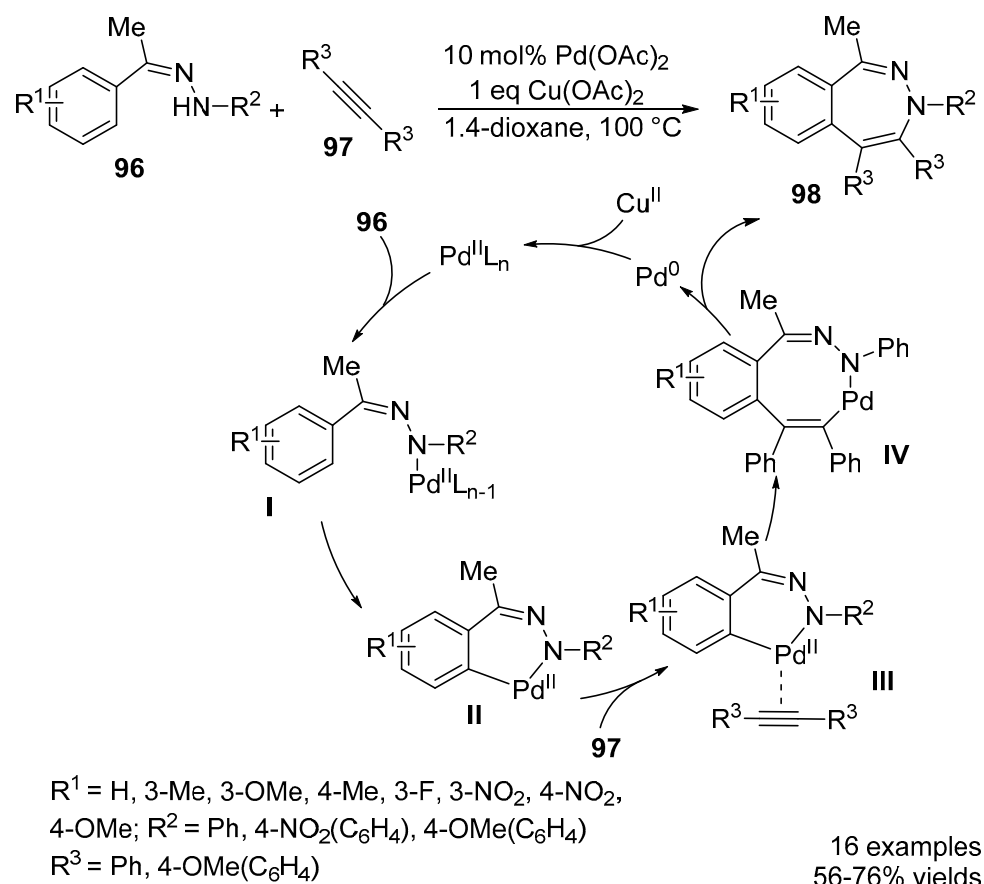
2.4. 2,3-Benzodiazepines

2,3-benzodiazepines are known for being tranquilizing agents and acting as non-competitive AMPA antagonists and their structure is found in biologically active compounds, such as girisopam and nerisopam, too. For this reason, an efficient method has been developed for their synthesis starting from 2-allyl benzo-ketones **94**, exploiting an aerobic Wacker oxidation on terminal olefin, and the subsequent reaction of hydrazine on the present and formed keto group (Scheme 46) [103]. The classic PdCl₂/CuCl₂ system in combination with molecular oxygen was better than any other conditions tested. Thus, after the olefin oxidation, N₂H₄ reacted with the C5 position via intermolecular condensation, proving the intermediate **I**, then the subsequent formal (5 + 2) annulation furnished the products **95**. Regarding the substitution pattern, electron-donating, electron-withdrawing, and electron-neutral groups were all suitable for the described reaction. Only when the aryl group (-Ar) was substituted with a -H, furnishing benzaldehyde as the starting material, the benzodiazepine was not obtained and the corresponding isoquinolone was isolated as the only product.



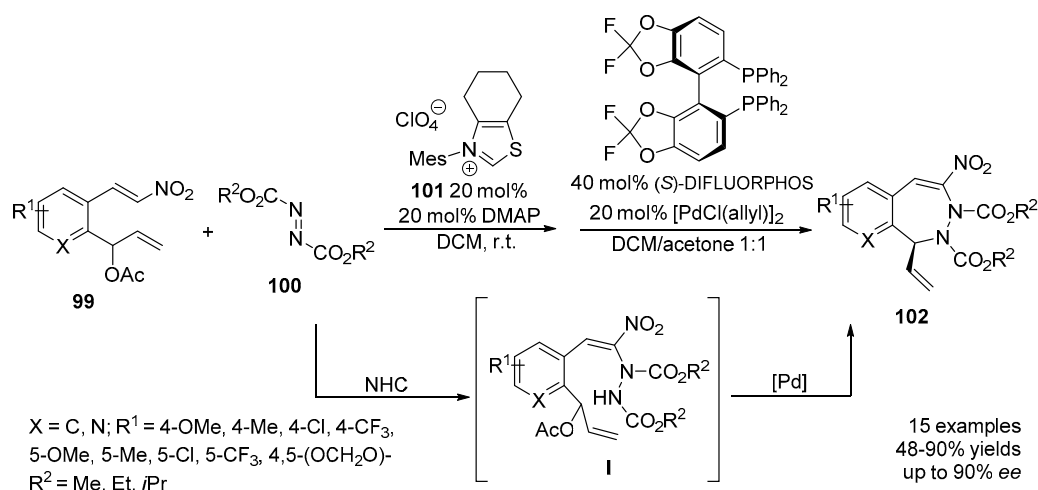
Scheme 46. A Wacker-type oxidation for the formation of 2,3-benzodiazepines **95**.

A protocol to access benzo[2,3]diazepines **98** was developed through a Pd-catalyzed [5 + 2] annulation of *N*-arylhydrazones **96** with alkynes **97** (Scheme 47) [104]. Pd(OAc)₂ was found to be optimal for the reaction conditions together with Cu(OAc)₂ as the oxidant in 1,4-dioxane. The reaction afforded the desired products in good to moderate yields with both electron donating or electron withdrawing groups. The key step was the metal-catalyzed *Csp*²-H annulation, affording the intermediate **II**. The following coordination of the Pd complex with the alkyne allowed the insertion, providing the eight-membered palladacycle **IV**, from which the metal elimination and the formation of the C–N bond gave the benzodiazepine derivatives **98**.



Scheme 47. A Pd(II)-catalyzed [5,2]-annulation, in the presence of Cu(II) as the oxidant.

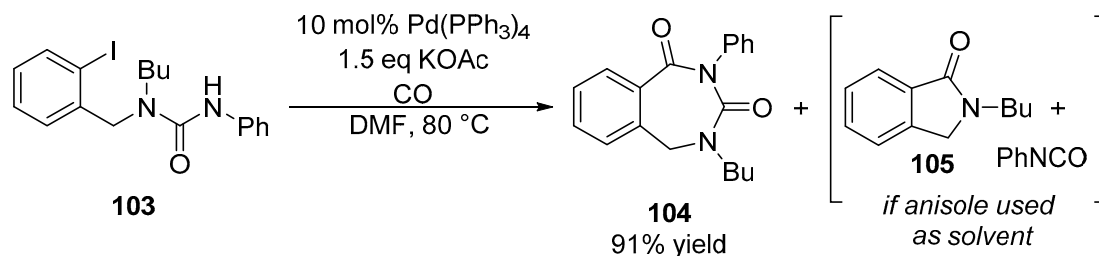
An asymmetric protocol, based on an initial NHC-catalyzed reaction of 1-(2-(2-nitrovinyl)aryl)allyl esters **99** with azodicarboxylates **100** followed by Pd-catalyzed intramolecular *N*-allylation, provided a new route to enantio-enriched 1*H*-2,3-benzodiazepines **102** (Scheme 48) [105]. The sequential addition of the corresponding reactants was necessary for enabling the formation of the desired product **102**, thus the NHC precursor (thiazolium carbene) **101** and DMAP in dry DCM was first stirred for 12 h at room temperature, then the palladium catalyst and ligand were added. The reaction conditions were optimized by varying the NHCs, palladium catalysts, ligands, solvents, and temperature, and the use of a mixture of acetone/DCM in a 1:1 ratio was found fundamental to increase the enantioselectivity in the Pd-catalyzed step. Further, (*S*)-DIFLUORPHOS, among the various ligands tested, gave the best results, providing an enantiomeric excess up to 90% in the presence of [PdCl(allyl)]₂ as the catalyst. The reaction was driven by the nucleophilic addition of the NHC catalyst to the substrates, resulting in the formation of the intermediate **I**. Then, the generation of the palladium π -allylic complex favored the intramolecular amidation to produce the 2,3-benzodiazepine products **102**.



Scheme 48. An asymmetric Pd-catalyzed intramolecular cyclization, promoted by a carbene catalyst.

2.5. 2,4-Benzodiazepines

The difficulty in preparing 2,4-benzodiazepines supports the lack of correlated works, mostly due to the instability of this core. In fact, the spontaneous rearrangement and ring contraction of the [2,4]-benzodiazepin-1,3-dione **104**, obtained in the presence of $\text{Pd}(\text{PPh}_3)_4$ as the catalyst, KOAc as the base, and CO, led to the corresponding 2,3-dihydro-isoindol-1-one **105** [106]. Nevertheless, the authors were able to prevent the rearrangement and to isolate the product **104** in 91% yield, replacing the anisole used as the solvent with DMF, likely able to stabilize the polar seven-membered ring (Scheme 49).



Scheme 49. A Pd(0)-catalyzed carbonylation affording 2,4-benzodiazepine **104**.

3. Conclusions

The present review summarizes the results in the area of palladium-catalyzed processes aimed at the preparation of different classes of benzodiazepines. The variety in the synthetic pathways was also dependent on the different starting materials. Among them, the use of domino processes shows the effectiveness of these procedures in terms of shortness and eco-compatibility and highlights the importance of these strategies for the synthesis of biologically relevant polyheterocyclic systems.

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