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Recent advances in cyclization reactions of *ortho*-substituted *gem*-dibromoolefins

Saideh Rajai-Daryasarei, *[ab] Navid Ranjbar Naieni [b] and Saeed Balalaie *[b]

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The preparation of cyclic compounds has received a significant amount of attention, because of their extensive presence in natural products, bioactive molecules, and materials science. Accordingly, the straightforward design and synthesis of cyclic compounds using readily accessible starting materials and reagents are among the main targets of synthetic chemists. In this regard, transformations involving *ortho*-substituted *gem*-dibromoolefins as good building blocks are recognized as powerful and efficient approaches for one-pot synthesis of cyclic compounds. This review focuses on approaches involving *ortho*-substituted *gem*-dibromoolefins that have been developed over the past two decades for the synthesis of cyclic compounds *via* both transition metal-catalyzed and metal-free cyclization methods.

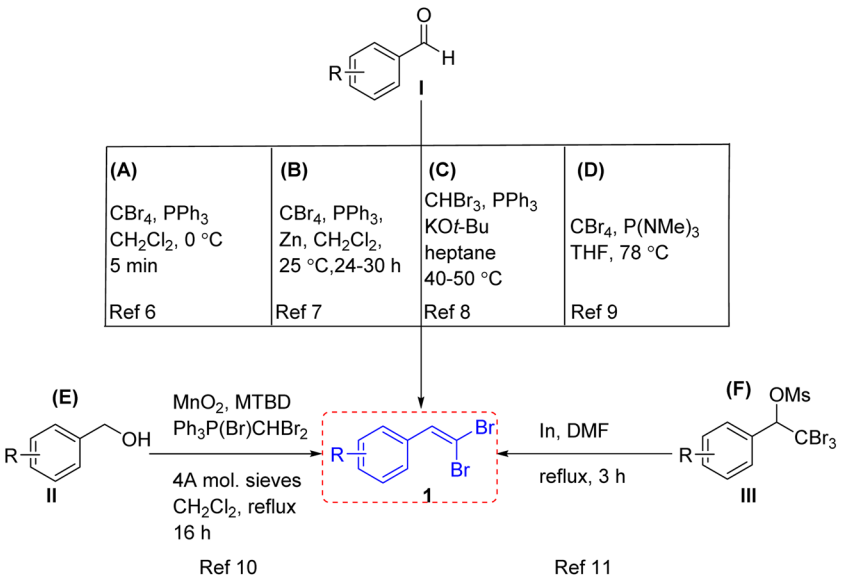
1. Introduction

Cyclic organic compounds, including carbo- and heterocycles, are found in a wide range of drugs, biomolecules, natural products, agrochemicals, and biologically active compounds, such as anti-HIV, antidiabetic, antimalarial, antibacterial, antitumor, herbicidal anti-inflammatory, antiallergic, antidepressant, antibiotic, antimicrobial, antiviral, antifungal, anticancer.[1] Moreover, cyclic compounds have broad applications in the field of materials science, and polymer chemistry, supramolecular chemistry, organic synthesis, and medicinal chemistry.[2] In light of the importance of this class of organic compounds, significant attention has been paid to the development of efficient and powerful protocols for the synthesis of cyclic structures. Among commonly utilized synthons, *gem*-dibromoolefins have found widespread applications in construction of organic compounds. They can be employed as interesting synthetic intermediates in a variety of non-metal-assisted chemical transformations.[3] Furthermore, *gem*-dibromoolefins are very prone towards oxidative addition with metal complexes compared to analogous monohaloalkenes, due to the existence of two geminal bromines bonded to the one alkenyl carbon. This makes the vinyl dihalide moiety of *gem*-dibromoolefins an appropriate and versatile bidentate electrophile for organometallic reactions, easily undergoing metal-catalyzed cross-coupling reactions.[4] *Gem*-dibromoolefins can be conveniently prepared by a variety of methods such as Wittig-type reactions, elimination-based reactions, and substitution reactions.[4,5] For example, in 1962, Ramirez and co-workers using the reaction of aromatic aldehyde with carbon-tetrabromide and triphenylphosphine, that is converted to (dibromomethylene)triphenylphosphane ($Ph_3P{=}CBr_2$) *in situ*, in CH_2Cl_2 at 0 °C for 5 min can produce *gem*-dibromoolefins **1** (Scheme 1A).[6] A modified version was later reported by Corey and Fuhs, in which zinc dust was used to reduce the initially produced Br_2PPh_3, thereby lowering the required amount of phosphine, improving the yield, and simplifying the separation process (Scheme 1B).[7] Another approach employed bromoform in place of carbon tetrabromide. The ylide $Ph_3P{=}CBr_2$, generated from bromoform and PPh_3 in the presence of KO*t*-Bu, reacted with aromaticaldehyde **I** to afford *gem*-dibromovinyl derivatives **1**, albeit in low yields (Scheme 1C).[8] A strategy reported by Combret *et al.* uses hexamethylphosphorous triamide [$P(NMe_2)_3$] in place of PPh_3, affording dibromomethylenation products **1** in satisfactory yields (Scheme 1D).[9] A method was also developed by Taylor and co-workers, involving a one-pot synthesis of 1,1-dibromoalkenes **1** from primary alcohols **II** *via* MnO_2-mediated oxidation followed by a Wittig reaction (Scheme 1E).[10] An alternative approach utilized indium metal to reduce mesylates of aryl-substituted tribromomethyl carbinols **III**, providing the corresponding vinylidene dibromides **1** in good yields (Scheme 1F).[11] In particular, the presence of an *ortho*-substitute to the *gem*-dibromoolefin moiety allows for cyclization reaction, resulting in versatile hetero- and carbocyclic compounds. Generally, the synthesis of *ortho*-substitute to the *gem*-dibromoolefin proceeds in a manner analogous to the approach first reported by Ramirez for the preparation of simpler *gem*-dibromoolefin.

Ortho-substituted *gem*-dibromoolefins include a unique combination of steric and electronic features that makes them attractive intermediates for cyclization and addition reactions. The geminal dibromo group is highly reactive and can undergo transformations including metal-catalyzed coupling,

[a]*Department of Chemistry, College of Science, University of Tehran, Tehran, Iran. E-mail: saeedehrajai@ut.ac.ir*

[b]*Peptide Chemistry Research Institute, K. N. Toosi University of Technology, P. O. Box 15875-4416, Tehran, Iran. E-mail: balalaie@kntu.ac.ir*



Scheme 1 Synthesis of *gem*-dibromovinyl derivatives.

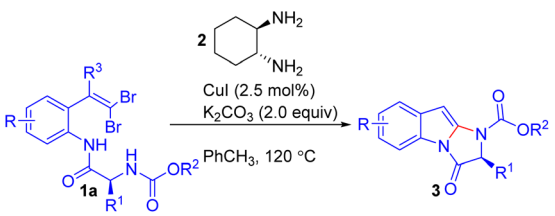
nucleophilic addition, and elimination reactions. On the other hand, these compounds have favorable spatial orientation due to the *ortho*-substituent, making them an ideal candidate for intramolecular cyclization, enabling efficient construction of cyclic and polycyclic frameworks. These properties render them valuable in the synthesis of heterocycles and complex molecular scaffolds *via* cascade or stepwise methods. Based on our investigation, no comprehensive report has been found that specifically focuses on the use of *ortho*-substituted *gem*-dibromoolefins in the synthesis of cyclic compounds. This compound contains two reactive sites that facilitate nucleophilic addition reactions. Consequently, we focus on organic reactions that employ these substrates for the construction of cyclic frameworks. This review is organized into two main sections based on the different cyclization reactions of *ortho*-substituted *gem*-dibromoolefins to construct cyclic compounds under transition-metal catalyzed or metal-free conditions. This review encompasses relevant literature published between 2004 and 2025 to highlight the significance of these starting materials in organic synthesis and to illustrate their potential for future applications. The future research for this compound not only affords novel strategies for the synthesis of specific cyclic compounds and complex molecules, but also promotes the development of the transition metal catalyzed reactions. Additionally, substituting precious metals like palladium, rhodium with cheaper and more environmentally friendly metals or organocatalytic systems and metal-free conditions may improve accessibility and reduce environmental impact.[12]

2. Transition-metal-catalyzed cyclization reactions

2.1. Copper-catalyzed cyclization

Copper catalysts have attracted considerable attention in organic synthesis due to their affordability, abundant availability, and relatively low toxicity.[13] The versatile nature of copper arises from its ability to readily access multiple oxidation states (Cu^0, Cu^I, Cu^{II}, and Cu^{III}), enabling both one-electron radical pathways and two-electron processes similar to palladium-catalyzed reactions.[14] Several reviews have highlighted the breadth and significance of copper-catalyzed and copper-mediated reactions.[15] This section specifically focuses on recent advances in copper-catalyzed cyclizations involving *ortho*-substituted *gem*-dibromoolefins, emphasizing mechanistic insights, substrate scopes, and the formation of valuable heterocyclic frameworks.

In 2006, Lautens and colleagues reported the first CuI-catalyzed tandem intramolecular amidation of *ortho*-substituted *gem*-dibromoolefins **1a** to synthesize substituted imidazoindolones **3** key motifs in bioactive compounds like asperlicin and fumiquinazolines *via* a two-step C–N bond formation sequence involving initial intramolecular amidation and subsequent coupling with a tethered carbamate (Scheme 2).[16] The authors found that using *trans*-1,2-cyclohexyldiamine **2** with K_2CO_3 in toluene at 120 °C gave the best yields and up to 98% enantiomeric excess. The scope of the reaction was explored using a variety of amino acid-derived *ortho*-substituted *gem*-dibromoolefins **1a**, showing that alkyl groups, including sterically hindered substituents like isopropyl and isobutyl, were well tolerated. Notably, substrates with

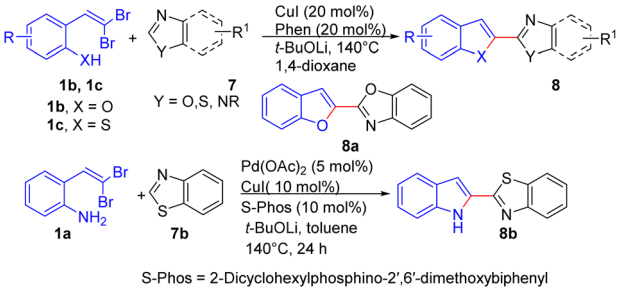


Scheme 2 Synthesis of substituted imidazoindolones.

heteroatoms or sensitive functional groups, such as carbamates, successfully formed five-membered imidazoindolone rings **3** without competing side reactions. A series of electron-donating and electron-withdrawing groups on the aromatic ring had minimal impact on the efficiency, except for the 5-methoxy group, which slightly reduced the yield due to steric hindrance.

Zhang *et al.* described a mild and simple method for synthesizing 2-bromoindoles **4** through a ligand-free CuI-catalyzed intramolecular cross-coupling of *gem*-dibromovinylaniline derivatives **1a** (Scheme 3).[17] The reaction proceeds smoothly in toluene at room temperature using K_3PO_4 as the base and CuI as the catalyst, affording the desired 2-bromoindole derivatives 4 in excellent yields. The authors evaluated different *N*-protecting groups on the aniline substrate and identified methanesulfonyl as the most effective, likely due to its coordinating ability and the ease of deprotonation of the aniline's 'NH' group by the base. Under these optimized conditions, a variety of 2-bromoindoles 4 were synthesized from *ortho*-substituted *gem*-dibromoolefins 1, including substrates with electron-withdrawing (*e.g.*, 4-Cl, 4-F) and electron-donating (*e.g.*, 4-Me, 4-OMe) substituents. The reaction showed broad functional group tolerance, successfully delivering the desired products 4 even with steric bulk near the dibromoolefin moiety or adjacent to the *N*-Ms group. The proposed mechanism involves initial coordination of CuI to the sulfonamide group, followed by oxidative insertion into the *gem*-dibromoolefin to form a cyclic copper intermediate 6, which subsequently undergoes reductive elimination to furnish the target 2-bromoindoles **4**.

In 2011, Lan and colleagues developed a one-pot Cu(II)-catalyzed reaction to synthesize benzofused heteroaryl azoles **8** (Scheme 4).[18] Two bonds including C(sp^2)–C(sp^2) and C(sp^2)–O bonds were constructed in one synthetic operation in the tandem cross-couplings of *ortho*-substituted *gem*-dibromoolefins **1b**/**1c** with azoles **7**. It is noteworthy that their strategy is not only appropriate for various benzofused heterocycles **8** (*e.g.*, benzofurans, benzothiophenes, and indole), but also a relatively wide range of azoles **7** including thiazoles, oxazoles, imidazoles, and oxadiazoles, resulting in good to excellent yields of the desired products **8**. Remarkably, the methodology effectively produced 2-(benzofuran-2-yl)-benzoxazole **8a**, an active ingredient in sunscreen formulations, with a 68% yield. Several synthesized compounds are

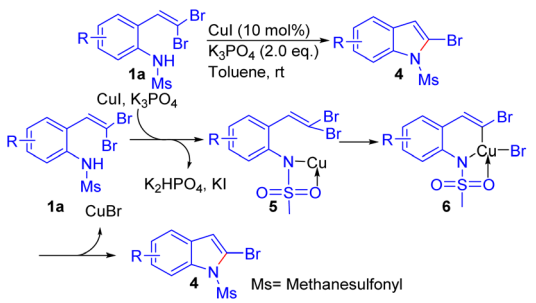


Scheme 4 Synthesis of benzofused heteroaryl azoles.

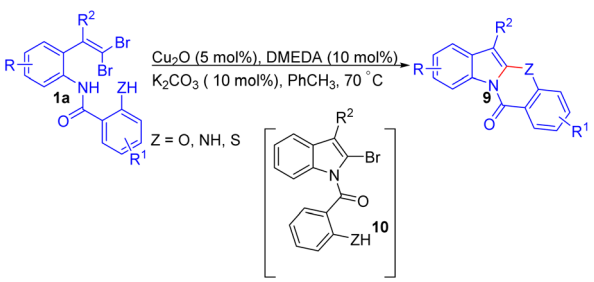
crucial biologically active alkaloids and display high potency as antagonists at human A2B adenosine receptors. Although the Cu(I)/Phen catalytic system effectively facilitated the coupling of 2-*gem*-dibromovinylphenol/thiols **1b**/**1c** with various azoles **7b**, the synthesis of 2-(indole-2-yl)-azoles **8b** from 2-*gem*-dibromovinylbenzenamine **1a** posed a challenge. However, a catalyst system generated *in situ* from $Pd(OAc)_2$/S-Phos/CuI and *t*-BuOLi provided a viable solution, successfully yielding 2-(indol-2-yl)-benzothiazole **8b** with a 52% yield.

In 2012, a versatile methodology for synthesizing polycyclic indole derivatives **9** from *gem*-dibromoolefins **1a** was introduced by Xia and colleagues (Scheme 5).[19] This approach utilized a mild and efficient Cu_2O-catalyzed domino reaction involving intramolecular C–N coupling and C–Z (Z = O, S, N) bond formation. The optimized conditions included Cu_2O as the catalyst, *N*,*N*′-dimethylethylenediamine (DMEDA) as the ligand, K_2CO_3 as the base, all in toluene at 70 °C under N_2. The method demonstrated broad tolerance, with most substituted *o*-*gem*-dibromovinyl substrates **1a** delivering polycyclic products **9** in excellent yields within 0.5–6 hours. Both electron-donating and electron-withdrawing groups on the indolyl or phenyl rings were tolerated, though substrates with strongly two electron-withdrawing groups (NO_2) produced only trace amounts of tetracyclic product **9** due to reduced nucleophilicity of both the NH and OH groups. The formation of monocyclized intermediate **10** as the key intermediate in this reaction was suggested by the authors.

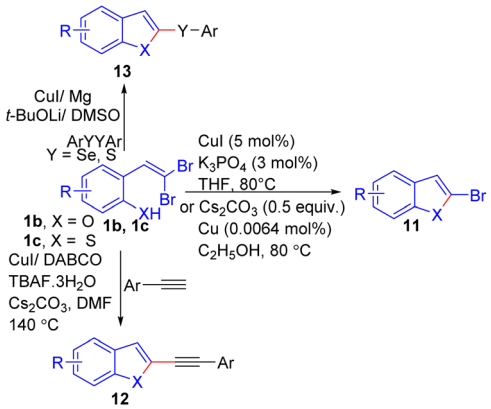
Several one-pot protocols have also been developed for synthesis of benzofuran/thiophen derivatives **11**, **12**, **13** using reaction of *ortho*-substituted *gem*-dibromoolefins **1b**/**1c** with other reagents in the presence of Cu catalyst in moderate to excellent yields.[20] These protocols are summarized in Scheme 6.



Scheme 3 Synthesis of 2-bromoindole derivatives.



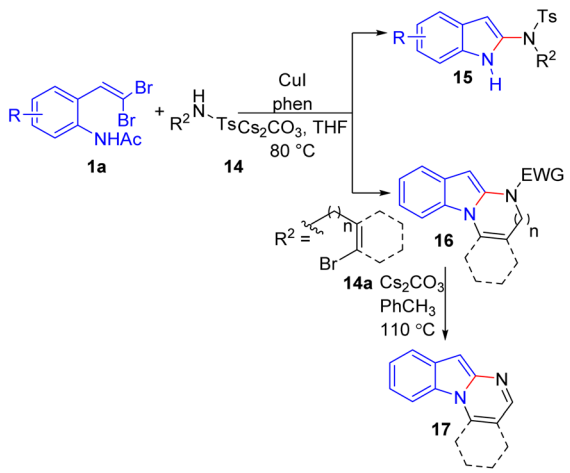
Scheme 5 Synthesis of polycyclic indole derivatives.



Scheme 6 Synthesis of benzofuran/thiophen derivatives.

In another study, Perumal's group reported a Cu(I)-catalyzed protocol for synthesizing 2-amidoindoles **15** and indolo[1,2-*a*]quinazolines **17** directly from *o-gem*-dibromovinylanilides and sulfonamides **1a** in a one-pot process *via in situ* ynamide formation followed by base-promoted intramolecular hydroamidation (Scheme 7).[21]

The optimal conditions involved using 5 mol% of CuI, 10 mol% of 1,10-phenanthroline, and 4 equivalents of Cs_2CO_3 in THF at 80 °C. Excellent yields were generally observed for substrates containing electron-rich moieties, halogen substituents, or heterocyclic motifs. Additionally, compatibility with aliphatic substituents such as *n*-butylsulfonamide was demonstrated, affording desired products. Sulfonamides (–Ts or –Ms) were identified as the best coupling partners for the formation of ynamides, resulting in excellent yields of 2-amidoindoles **15** in shorter time durations. The reaction was not successful with acyclic amides or carbamates, which the authors attributed to their lower acidity and the steric hindrance of other nitrogen nucleophiles, making the formation of ynamides very slow and difficult. The reaction was effective with various *N*-tosyl-*o*-bromobenzamides **14a**, producing tetrahydroindolo[1,2-*a*]quinazolines **16** in excellent yields. The synthesized tetrahydroindolo[1,2-*a*]quinazolines **16** were then refluxed under basic conditions to yield indolo[1,2-*a*]quinazolines **17**.



Scheme 7 Synthesis of 2-amidoindoles and indolo[1,2-*a*]quinazolines.

In 2015, Li *et al.* developed a copper-catalyzed multicomponent cascade reaction for the synthesis of 3-cyano-1*H*-indoles **18**, 9*H*-pyrimido[4,5-*b*]indoles **19**, and 9*H*-pyrido[2,3-*b*]indoles **20** from *o-gem*-dibromoolefine derivatives **1d**, aldehydes, and aqueous ammonia (Scheme 8).[22] This one-pot method offers high efficiency and selectivity, with the products determined by controlling the concentration of ammonia and the molar ratio of reagents, furthermore, it tolerates a wide variety of aldehydes, with aryl and alkyl substituents providing good to excellent yields. The authors proposed three distinct mechanisms for the formation of the products during their copper-catalyzed cascade reaction.

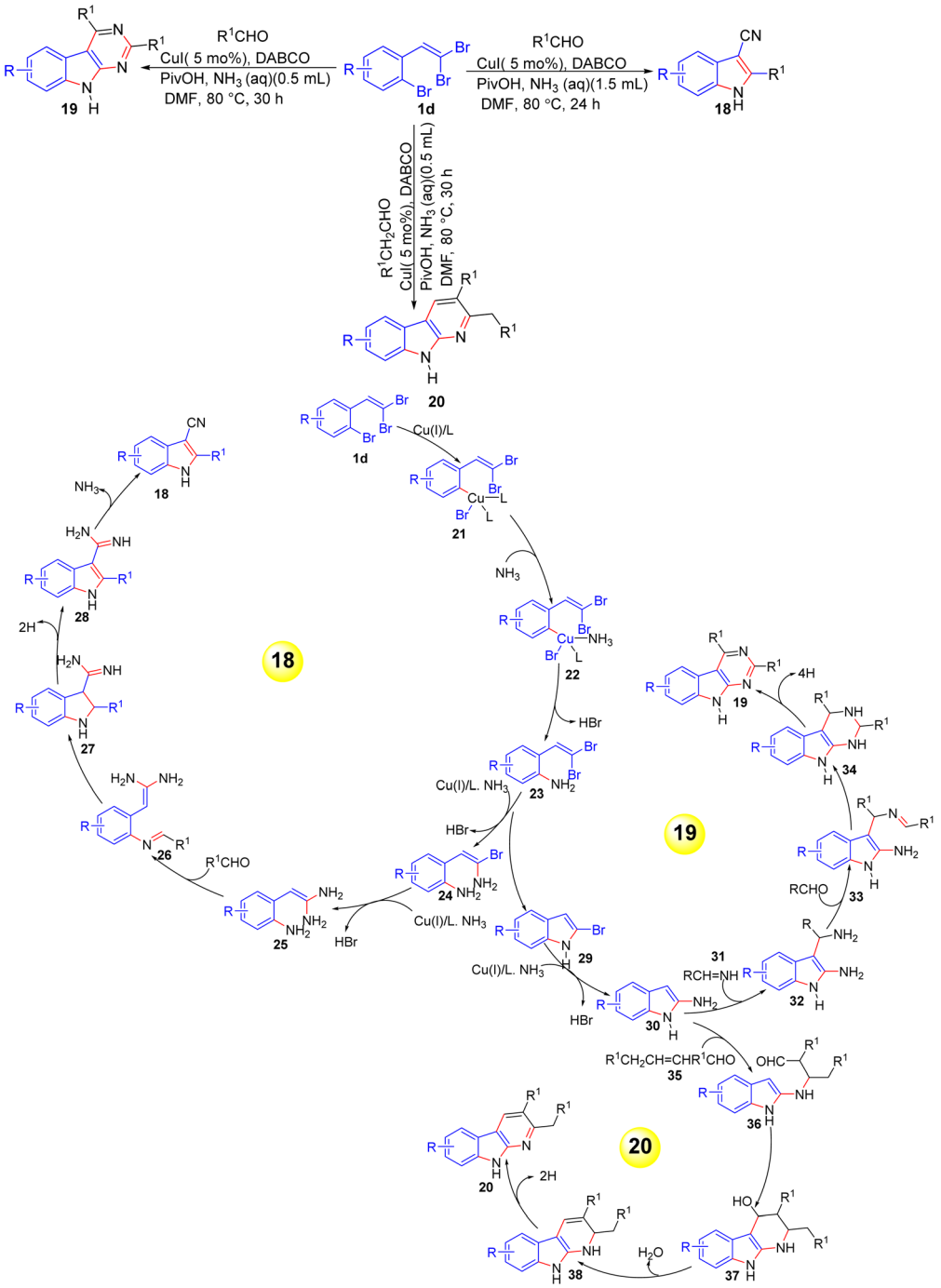
2.1.1. Mechanism for 18. The formation of **18** begins with Cu(I)-catalyzed aryl amination of 1-bromo-2-(2,2-dibromovinyl) benzene **1d**, producing intermediate **23**. Under high ammonia concentration, intermediate **23** undergoes sequential vinyl amination to form intermediates **24** and **25**. Condensation of **25** with aldehyde leads to imine **26**, followed by intramolecular nucleophilic addition to form intermediate **27**. Oxidative dehydrogenation of **27** yields **28**, and final ammonia elimination gives the cyanoindole products **18**.

2.1.2. Mechanism for 19. Under lower ammonia concentration, the same intermediate **23** first undergoes intramolecular C–N coupling to form 2-bromoindole **29**. Subsequent aryl amination results in the formation of 2-aminoindole **30**, which then reacts with imine **31** (formed from aldehyde and ammonia) to produce intermediate **32**. Further condensation of **32** with another molecule of aldehyde leads to imine **33**. Nucleophilic cyclization of **33** affords tetrahydro-1*H*-pyrimido[4,5-*b*]indole **34**, which, upon oxidative aromatization, yields **19**.

2.1.3. Mechanism for 20. The formation of **20** proceeds with intermediate **30** undergoing Michael addition on an α,β-unsaturated aldehyde **35** formed from self-aldol condensation of acetaldehyde, leading to access intermediate **36**. The resulting adduct **36** undergoes intramolecular aldol-type cyclization to form intermediate **37** and **38**. Oxidative dehydrogenation of **38** gives the final pyrido[2,3-*b*]indole product **20**.

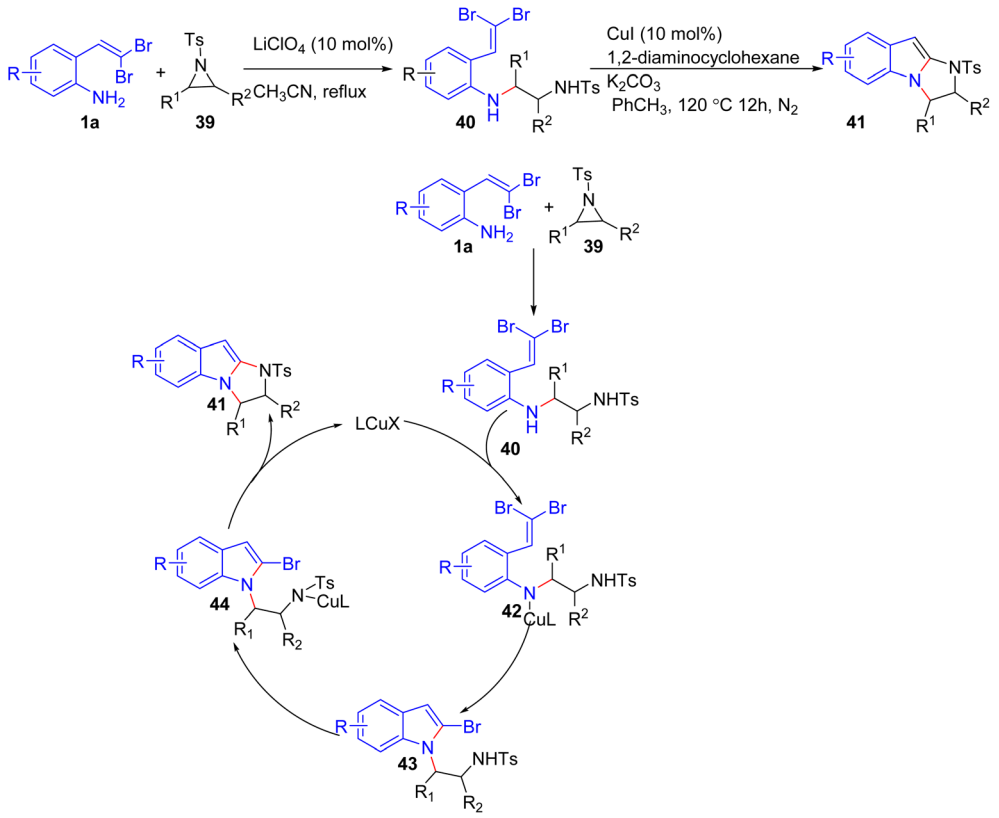
Ghorai *et al.* developed a new synthetic route for producing substituted imidazoindoles **41** in high yields with excellent ee values (Scheme 9).[23] Activated aziridines **39** undergo ring-opening reactions with *o-gem*-dibromovinylanilines **1a** in the presence of $LiClO_4$ as a Lewis acid, producing compounds **40**, then, this reaction is followed by a copper-catalyzed domino strategy two consequent C–N coupling to formation of imidazoindoles **41**. Under optimized CuI-catalyzed conditions, compounds **40** formed cyclized products **41** with good to excellent yields. It is worth that, 2-bromobenzoheterocycle **43** is as key intermediate in this transformation.

A novel method to access 2-(arylselanyl)benzo[*b*]chalcogenophenes **47** through Cu(I)-catalyzed annulation of vinyl selenides **46** that is formed from reaction of *gem*-dibromoolefins **1b**/**1c**/**1e** with diaryl diselenides **45**, has been documented by Perin *et al.* (Scheme 10).[24] They were the first group to report a general protocol to access seleno-

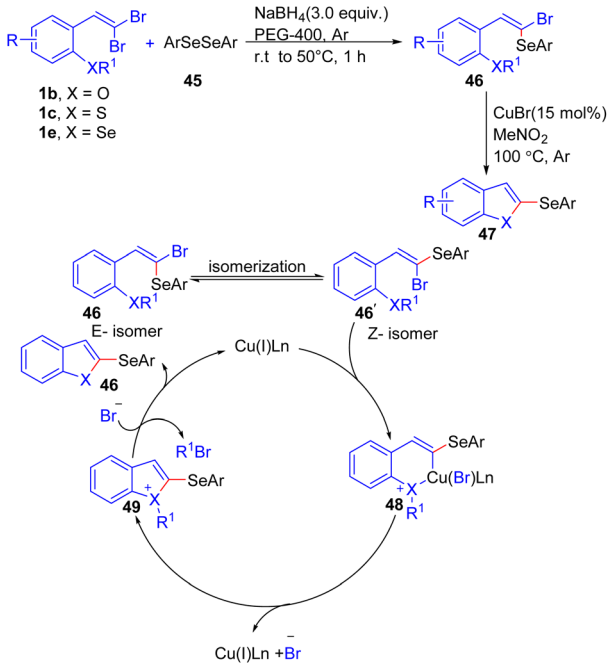


Scheme 8 Synthesis of 3-cyano-1*H*-indoles **18**, 9*H*-pyrimido[4,5-*b*]indoles **19**, and 9*H*-pyrido[2,3-*b*]indoles **20**.

functionalized benzo[*b*]chalcogenophenes **47**. First, by using $NaBH_4$ as a reducing agent and PEG-400 as the solvent under inert conditions, *ortho*-substituted *gem*-dibromoolefins **1** were reacted with diaryl diselenides **45**, affording (*E*)-1-bromo-1-arylselenoalkenes **46** as the products. Then, by reacting **46** with CuBr in nitromethane, 2-(arylselanyl)benzo[*b*]chalcogenophenes **47** were obtained with good yields. The authors proposed this process begins with an isomerization step, converting the *E*-isomer **46** to the *Z*-isomer **46′**, which is better suited for oxidative addition to the Cu(I) species, forming the selenonium intermediate **48**. Remarkably, experimental evidence supports this hypothesis, as a control experiment using the pure *E*-isomer **46** under the reaction conditions resulted in 45% isomerization to the *Z*-isomer **46′**. Subsequently, an Ullmann-type coupling generates intermediate **48**, releasing the copper catalyst and bromide. Finally, the bromide acts as a nucleophile, attacking the alkyl group *via* an S_N2 mechanism to produce the desired product **47** and 1-bromoalkane as a by-product (Scheme 10).

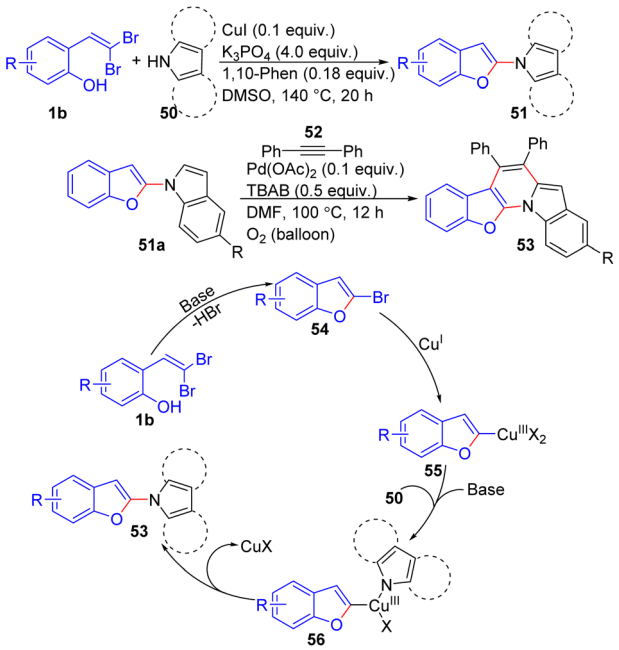


Scheme 9 Synthesis of substituted imidazoindoles.



Scheme 10 Synthesis of 2-(arylselanyl)benzo[*b*]chalcogenophenes.

Under copper-catalyzed tandem reaction conditions, Rao and Islam developed a versatile method for the synthesis of 1-(2-benzofuryl)-*N*-heteroarenes **51** from *ortho*-substituted *gem*-dibromoolefins **1b**, demonstrating a broad substrate scope and high yields (Scheme 11).[25] Further, these products were effectively utilized in the formation of polycyclic benzofuro-indolo-



Scheme 11 Synthesis of 1-(2-benzofuryl)-*N*-heteroarenes.

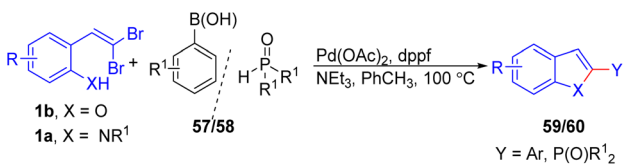
pyridine architectures **53** through palladium-catalyzed dehydrogenative coupling. The optimized reaction conditions for the copper-catalyzed cross-coupling of 2-(2,2-dibromovinyl) phenol **1b** and indole **50** were found to be DMSO as the solvent, K_3PO_4, CuI, and 1,10-phenanthroline as the base, copper catalyst, and additive, respectively, at 140 °C for 20 hours. The reported methodology for copper-catalyzed cross-coupling reactions of *o-gem*-dibromides **1b** with *N*-heteroarenes **50** proved to be versatile and efficient, yielding a range of bis-heterocycles **51** in good to excellent yields regardless of the presence of electron-donating or -withdrawing functional groups. The mechanism the authors proposed, involves a base-promoted cyclization of 2-(2,2-dibromovinyl)phenol **1b** to form 2-bromobenzofuran **54**. Then, intermediate **54** is converted to complex **55** in the presence of Cu(I), which, complex **55** reacts with the *N*-heteroarene **50** to generate the highly reactive Cu(III) complex **56**. Finally, reductive elimination reaction of intermediate **56** delivers desired the 1-(2-benzofuryl)-*N*-heteroarenes **53**.

2.2. Palladium-catalyzed cyclization

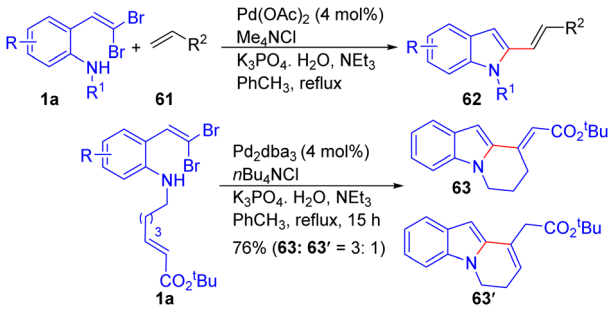
Palladium is widely regarded as one of the most versatile and commonly employed transition metals in heterocyclic synthesis, owing to its ability to mediate diverse reactions under mild conditions. Its broad utility originates from the accessible interconversion among its oxidation states (Pd^0, Pd^{II}, and Pd^{IV}), each exhibiting distinct chemical behaviors. Palladium catalysis typically requires only catalytic quantities of metal and exhibits exceptional functional group tolerance, usually minimizing the need for protecting groups. This section highlights recent developments in palladium-catalyzed transformations of *ortho*-substituted *gem*-dibromoolefins.[26]

Thielges *et al.* developed a tandem Pd-assisted cyclization–coupling reaction for the synthesis of 2-functionalized benzo[*b*] furans and indoles **59**/**60** starting from *ortho*-substituted *gem*-dibromoolefins **1b**, **1a** and boronic acids **57**/dialkylphosphites **58** (Scheme 12).[27] By employing palladium acetate [$Pd(OAc)_2$] and 1,1′-bis(diphenylphosphino)ferrocene (dppf) as a ligand in toluene with triethylamine as base, the reaction achieves excellent yields while minimizing side products.

Another great example of utilizing *o-gem*-dibromovinylanilines **1a** to construct complex indole systems is provided by Lautens *et al.*, who reported a Pd-catalyzed tandem C–N/Heck reaction for the synthesis of 2-vinylic indoles **62** and their tricyclic derivatives **63**/**63′** in the presence of Me_4NCl instead of expensive phosphine ligands (Scheme 13).[28] The authors demonstrated that the reaction tolerates a broad range of alkenes **61**, including those bearing electron-donating (*e.g.*, methoxy) and electron-withdrawing groups (*e.g.*, nitrile), as well



Scheme 12 Synthesis of 2-functionalized benzo[*b*]furans and indoles.

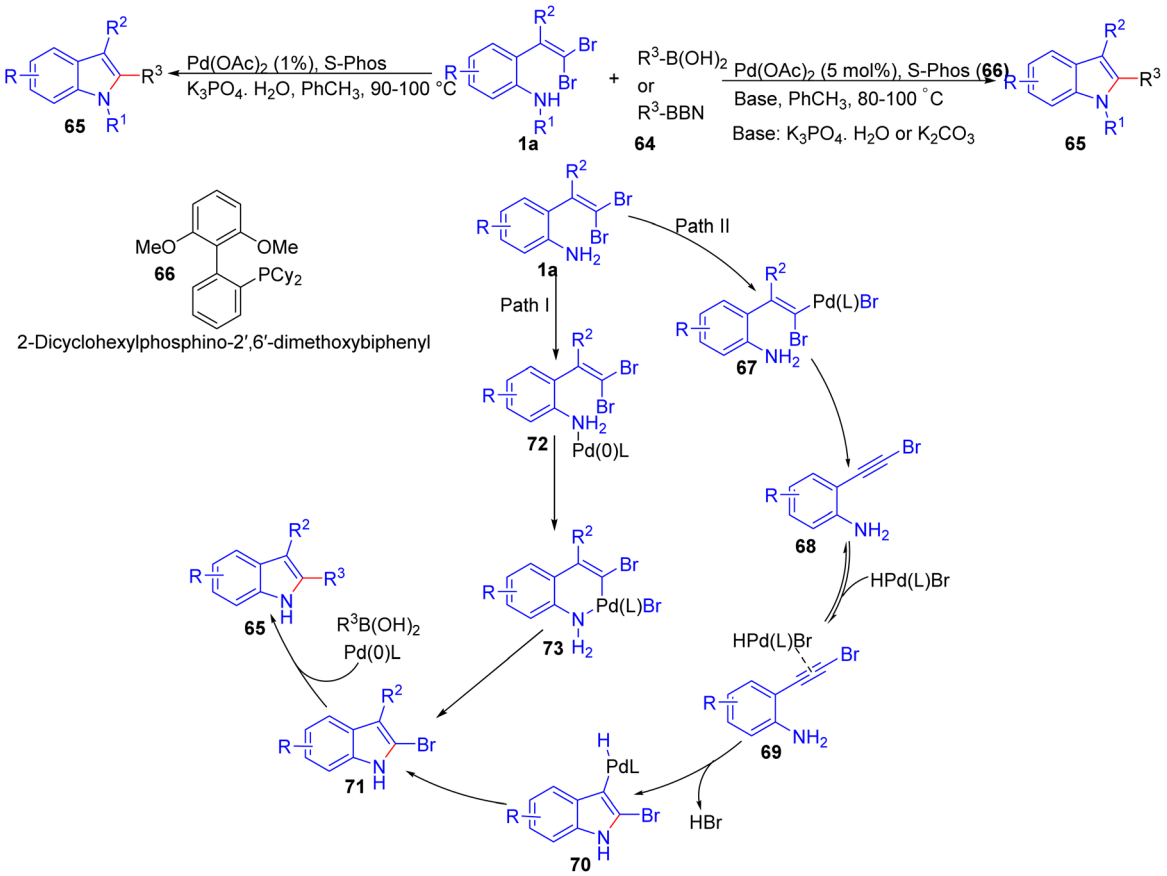


Scheme 13 Synthesis of 2-vinylic indoles and their tricyclic derivatives.

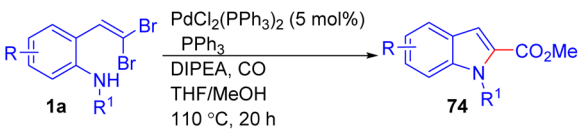
as functional groups like esters and sulfones, showcasing the versatility of this method. Additionally, a variety of *N*-substituted dibromovinylanilines **1a** were compatible, providing 2-vinylic indoles **62** with diverse substitution patterns. The enoate **1** was employed in the presence of tris(dibenzylideneacetone)dipalladium (Pd_2dba_3) (4 mol%) with *n*-Bu_4NCl (1 equiv.) and $NEt_3/K_3PO_4 \cdot H_2O$ in toluene at 120 °C, for this study, and gave the desired tricyclic adduct **63** in good yield.

In 2005, Fang and Lautens reported a protocol to generate 2-substituted indoles **65** *via* a Pd-catalyzed tandem C–N/Suzuki–Miyaura coupling starting from dibromovinylanilines (Scheme 14).[29] Optimized reaction conditions were $Pd(OAc)_2$ coupled with Buchwald's S-Phos ligand **66** in the presence of K_3PO_4/H_2O in toluene at 90–100 °C. Three years later, they further developed the same methodology, and proposed a possible mechanism and expanded the scope (Scheme 14).[30] The reaction scope was explored with various *gem*-dihalovinylaniline substrates **1a**, demonstrating broad functional group tolerance across both electron-rich and electron-deficient substituents. A range of aryl, alkenyl, and alkyl boron reagents **64** were successfully incorporated, giving the desired indole products **65** in good to excellent yields. The versatility of this methodology is further highlighted by its ability to synthesize 2,3-disubstituted and 1,2,3-trisubstituted indoles **65** through a sequential coupling strategy. Based on several control experiments, the authors proposed two possible pathways: one involves initial alkynyl **68** formation (path II) followed by 5-*endo-dig* cyclization to generate the C–N bond before undergoing Suzuki coupling, while the alternative is a direct Buchwald–Hartwig amination (path I) followed by the Suzuki coupling.

Alper and their group reported a tandem Pd-catalyzed N, C-coupling/carbonylation sequence for the synthesis of 2-carboxyindoles **74** from *gem*-dibromovinyl aniline substrates **1a** (Scheme 15).[31] This reaction employs $PdCl_2(PPh_3)_2$ in a mixture of THF and methanol under 10 atm of CO at 110 °C, affording the target 2-carboxyindole derivatives **74** in good to excellent yields. The authors noted that the combination of THF and methanol as solvents significantly enhanced product formation compared to using either solvent alone. The protocol showed extensive functional group tolerance, accommodating halogen substituents (*e.g.*, chlorine, fluorine), as well as electron-donating (*e.g.*, methoxy, methyl), without significantly affecting the reaction efficiency.

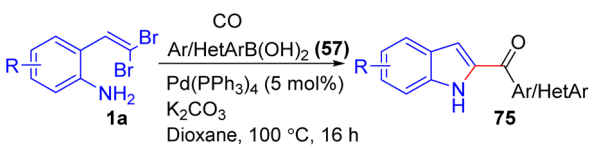


Scheme 14 Pd-catalyzed tandem reaction to formation functionalized indoles.



Scheme 15 Synthesis of 2-carboxyindoles.

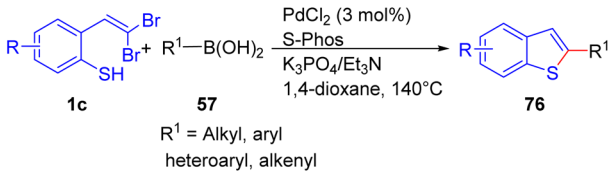
Florent *et al.* disclosed a palladium-catalyzed one-pot domino reaction for synthesizing 2-aroyl- and 2-heteroaroylindoles **75** from *o-gem*-dibromovinylanilines **1a**, boronic acids **57**, and carbon monoxide (Scheme 16).[32] The reaction, using $Pd(PPh_3)_4$ and K_2CO_3 in dioxane under 12 bar of CO at 100 °C, proceeds *via* C, N-coupling, carbonylation, and Suzuki coupling, yielding 2-aroylindoles **75** in moderate to good yields. The scope of this palladium-catalyzed domino reaction demonstrated notable versatility, accommodating a wide range of *gem*-dibromovinylanilines **1a** and boronic acid derivatives **57**.



Scheme 16 Synthesis of 2-aroyl- and 2-heteroaroylindoles.

Electron-rich boronic acids **57**, such as 4-methoxyphenyl and 3,4,5-trimethoxyphenyl, gave higher yields, while sterically hindered substrates like 2-methoxyphenylboronic acid resulted in slightly lower efficiency. Electron-deficient and halogen boronic acids **57**, such as 4-chlorophenyl and 4-trifluoromethylphenyl, were also compatible, producing the desired products **75** in good yields. Heteroaryl boronic acids **57**, including thiophene, benzofuran, and dibenzofuran derivatives, were successfully incorporated, broadening the method's applicability to heterocyclic frameworks. However, reactions involving isoquinolin-3-boronic acid were less efficient, which the authors attributed to interference from the nitrogen atom on the boronic acid **57**, resulting in lower yields of the desired products **75**. The reaction also tolerated various substituents on the *o-gem*-dibromovinylaniline backbones **1a**, with electron-donating groups enhancing yields while electron-withdrawing groups showed moderate reactivity.

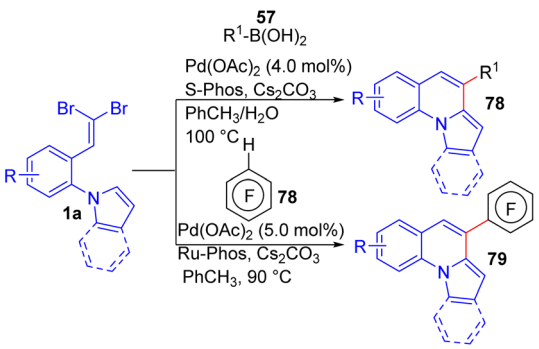
In 2009, Lautens and their colleagues described the first example of a tandem catalytic process that incorporates C–S coupling, and the first example of the palladium-catalyzed reaction of a *o-gem*-dibromovinylthiol **1c** to access benzothiophenes **76** in moderate to good yields (Scheme 17).[33] Utilizing $PdCl_2$/S-Phos as their catalytic system, they synthesized a series of functionalized benzothiophenes **76** *via* C–S bond-forming and Suzuki–Miyaura coupling reaction. Electron-



Scheme 17 Synthesis of benzothiophenes.

poor, sterically hindered boronic acids and heteroaromatic boronic acids **57** displayed reactivity comparable to electron-rich 3,4- dimethoxyphenylboronic acid, yielding desired products **76** up to 99%. Both aryl and vinyl trifluoroborate salts were successfully coupled, albeit requiring an increase in the amount of base used. Remarkably, they investigated trialkyl boranes and boronic esters as a patterner that provided access to corresponding products with a good yield.

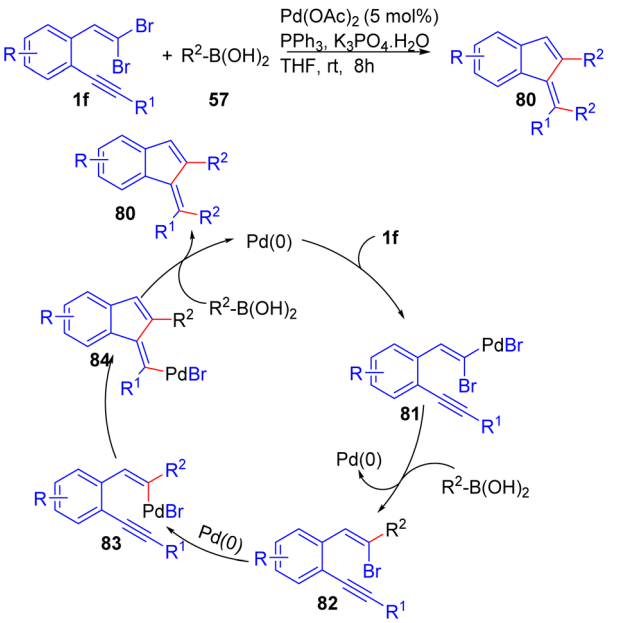
Chai and Lautens disclosed a highly efficient, water-accelerated, palladium-catalyzed reaction of *ortho*-substituted *gem*-dibromoolefins **1a** with a boronic acid derivatives **57** *via* a tandem Suzuki–Miyaura coupling and direct arylation process in the presence of S-Phos as ligand and Cs_2CO_3 as base in toluene at 100 °C to access pyrrolo[1,2-*a*]quinolines **78** (Scheme 18).[34] The scope of the reaction was explored using diverse electron-rich and electron-poor boronic acids **54** and substituents on the aromatic ring, revealing excellent compatibility. However, very electron-poor or -rich boronic acids **57** showed reduced yields. The methodology was extended to alkenyl, alkyl, and sterically hindered boronic acids, achieving good results. Substituents on the dibromo alkene partner **1a** were varied, with moderate to excellent yields obtained. Heteroaromatic ring systems like indole and pyridine derivatives successfully led to formation products. It is worth mentioning that, the water has a dramatic effect on reactivity of the substrate and the decreasing of the byproduct. Three years later, Wu *et al.* also reported the synthesis of 4-polyfluoroaryl pyrrolo[1,2-*a*]quinolines **79** *via* a palladium-catalyzed C–H bond activation reaction of *ortho*-substituted *gem*-dibromoolefins **1a** bearing pyrrole moieties with polyfluoroarenes **78** under similar reaction conditions. By this methodology, a study on the reaction scope using several electron-rich and electron-deficient substrates was performed, allowing the synthesis of desired products **79** in poor to very good yields.[35]



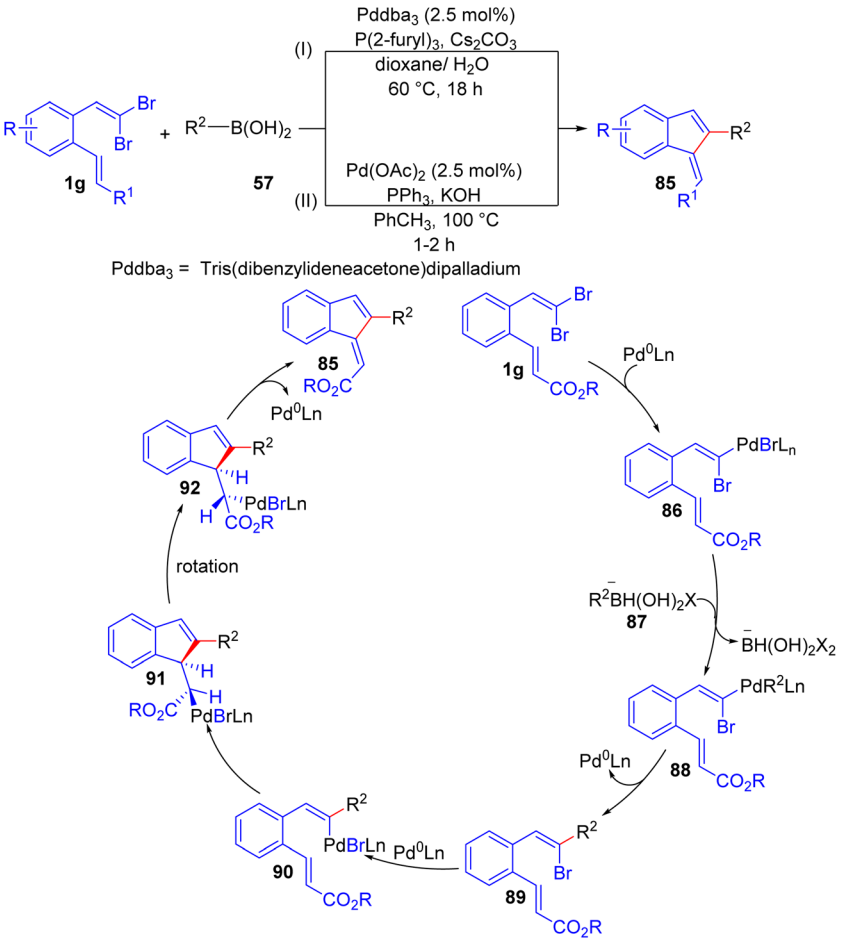
Scheme 18 Synthesis of pyrrolo[1,2-*a*]quinoline derivatives.

Wu's group developed a method to synthesize 1-methyleneindenes **80** using *ortho*-substituted *gem*-dibromoolefins **1f** in a palladium-catalyzed tandem reaction with arylboronic acids **57**, efficiently yielding functionalized 1-methyleneindenes **80** under mild conditions with high selectivity (Scheme 19).[36] Mechanistically, the reaction follows a sequence of palladium-catalyzed oxidative additions, transmetallation, and reductive eliminations, where the *ortho*-substituted *gem*-dibromoolefins **1f** undergoes key transformations, allowing for subsequent coupling and cyclization steps. The reaction scope demonstrated broad versatility, accommodating a variety of arylboronic acids **57** with both electron-donating and electron-withdrawing substituents. Even alkyl-substituted boronic acids, such as *n*-butylboronic acid, participated smoothly, further highlighting the flexibility of the method. The reaction also tolerated steric hindrance around the aryl group, with *o*-substituted arylboronic acids showing good reactivity. Additionally, the use of 1-(2,2-dibromovinyl)-2-alkynylbenzenes **1f** proved efficient in delivering the desired products **80**, with the reaction proceeding smoothly under mild conditions.

Bryan and Lautens successfully developed a Pd-catalyzed tandem Suzuki/intramolecular Heck reaction of *o*-substituted *gem*-dibromoolefins **1g** and boronic acid **57** to access methylenindene scaffolds **85**, employing Pd_2dba_3 as catalysts, and Cs_2CO_3 as the base (Scheme 20(I)).[37] The choice of ligand proved crucial in selectivity of the reaction, and trifurylphosphine (TFP) was selected as the best ligand in this transformation. The reaction accommodated diverse boronic acids **57** and Heck acceptors, with improved efficiency for electron-rich systems. Electron-poor substrates and steric hindrance reduced yields and reaction rates, respectively. A thiophenyl substrate **1g** showed slow reactivity due to sulfur coordination, hindering the Heck process and resulting in low yields. Mechanistic pathway



Scheme 19 Synthesis of 1-methyleneindenes.

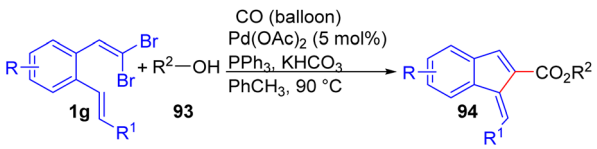


Scheme 20 Pd-catalyzed tandem Suzuki/intramolecular Heck reaction of *o*-substituted *gem*-dibromoolefins and boronic acid.

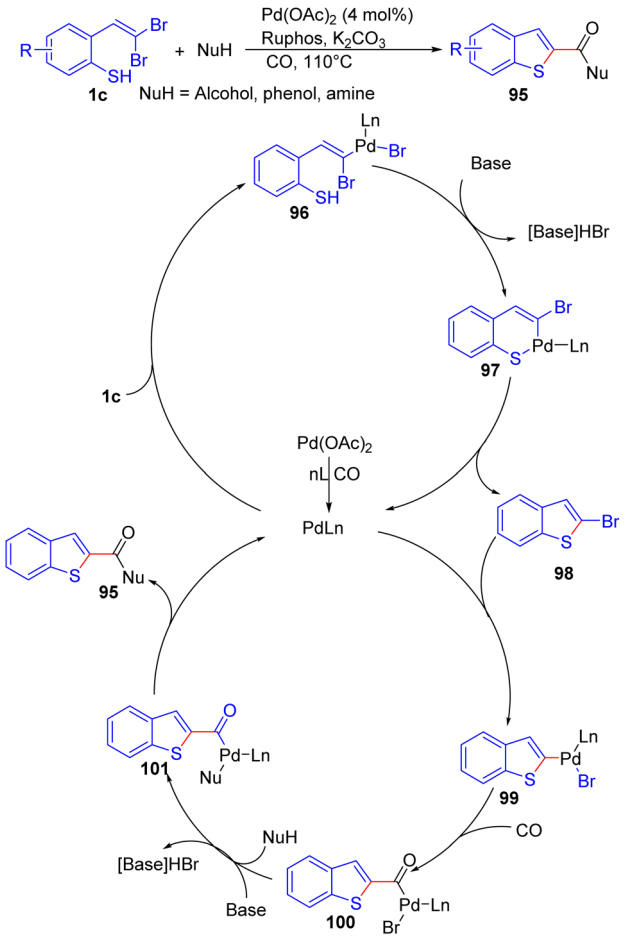
involves oxidative addition of *o*-substituted *gem*-dibromoolefins **1g** to Pd^0, followed by transmetalation with a boronate **87**, and reductive elimination of intermediate **89**, regenerating the Pd^0 species. Then, intermediate **89** is converted to the alkenylpalladium **90** in the presence of Pd^0. Finally, carbopalladation of **90** followed by β-hydride elimination affords the methyleneindene **85**. In the same year, Wu *et al.* published a synthesis of 1-methylene-1*H*-indenes **85** *via* same starting materials in the presence of $Pd(OAc)_2$ (2.5 mol%) and PPh_3 (5 mol%) as catalyst with KOH (3.0 equiv.) as base in toluene (Scheme 20(II)).[38] Short reaction time is the most important feature of this method compared to the reported method by Lautens.

Ye and Wu described a palladium-catalyzed cyclization of *o*-substituted *gem*-dibromoolefins **1g**, and carbon monoxide, with phenol or alcohol **93** to produce 1-methylene-1*H*-indene-2-carboxylates **94** through a cascade process that integrated carbonylation and a Heck reaction (Scheme 21).[39] They believed that acetate anion in the palladium acetate is necessary for this transformation, because, other palladium source led to suppress formation of desired product **94**. The presence of various functional groups on the aromatic ring of *o*-substituted *gem*-dibromoolefins **1g** generally resulted in good products **94** yield. However, replacing the R^1 position with a ketone or aryl group led to only trace amounts of product formation.

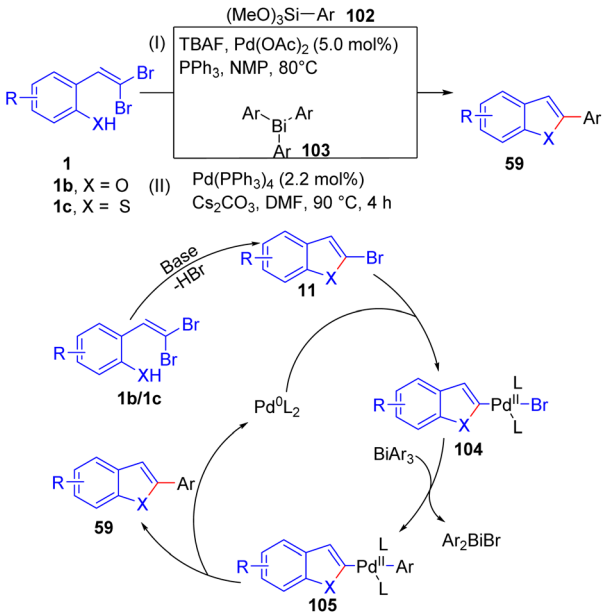
Zeng and Alper documented a highly selective synthetic route to 2-carbonylbenzo[*b*]thiophene scaffolds **95** starting from *o*-substituted *gem*-dibromoolefins **1c** with alcohol, phenol and amine as nucleophiles and carbon monoxide in 2011 (Scheme 22).[40] Their methodology involves palladium-catalyzed intramolecular C–S coupling/intermolecular carbonylation cascade sequences utilizing a $Pd(OAc)_2$/2-dicyclohexylphosphino-2′,6′-diisopropoxybiphenyl (RuPhos) catalytic system with K_2CO_3 acting as the base. A proposed mechanism for the formation of 2-carbonylbenzo[*b*]thiophenes **95** is illustrated in Scheme 22. The process commences with the oxidative addition of **1c** to the *in situ* generated pd^0 species, resulting in palladium complex **96**. Subsequently, base-



Scheme 21 Synthesis of 1-methylene-1*H*-indene-2-carboxylates.



Scheme 22 Synthesis of 2-carbonylbenzo[*b*]thiophene.

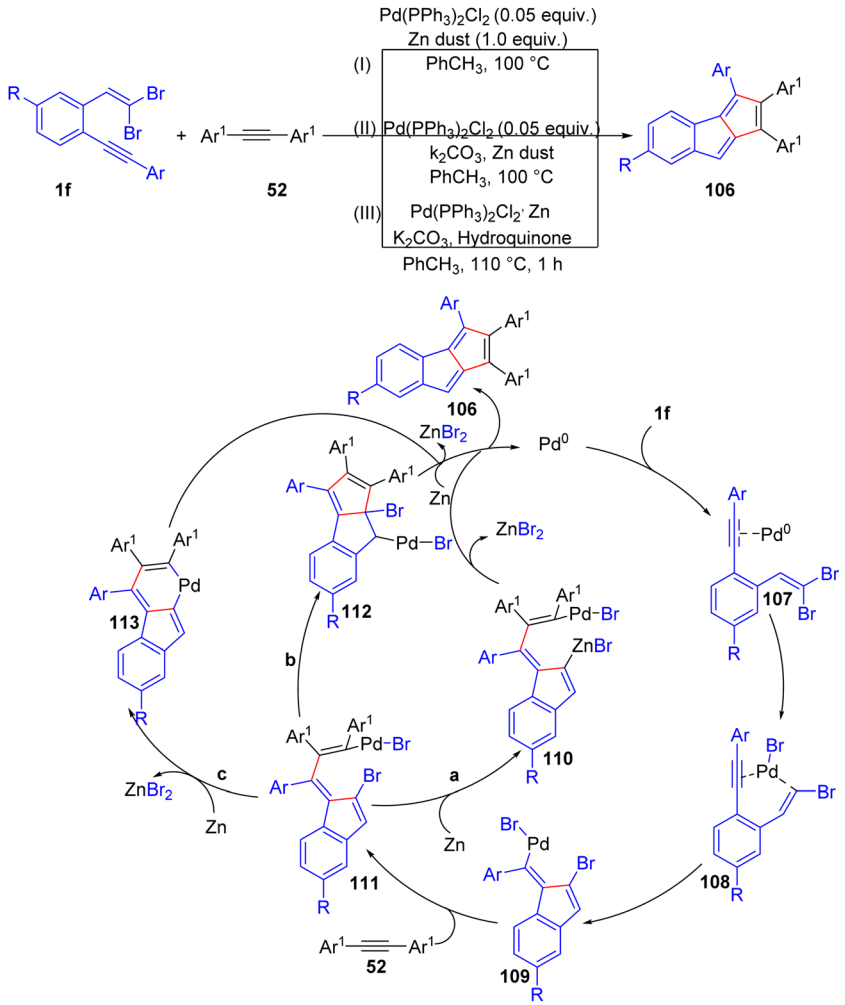


Scheme 23 Synthesis of 2-arylbenzofurans(thiophenes).

catalyzed intramolecular cyclization leads to the formation of palladacycle **97**. Reductive elimination of **97** delivers intermediate 2-halobenzo[*b*]thiophene **98** and regenerates the pd^0 species. The subsequent oxidative addition of **98** to pd^0 species forms complex **99**, followed by CO insertion into the carbon–palladium bond, giving rise to intermediate **100**. Aroylpalladium complex **100** is converted to intermediate **101** by base. The reductive elimination of **101** furnishes the final product **95** and regenerates the active pd^0 species.

In addition, synthesis 2-arylbenzofurans/thiophenes **59** *via* tandem elimination–intramolecular addition–Hiyama reaction of *o*-substituted *gem*-dibromoolefins **1b**/**1c** and organosilanes **102** in the presence of $Pd(OAc)_2/PPh_3$ as metal catalyst system with TBAF serving as an oxidant was developed by Wang *et al.* (Scheme 23(I)).[41] In this transformation, the presence of electron-donating groups at the *para*-position generally led to higher yields. The reaction conditions proved effective for a range of functional groups on the benzene ring, demonstrating the versatility of this tandem reaction. In addition, the Rao group reported a tandem chemoselective synthesis of 2-arylbenzofurans **59** from *o*-substituted *gem*-dibromoolefins **1b**/**1c** under palladium-catalyzed conditions, involving three consecutive coupling reactions with triarylbismuth reagents **103**, resulting in high yields (Scheme 23(II)).[42] The optimal conditions involved using *o*-substituted *gem*-dibromoolefins **1b**/**1c** with $BiAr_3$ **103** in the presence of $Pd(PPh_3)_4$ and Cs_2CO_3 as the base in DMF under heating conditions, this setup provided the best yield of 75%. Other bases and solvents were less effective. This method demonstrates site-selective and chemoselective tandem couplings, providing diverse functionalized 2-arylbenzofurans **59** in a one-pot operation. The authors proposed this mechanism based on several screening and control studies, starting with the base-mediated cyclization of *o*-substituted *gem*-dibromoolefins **1f** to form **11**. This intermediate **11** then undergoes cross-coupling with the bismuth reagent **103** under palladium-catalyzed conditions to produce 2-arylbenzofuran **59**. Notably, 2-bromobenzoheterocycle **11** can form without a metal catalyst.

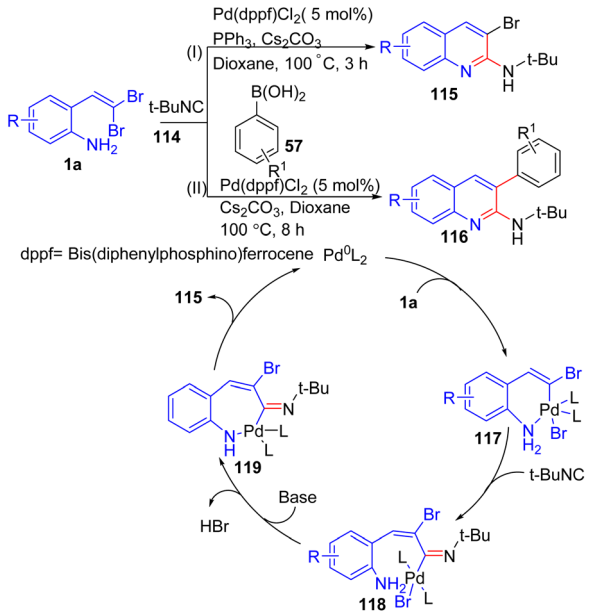
Meanwhile, Rivera-Fuentes and their group developed a facile method to access monoannelated pentalenes **106** *via* cascade carbopalladation reaction between alkynes **52** and *o*-substituted *gem*-dibromoolefins **1f** (Scheme 24(I)).[43] This protocol effectively provides access to a range of pentalene derivatives **106** that were previously challenging to prepare. A key advantage of this methodology lies in the accessibility of the starting materials, which are either commercially available or can be synthesized in a few steps following well-established protocols. They proposed a catalytic cycle (Scheme 24) initiated by coordination of palladium to the alkyne moiety of *o*-substituted *gem*-dibromoolefins **1f**. Following, the intermediate **108** is formed from the oxidative addition of Pd^0 to the C–Br bond. The subsequent intramolecular carbopalladation at the alkyne leads to formation a transient fulvene **109**, which undergoes reaction with alkyne **52**, affording intermediate **110**. Three plausible termination routes were hypothesized to deliver desired product **106** by authors: (a) oxidative addition of zinc to the C–Br bond **111**, followed by an intramolecular Negishi-type sequence. (b) Intramolecular carbopalladation at the fulvene



Scheme 24 Synthesis of monoannelatedpentalenes.

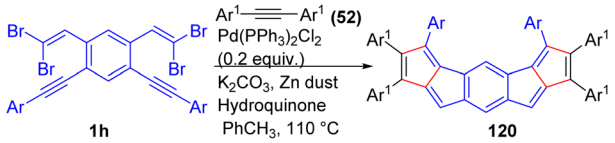
110, followed by zinc-assisted reductive elimination. (c) Two-electron reduction of the Pd(II) intermediate **110** by zinc, a second oxidative addition, formation of a palladacycle **113**, and reductive elimination. A short time later, Diederich and co-workers also extended this methodology to improve its yield (Scheme 24(II)).[44] Better reaction efficiency was achieved by incorporating two equivalents of K_2CO_3, which significantly increased the yield of benzopentalene **106** from 42% to 68%. Maintaining a high excess of diarylacetylene **52** (20 equivalents) was found to be crucial as well, as decreasing it to 10 equivalents reduced the yield to 48%. It should be noted, this methodology was further extended to synthesize pentalenes **106** with novel fusion patterns *via* intramolecular carbopalladation, achieved by attaching an additional alkyne **52** to the *o*-substituted *gem*-dibromoolefins **1f**. Meanwhile, very recently, Gazdag *et al.* also utilized Rivera-Fuentes and their group's method[45] to generate a wide variety of monobenzopentalenes derivatives **106** and reported how different substituents can affect their photophysical properties (Scheme 24(III)). A series of substituted monobenzopentalenes **106** were synthesized in 18–85% yields, showcasing the potential of the cascade reaction for forming three new C–C bonds. The methodology proved versatile, enabling the synthesis of molecules with electron-donating and electron-withdrawing functional groups directly attached to the benzopentalene cores **106** and substituents on the aryl groups.

Jiang and co-workers introduced a palladium-catalyzed method for synthesizing 2-amino-3-bromoquinolines **115** *via* isocyanide **114** insertion/intramolecular cyclization of *ortho*-substituted *gem*-dibromoolefins **1a** (Scheme 25(I)).[46] Conducted in 1,4-dioxane at 100 °C, the reaction delivers the desired quinoline cyclization and as well as reductive elimination, yielding the 2-amino-3-bromoquinoline products **115** and the regenerates the active Pd^0 species. The reaction scope covers various *o*-substituted *gem*-dibromoolefins **1a** with both electron-donating and electron-withdrawing substituents on the aromatic ring, producing polyhalogenated quinolines **115**. This method was further extended to a one-pot process for synthesizing 3-substituted-2-aminoquinolines **115** through Suzuki, Sonogashira, or Heck coupling reactions, providing a scalable approach to a wide range of quinoline derivatives. When, their group performed this reaction with arylboronic acids **57** led to formation of 3-aryl-2-aminoquinolines **116** (Scheme 25(II)).[47]



Scheme 25 Synthesis of 2-amino-3-bromoquinolines and 3-aryl-2-aminoquinolines.

This reaction follows a mechanism similar to their previous work, involving palladium-catalyzed isocyanide insertion and intramolecular cyclization of *o*-substituted *gem*-dibromoolefins **1a** and finally, Suzuki coupling with arylboronic acids **57**. The reaction scope of this method was notably broad, with various *o*-substituted *gem*-dibromoolefins **1a** and arylboronic acids **57** successfully participating in the reaction. Substituents on the *o*-substituted *gem*-dibromoolefins **1a**, whether electron-donating or electron-withdrawing, were well tolerated, offering flexibility in designing functionalized quinolines. A key observation was that the nature of the arylboronic acids **57** significantly impacted yields. Electron-donating groups, such as methoxy or methyl, consistently provided higher yields, while halogen groups, like fluoro or chloro, led to slightly reduced efficiencies. An intriguing aspect of the scope was the method's ability to accommodate heteroaryl boronic acids **57**. For example, 3-thienylboronic acid participated smoothly in the reaction, delivering the corresponding 3-thienyl-2-aminoquinoline **116** in high yield, showcasing the adaptability of the method for synthesizing heterocyclic quinolines.

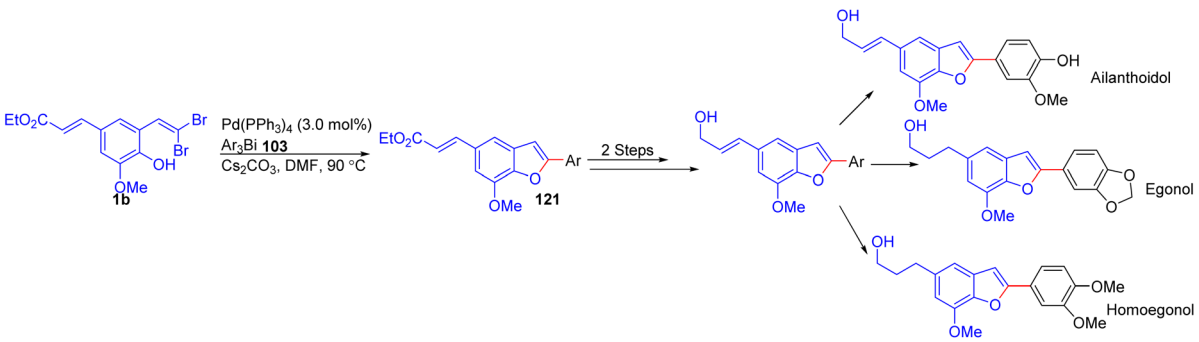


Scheme 26 Synthesis of π-extended bispentalene derivatives.

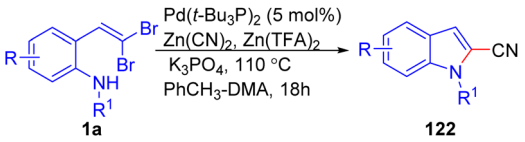
The synthesis of π-extended bispentalene derivatives **120** with different fusion patterns and functional groups on the peripheral phenyl groups through a modified double carbopalladation cascade reaction between acetylenes **52** and bis(*gem*-dibromoolefins) **1h** with the formation of six C–C bonds during the one-pot reaction was reported by Diederich and coworkers (Scheme 26).[48] This research team also investigated the effects of antiaromatic subunits within $[4n + 2]$ π-systems by synthesizing bispentalenes possessing $[4n + 2]$ π-electron perimeters and antiaromatic characteristics. It should be noted, when they investigated reaction in the presence of hydroquinone, significantly improved the reaction outcome, forming six new C–C bonds in a one-pot cascade reaction. Notably, this approach also allowed for a substantial decrease in the required acetylene reagent, from 40 equivalents to just 6 equivalents.

In a 2016 study, Rao and Murty developed a concise synthetic strategy for the preparation of several benzofuran-based natural products, including ailanthoidol, egonol, and homoegonol, among others (Scheme 27).[49] The key methodology employed was a Pd-catalyzed domino cyclization/coupling reaction utilizing *o*-substituted *gem*-dibromoolefins **1b** and triarylbismuth reagents **103**. This one-pot process efficiently generated the core benzofuran skeleton, which was subsequently functionalized to yield the target natural products. The reported methodology proved tolerant, accommodating a range of *o*-substituted *gem*-dibromoolefins **1b** and various triarylbismuth reagents **103** to synthesize 2-arylbenzofuran derivatives **121** in high yields.

Lautens *et al.* have introduced a highly effective Pd-catalyzed method for synthesizing 2-cyanoindoles **122** from *o*-substituted *gem*-dibromoolefins **1a** and $Zn(CN)_2$ as the cyanide source in the presence of $Zn(TFA)_2$ to enhance catalytic performance in toluene (Scheme 28).[50] Notably, in the absence of DMA as



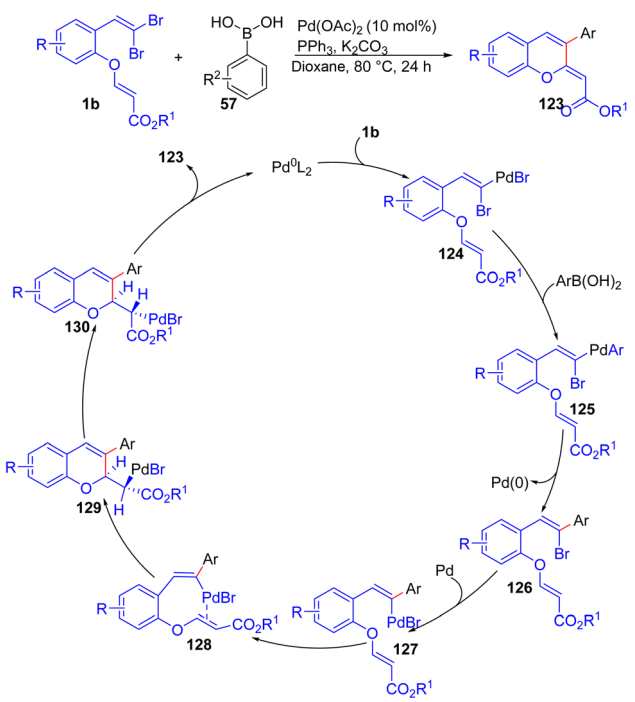
Scheme 27 Preparation of several benzofuran-based natural products.



Scheme 28 Synthesis of 2-cyanoindoles.

a cosolvent, the starting material was fully consumed, resulting primarily in cyclization with 2-bromoindole **29** as the major product and no cyanation occurring. The optimized methodology showed to be compatible with a range *o*-substituted *gem*-dibromoolefins **1a** bearing electron-donor and electron-withdrawing groups on the aryl rings, yielding the respective products **122** in moderate to good yields.

A 2018 study by Song *et al.* presents a novel synthesis of functionalized 2*H*-chromenes **123** *via* Pd-catalyzed cascade reactions of *o*-substituted *gem*-dibromoolefins **1b** with aryl boronic acids **57**, combining two C–C bond-forming reactions *via* intermolecular Suzuki coupling and intramolecular Heck coupling in a one-pot reaction (Scheme 29).[51] By this novel and simple approach, the authors prepared variety of desired products **123** in moderate to good yields. The formation of **123** from **1b** and **57** was proposed to involve the oxidative addition of Pd^0 into the C–Br bond of **1b**, forming intermediate **124** which is converted to intermediate **125** by transmetalation with **57**. Then, intermediate **125** undergoes reductive elimination to deliver **126** and regenerate Pd^0. Another oxidative addition into the vinyl C–Br bond of **126** forms **127**, leading to intermediates **128** and then **129** through palladium coordination and insertion reaction. Rotation around the Cα–Cβ bond in intermediate



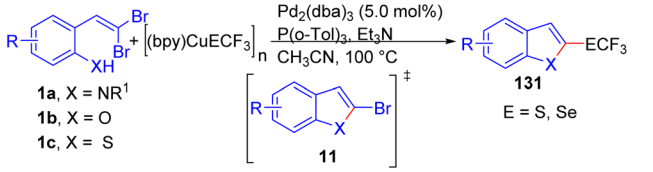
Scheme 29 Synthesis of functionalized 2*H*-chromenes.

129 produces **130**, which, after HPdBr elimination, affords **123** and regenerates Pd^0.

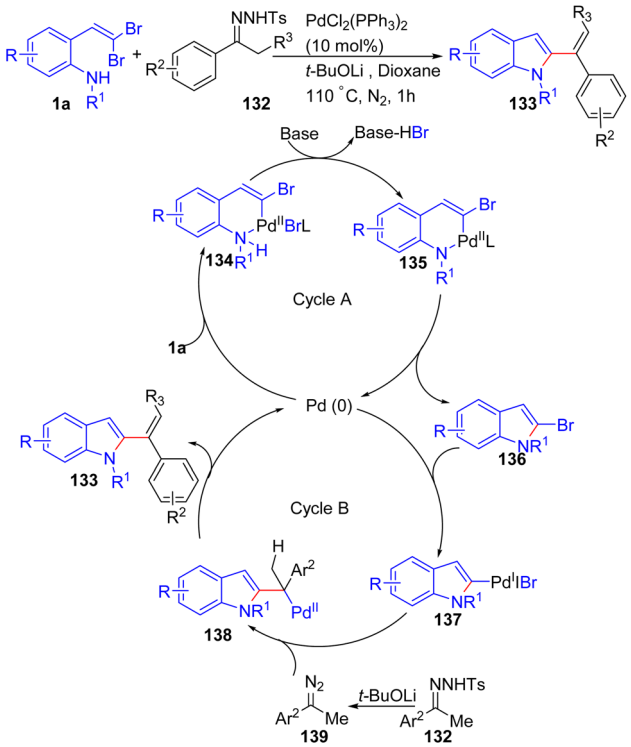
In 2019, Zhang and Weng pioneered a general strategy for synthesizing 2-trifluoromethylthio(seleno)-substituted benzofused heterocycles **131** through reaction of *o*-substituted *gem*-dibromoolefins **1a**/**1b**/**1c** with (bpy)$CuSCF_3$ or with [(bpy)$CuSeCF_3$]$_2$ in the presence of $Pd_2(dba)_3$ and P(*o*-Tol)$_3$ as the catalyst and ligand, respectively in acetonitrile solvent at 100 °C for 24 hours (Scheme 30).[52] They suggested a mechanism involving palladium-catalyzed intramolecular cross-coupling of **1a**/**1b**/**1c** to form 2-bromobenzoheterocycle **11** as key intermediate, which then undergoes trifluoromethylthiolation with (bpy)$CuSCF_3$ or with [(bpy)$CuSeCF_3$]$_2$ to yield the desired product **131**. In addition, this strategy was applied to prepare 2-trifluoromethylthiolated benzothiophenes and indoles.

Liu *et al.* described a novel palladium-catalyzed intermolecular coupling reaction of *o*-substituted *gem*-dibromoolefins **1a** and *N*-tosylhydrazones **132** to efficiently construct 2-(1-phenylvinyl)-indoles **133**, obtaining indoles bearing 1,1-disubstituted alkenes in one step with a short reaction time, a broad substrate scope and high yields (Scheme 31).[53] The reaction begins with cycle A, where the oxidative addition of palladium to *o*-substituted *gem*-dibromoolefins **1a** forms the palladacycle **134**. Deprotonation of aniline then produces palladium complex **135**, which undergoes reductive elimination to give compound **136**. The authors also reported that this compound **136** can be observed by TLC and GC-MS but disappears by the end of the reaction. In cycle B, the oxidative addition of compound **136** to palladium affords palladium(II) complex **137**, which is converted to alkylpalladium species **138** by a carbene intermediate from diazo compound **139**. Finally, β-hydrogen elimination of complex **138** delivers the desired product, 2-(1-phenylvinyl)-indole **133**.

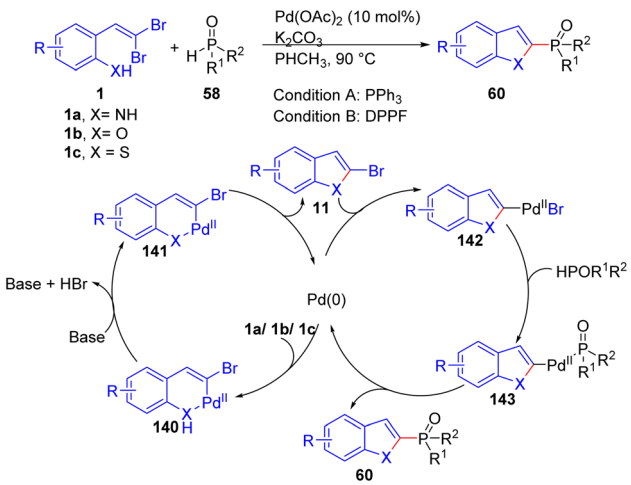
Chen and colleagues recently documented the synthesis of phosphorylated heteroaromatics **60** *via* palladium-catalyzed domino cyclization/phosphorylation of *o*-substituted *gem*-dibromoolefins **1a**/**1b**/**1c**, when the X = O, S is in the starting material, suitable ligand is PPh_3 under optimized reaction conditions, while DPPF was selected as appropriate ligand for X = NH in this transformation (Scheme 32).[54] A series of control experiments were conducted to propose a plausible mechanism. The process begins with the oxidative addition of Pd^0 to the C–Br bond of *o*-substituted *gem*-dibromoolefins **1a**/**1b**/**1c**, followed by coordination with the XH group, forming the intermediate **140**. Subsequent deprotonation of XH leads to the formation of the six-membered palladacycle complex **141**. Then



Scheme 30 Synthesis of 2-trifluoromethylthio(seleno)-substituted benzofused heterocycles.



Scheme 31 Synthesis of 2-(1-phenylvinyl)-indoles.

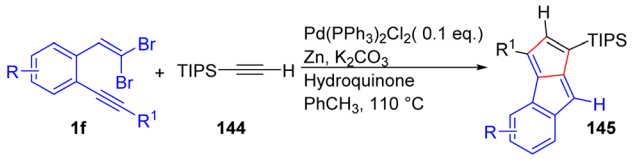


Scheme 32 Synthesis of phosphorylated heteroaromatics.

palladacycle complex undergoes reductive elimination, producing intermediate **11** and releasing the Pd^0 species.

Oxidative addition of Pd^0 to the C–Br bond of **11** delivers the intermediate **142**. Intermediate **143** is generated by ligand exchange with $HP(O)R^1R^2$. Finally, intermediate **143** undergoes reductive elimination, affording the phosphorylated heteroaromatics **60**.

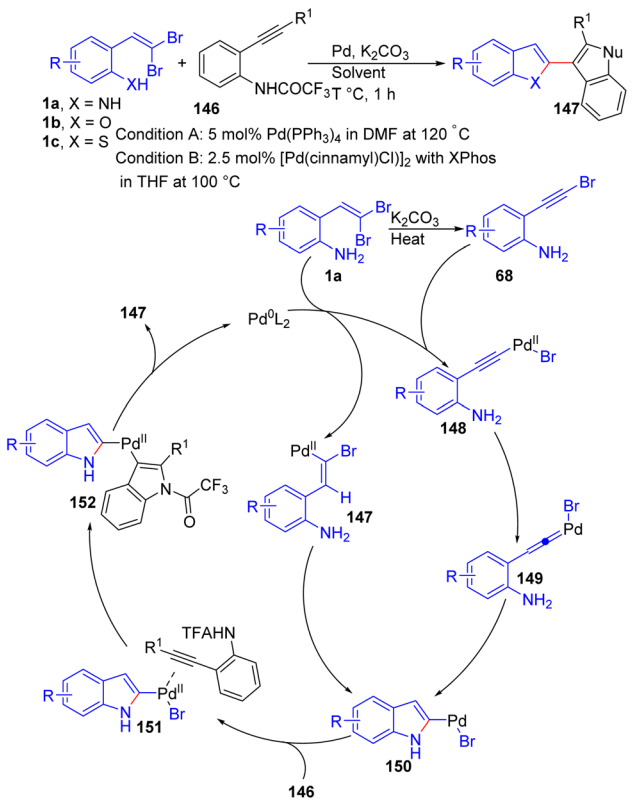
Recently, based on the same methodology used by Rivera-Fuentes[43] and their group, Mayer and London attempted to access monoareno-pentalenes **145** that have an olefinic H on each 5-membered ring through regioselective carbopalladation



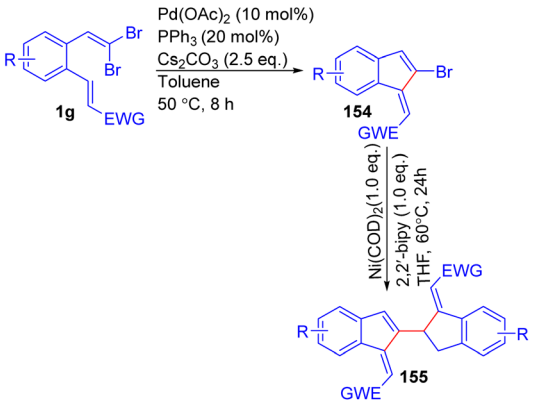
Scheme 33 Monoareno-pentalenes with two olefinic protons.

cascade reaction between *o*-substituted *gem*-dibromoolefins **1f** and TIPS-acetylene **144** (Scheme 33).[55] Overall, the authors proposed these novel pentalenes, possessing two olefinic protons, could serve as valuable experimental tools for further exploring magnetic (anti)aromaticity effects.

Lautens and his team recently reported a broad-scope method for synthesis bis-heterocycles **147**. This new method involves a palladium-catalyzed tandem C–N coupling/Cacchi reaction starting from *o*-substituted *gem*-dibromoolefins **1a**/**1b**/**1c**, generating two heterocycle rings **147** (Scheme 34).[56] The reaction between dibromoolefines **1a**/**1b**/**1c** and alkyne-tethered anilines **146**, employing 5 mol% $Pd(PPh_3)_4$, K_2CO_3 in DMF (0.1 M) at 120 °C, gave desired products **147** with good to excellent yields. It should be noted that, having the alkyne-tethered aniline **146** as a trifluoroacetamide was necessary for high yields. In addition, use of a dibromoolefinic phenol/thiophenol instead of aniline provided the corresponding benzofuran/benzothiophene bis-heterocycles. Notably, when, dibromoolefinic phenols as starting material were used, they employed new condition including



Scheme 34 Formation of bis-heterocycles.

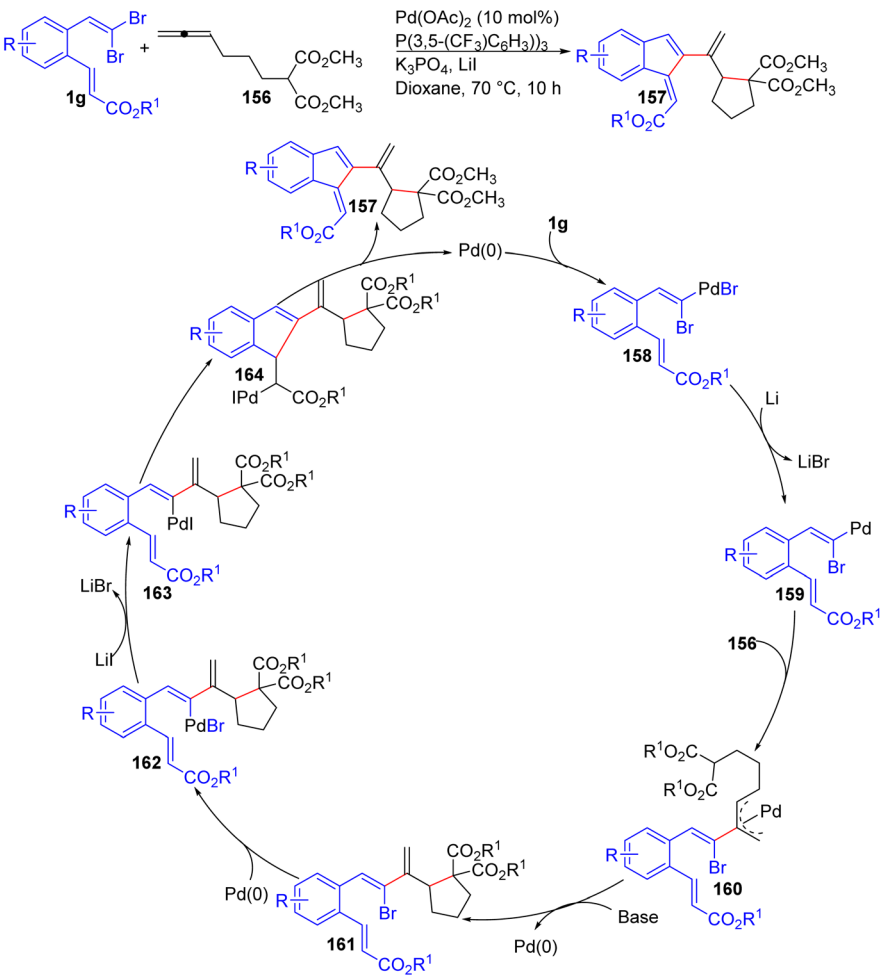


Scheme 35 Synthesis of bis-benzofulvenes.

[Pd(cinnamyl)Cl]$_2$ as catalyst and 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl (XPhos) as ligand in THF at 100 °C. The mechanism depicted in Scheme 34 was suggested for this transformation, that involves formation of a bromoalkyne **68** as a competent intermediate in the reaction.

In 2023, Ganesh *et al.* described the synthesis of bis-benzofulvenes **155** through a palladium-catalyzed intramolecular Heck coupling followed by Ni-mediated C(sp^2)–Br dimerization (Scheme 35).[57] The reaction was designed to explore the optoelectronic properties of the resulting bis-benzofulvenes, which are of interest due to their extended conjugation and potential applications in functional materials. During their exploration of reaction conditions, Ganesh's group found that the yield was significantly affected by the choice of phosphine ligand and the conditions for the Ni-mediated dimerization. Bulky phosphines, like $PtBu_3$, generally led to poor yields, while smaller cone angle ligands such as triphenylphosphine (PPh_3) improved yields, reaching up to 89% for bromobenzofulvene **154**. This adaptability highlights the method's potential for creating structurally varied bis-benzofulvenes **155** with wide applications, particularly in the development of functional materials with tailored electronic properties. The reaction maintained high efficiency under mild conditions, making it applicable for a broad range of synthetic applications, particularly in the field of optoelectronic material.

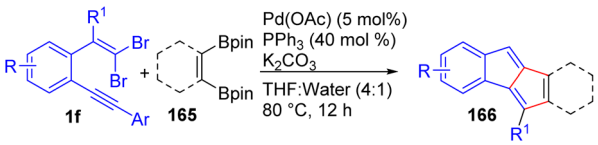
Zhou *et al.* reported a Pd-catalyzed bicyclization of o-substituted *gem*-dibromoolefins **1g** with allenyl malonates **156**, synthesizing bicyclic compounds 157 *via* a one-pot cascade reaction (Scheme 36).[58] The reaction proceeds using $Pd(OAc)_2$ as the catalyst, a phosphine ligand (P[3,5-$(CF_3)_2C_6H_3$]$_3$), and K_3PO_4



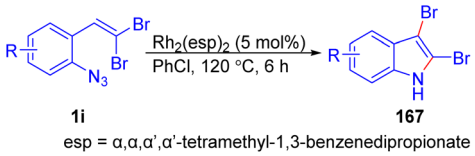
Scheme 36 Pd-catalyzed bicyclization of *ortho*-substituted *gem*-dibromoolefins.

in 1,4-dioxane, with LiI as an additive, constructing three C–C bonds and two new rings in one single step. The process begins with oxidative addition of Pd^0 into the C–Br bond of the *o*-substituted *gem*-dibromoolefins **1g**, forming a vinylpalladium intermediate **158**. Halide exchange generates a reactive intermediate **159**, which undergoes intermolecular carbopalladation with the allenyl malonate **156** to yield a π-allylpalladium species **160**. Next, internal cyclization of **160** affords intermediate **161** which is converted to intermediate **162** by oxidative addition. Subsequent halide exchange and intramolecular Heck reaction lead to ring closure, and β-hydride elimination regenerates the Pd^0 catalyst while forming the final bicyclic product **157**. Control experiments also confirmed the sequential nature of the reported reaction. Furthermore, the reported methodology proved to be highly tolerant. Various *o*-substituted *gem*-dibromoolefins **1g** bearing electron-donating groups, such as methyl and methoxy substituents, were effectively transformed into the corresponding bicyclic products **157** with high efficiency. Substrates with electron-withdrawing groups, including nitro, ester, and trifluoromethyl functionalities, also reacted smoothly under the optimized conditions, yielding the desired compounds **157** in excellent yields. Moreover, the reaction conditions accommodated not only symmetrical but also unsymmetrical allenyl malonate derivatives **156**, allowing for the synthesis of structurally diverse bicyclic products **157**. Heteroatom-containing allenes, such as those derived from allenic alcohols or amines, also participated successfully in the reaction, producing five-membered heterocyclic products in moderate to good yields.

Very recently, Ganesh and co-workers have developed Pd(0)-catalyzed cascade Suzuki/carbopalladation strategy for the efficient synthesis of diverse unsymmetrical dibenzopentalenes **166** from *gem*-dibromo olefins **1f** and benzene-1,2-diboronic esters **165** (Scheme 37).[59] Optimization studies revealed that $Pd(OAc)_2$ (10 mol%) in combination with PPh_3 (40 mol%) and K_2CO_3 in THF/H_2O (4 : 1) was crucial for achieving efficient cascade coupling, with water serving as an essential cosolvent to improve K_2CO_3 solubility. Under these conditions, a wide variety of *gem*-dibromo olefins bearing electron-donating, electron-withdrawing, and heteroaryl substituents were smoothly transformed into unsymmetrical dibenzopentalenes **166** in 39–84% yields. In addition, the authors further examined photophysical and electrochemical studies highlighting the unique optoelectronic properties of these antiaromatic scaffolds. UV-vis spectra revealed weak, broad absorptions across 400–700 nm, consistent with symmetry-forbidden HOMO → LUMO transitions, whereas cyclic voltammetry of representative dibenzopentalenes, supported by DFT and TD-DFT calculations, confirmed characteristic redox behavior.



Scheme 37 Synthesis of unsymmetrical dibenzopentalenes.



Scheme 38 Synthesize of 2,3-dibromoindoles.

2.3. Rhodium-catalyzed cyclization

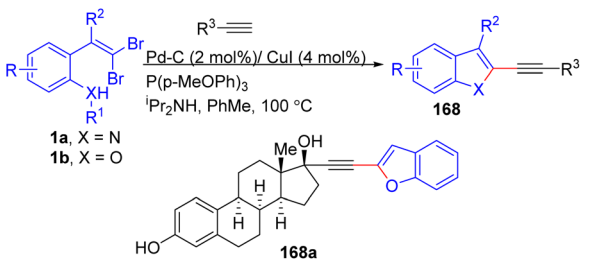
Rhodium is recognized as modern catalyst in chemistry due to high efficiency and selectivity in various chemical reactions and serves as a suitable catalyst in diverse fields, such as synthesis of pharmaceuticals and fine chemicals.[60]

Recently, Hata *et al.* reported a Rh-catalyzed intramolecular cyclization and rearrangement of *o*-substituted *gem*-dibromoolefins **1i** to synthesize 2,3-dibromoindoles **167** (Scheme 38).[61] When, they carried out reaction of *o*-substituted *gem*-dibromoolefins **1i** using $Rh_2(esp)_2$ as catalyst, giving 2,3-dibromoindoles **167** in 51–74% yields. This reaction is performed *via* the intramolecular cyclization of rhodium nitrene generated *in situ* and the rearrangement of one halogen group.

2.4. Dual-metal-catalyzed cyclization

Dual-metal-catalyzed reactions involving *o*-substituted *gem*-dibromoolefins have emerged as powerful synthetic strategies, combining the complementary properties of two distinct metal catalysts or two subsequent different metal-catalyzed reactions to achieve transformations unattainable or inefficient with a single metal system. These methodologies leverage synergistic effects between metals to facilitate sequential catalytic cycles or tandem processes. By capitalizing on distinct reactivities, dual-metal catalysis enables intricate cyclizations and functionalizations under relatively mild conditions. This section discusses recent progress in employing dual-metal catalysis for transformations of *o*-substituted *gem*-dibromoolefins.[62]

Another perfect example of utilizing *o*-substituted *gem*-dibromoolefins **1a**/**1b** in tandem Ullman/Sonogashira coupling was reported by Nagamochi *et al.* (Scheme 39).[63] Using readily available *o*-substituted *gem*-dibromoolefins **1a**/**1b** and terminal alkynes, they synthesized a series of 2-alkynyl indoles and benzofurans **168** *via* CuI-catalyzed intramolecular Ullman and Pd/C-catalyzed Sonogashira coupling cascades. Various aromatic and aliphatic terminal alkynes with different electronic properties using *o*-substituted *gem*-dibromoolefins **1a**/**1b**



Scheme 39 Synthesis of 2-alkynyl indoles and benzofurans.

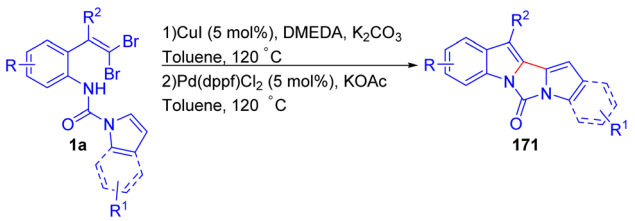
yielded 2-alkynyl indoles **168** in moderate to good yields. Altering electron-donating and electron-withdrawing groups on the dibromoolefin substrates **1a**/**1b** did not affect the tandem.-reaction's efficacy, delivering desired products **168** in 55–84% yields. Notably, the authors also successfully synthesized a complex steroid derivative with two acidic hydroxyl groups, achieving a good yield.

Bao's group reported a convenient one-pot protocol for synthesizing pyrimido[1,6-*a*]indol-1(2*H*)-one derivatives **170** through a nucleophilic addition/Cu-catalyzed *N*-arylation/Pd-catalyzed C–H activation sequence (Scheme 40).[64] The methodology employes *o*-substituted *gem*-dibromoolefins **1j** and *N*-alkyl-anilines **169** as starting materials, which underwent a three-step process to afford the desired indole-fused frameworks **170** in moderate to good yields. Initial studies identified CuI with *N*,*N*′-dimethylethylenediamine (DMEDA) and K_2CO_3 as optimal for the *N*-arylation step, and Pd(dppf)Cl_2 with KOAc for the direct arylation conditions. The authors found that the reaction scope was broad, tolerating both electron-rich and electron-deficient substituents on the *o*-substituted *gem*-dibromoolefins **1j**, and producing functionalized pyrimido[1,6-*a*]indol-1(2*H*)-ones **170** with minimal steric hindrance effects. When exploring *N*-alkyl-anilines **169**, electron-donating groups such as 4-Me, 4-MeO, and 3-Me on the aniline ring yielded products **170** efficiently, while electron-withdrawing groups like 4-NO_2 and 4-Ac were detrimental, likely due to reduced nucleophilicity. The reaction's versatility extended to *N*-benzyl and *N*-naphthyl derivatives, demonstrating applicability to more sterically demanding substrates.

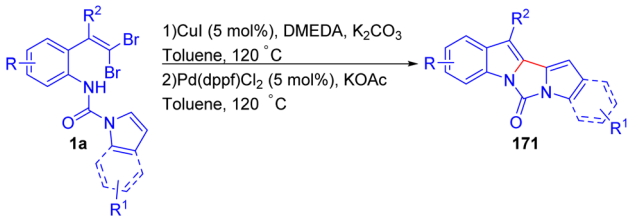
Bao *et al.* developed a one-pot two-step strategy for the synthesis of unsymmetrical 2,2′-biindolyl derivatives **171** *via* a sequential Cu-catalyzed *N*-arylation and Pd-catalyzed direct arylation using *o*-substituted *gem*-dibromoolefins **1a** (Scheme 41).[65] Initial optimization showed that CuI, in combination with *N*,*N*′-dimethyl ethylenediamine (DMEDA) and K_2CO_3, was effective for the *N*-arylation step, while Pd(dppf)Cl_2 with KOAc promoted the subsequent direct arylation, yielding the desired products **171** in moderate to good yields. Interestingly, the reaction tolerated a range of electron-donating and electron-withdrawing substituents on the *o*-substituted *gem*-dibromoolefins **1a**, and the protocol proved efficient for both sterically hindered and less hindered substrates, unlike many existing methods. This flexibility was further demonstrated by synthesizing biindolyls **171** with substituents like 4,5-diMeO and 4-Cl, 4-Br, 5-Br, as well as unsymmetrical biindolyls **171** incorporating different substituents on each indole ring. A notable finding was that when indole was replaced by pyrrole, the reaction proceeded smoothly, albeit with lower yields, extending the methodology's utility to related heterocycles. However, when both indole rings bearing electron-withdrawing substituents, the reaction was unsuccessful, possibly due to instability of the starting materials.

In 2012, Bao and co-workers described a one-pot synthesis of 6*H*-isoindolo[2,1-*a*]indol-6-ones **173** using a similar strategy as their previous works (Scheme 42).[66] The reaction employs *o*-substituted *gem*-dibromoolefins **1a** and benzoyl chlorides **172** as starting substrates, and CuBr and Pd(dppf)Cl_2 as a dual catalytic system. Optimization studies revealed that CuBr, in combination with DMEDA and K_2CO_3, is the most effective for the initial C–N coupling cyclization, leading to formation (2-bromo-1*H*-indol-1-yl)(aryl)methanones **174**, while Pd(dppf)Cl_2 and KOAc promote the subsequent C–H activation step, affording desired products **173**. Electron-withdrawing groups on the aniline component were found to enhance the efficiency of the copper-catalyzed cyclization, providing high yields of the indole intermediate, while electron-donating substituents on the benzoyl chloride accelerated the palladium-catalyzed C–H activation. Notably, when *m*-methyl benzoyl chloride **172** was used, a single regioisomer was obtained demonstrating high regioselectivity in the C–H activation step. The methodology showcased broad functional group tolerance, enabling the synthesis of a diverse set of 6*H*-isoindolo[2,1-*a*] indol-6-one derivatives **173** with varied substitution patterns, suggesting its potential utility in complex molecule synthesis and pharmaceutical applications.

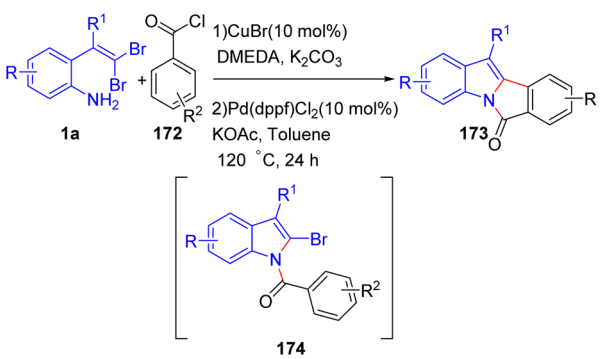
A ligand-free, one-pot procedure has been developed by Wang *et al.*.for the synthesis of 2-arylbenzofurans(thiophenes) **59**, through tandem elimination–cyclization–desulfitative arylation of *o*-substituted *gem*-dibromoolefins **1b**/**1c** in the



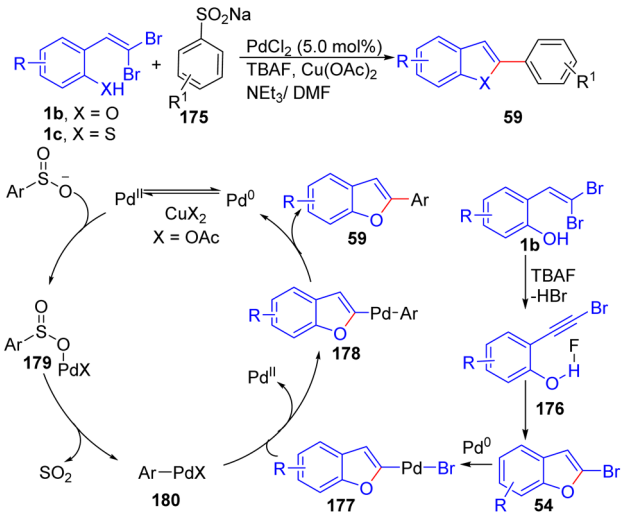
Scheme 40 Synthesis of pyrimido[1,6-*a*]indol-1(2*H*)-one derivatives.



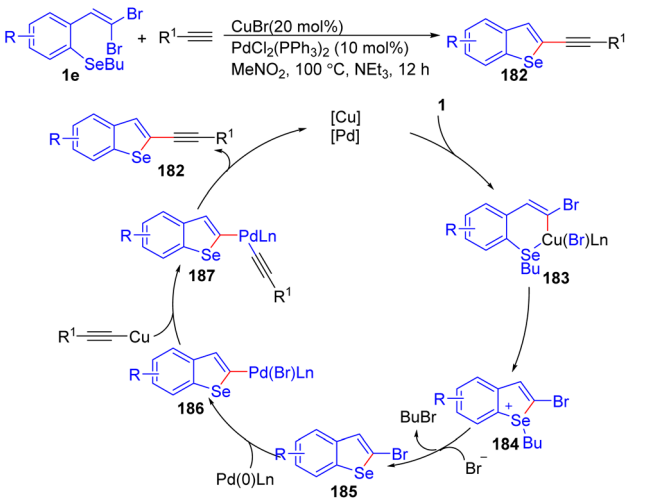
Scheme 41 Synthesis of unsymmetrical 2,2′-biindolyl derivatives.



Scheme 42 Synthesis of 6*H*-isoindolo[2,1-*a*]indol-6-ones.



Scheme 43 A ligand-free, one-pot synthesis of 2-arylbenzofurans(thiophenes).



Scheme 45 Synthesis of functionalized 2-alkynylbenzo[*b*]selenophenes.

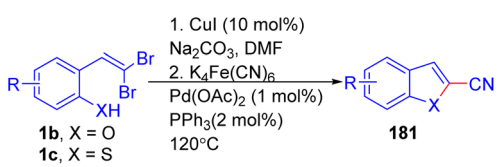
presence of sodium arylsulfinate **175**, TBAF, $PdCl_2$, $Cu(OAc)_2$ and NEt_3 (Scheme 43).[67] A proposed mechanism involves the TBAF-promoted elimination of HBr from *o*-substituted *gem*-dibromoolefins **1b**/**1c** to form intermediate **176**, which undergoes intramolecular nucleophilic addition, giving 2-bromobenzofuran **54**. Concurrently, sodium arylsulfinate **175** reacts with Pd^{II}, forming intermediate **179**, which undergoes desulfitation to deliver aryl-Pd^{II}-X species **180** and SO_2. **180** then reacts with **177**, generated *via* oxidative addition of 2-bromobenzofuran **54** to Pd^0, resulting in intermediate **178** through transmetalation. Reductive elimination of **178** affords the final product **59** and regenerates Pd^0.

A one-pot palladium and copper-catalyzed Ullmann reaction/cyanation of *o*-substituted *gem*-dibromoolefins **1b**/**1c** *via* $K_4Fe(CN)_6$ as a non-toxic cyanating reagent, to generate 2-cyanobenzofurans(thiophenes) **181** was described by Zhou and coworkers (Scheme 44).[68]

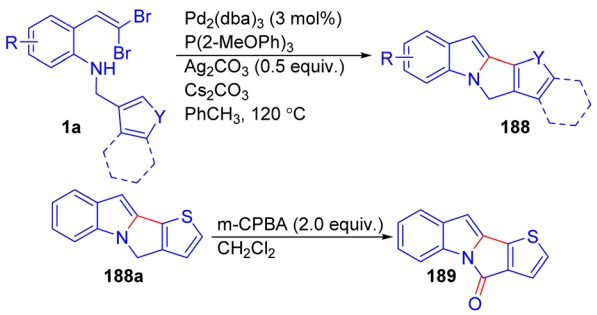
The reaction scope was tested with various *o*-substituted *gem*-dibromoolefins **1b**/**1c**, yielding products **181** with good to excellent yields. The presence of electron-donating or halogen groups at the *para*-position of phenols resulted in higher yields compared to strong electron-withdrawing groups such as NO_2.

Another excellent example of utilizing *o*-substituted *gem*-dibromoolefins **1e** to construct 2-substituted benzo[*b*]selenophenes **182** was reported by Bilheri *et al.* using $PdCl_2/PPh_3$ as the catalyst and CuBr as the cocatalyst, they synthesized a series of functionalized 2-alkynylbenzo[b]selenophenes **182** *via* sequential cyclization/Sonogashira cross-coupling reactions (Scheme 45).[69] Through several experiments, the authors hypothesized the reaction commences with the oxidative addition of copper to *o*-substituted *gem*-dibromoolefins **1b**/**1c**, leading to 2-bromobenzo[*b*]selenophene **185** *via* an intramolecular Ullmann reaction, followed by nucleophilic substitution on the selenium atom. Subsequently, the oxidative addition of 2-bromobenzo[*b*]selenophene **185** to the palladium species leads to formation intermediate **186**. In the next step, the copper-activated alkyne reacts with intermediate **184**, affording intermediate **187**. Finally, reductive elimination of intermediate **187** delivers the desired product **182** while regenerating the catalysts for further cycles. This concise sequence demonstrates the efficiency of the combined copper- and palladium-catalyzed reactions for the synthesis of functionalized benzo[*b*]selenophene derivatives **182**.

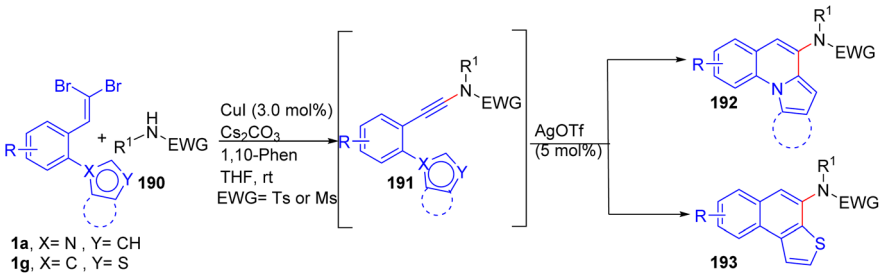
Bryan and Lautens developed a Pd-catalyzed domino Buchwald–Hartwig amination and direct arylation reaction to access tetracyclic and pentacyclic indole derivatives **188** from *o*-substituted *gem*-dibromoolefins **1a** (Scheme 46).[70] During optimization, the authors found that increasing the ligand/Pd ratio improved yields, suggesting that liberated halides were poisoning the catalyst. To resolve this issue, they introduced Ag_2CO_3 to sequester the halides, resulting in cleaner reactions and enabling a lower ligand/Pd ratio. The reaction demonstrated



Scheme 44 Generation of 2-cyanobenzofurans(thiophenes).



Scheme 46 Synthesis of tetracyclic and pentacyclic indole derivatives.

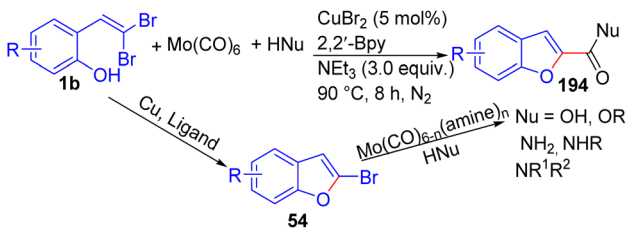


Scheme 47 Synthesis of pyrrolo-/indolo[1,2-*a*]quinolines and naphtho[2,1-*b*]thiophenes.

broad functional group tolerance, accommodating halides, electron-donating, and electron-withdrawing groups. Notably, the selective oxidation of the methylene group in the desired product using *m*-CPBA delivered lactam **189**.

A two-step, one-pot cyclization synthesis of pyrrolo-/indolo [1,2-*a*]quinolines **192** and naphtho[2,1-*b*]thiophenes **193** from *o*-substituted *gem*-dibromoolefins **1** and sulphonamides **190** *via* Cu(II)-catalyzed dehydrobromination and Ag(I)-catalyzed activation of the triple bond under mild conditions was reported by Perumal and co-workers (Scheme 47).[71] Importantly, the several products exhibited photophysical properties. The formation of ynamide **191** as the key intermediate, which is generated from reaction of *o*-substituted *gem*-dibromoolefins **1** with sulphonamides **190** in the presence of Cu as catalyst in this reaction was suggested by the authors.

Hu *et al.* have demonstrated a versatile, modular synthesis of a diverse range of benzofuran-2-carboxylic acids, esters, and amides **194**, this streamlined approach integrates a Cu-catalyzed intramolecular C–O coupling and a $Mo(CO)_6$-mediated intermolecular carbonylation reaction in a single-step procedure, efficiently furnishing the desired products **194** in high yields without the need for Pd catalysts or CO gas (Scheme 48).[72] The optimal reaction conditions involved were 5 mol% $CuBr_2$ as the catalyst, 5 mol% 2,2′-Bpy as the ligand, 3.0 equiv. of Et_3N as the base, 0.6 equiv. of $Mo(CO)_6$ as the solid CO source, in ethanol, at 90 °C for 8 hours under nitrogen atmosphere. In general, a wide range of functional groups such as Me, OMe, *t*-Bu, Ph, F, Cl, Br, $COOCH_3$, and other similar substituents were well-tolerated in the reaction for the synthesis of benzofuran-2-carboxylic esters, acids, and amides **194**. However, the 4-nitro substituent was not compatible with this reaction, giving complex reductive byproducts, and ammonia as an external *N*-nucleophile was less active than organic amines, leading to a lower yield of the desired product. The tandem carbonylation reaction was proposed to follow a two-step mechanism, with a copper-catalyzed intramolecular Ullman cross-coupling of *o-gem*-dibromovinylphenols **1b** to form 2-bromobenzofuran intermediates **54**, followed by a carbonylative transformation by activated $Mo(CO)_6$ in the presence of amine ligands. It should be noted in this reaction, $Mo(CO)_6$ acted as both a carbonyl donor and catalyst.

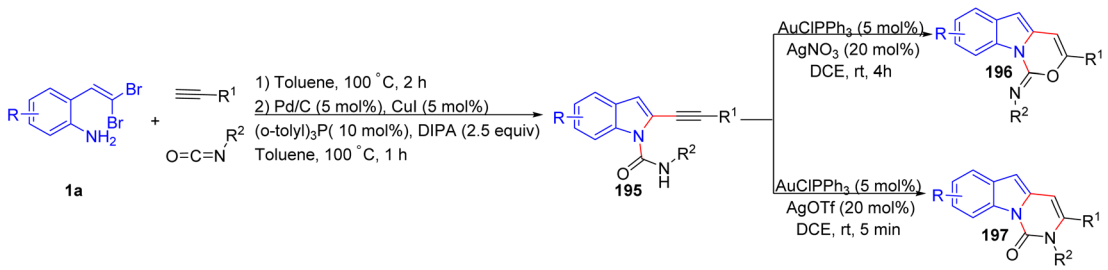


Scheme 48 Synthesis of a diverse range of benzofuran-2-carboxylic acids, esters, and amides.

Gupta *et al.* have described annulation of *o*-substituted *gem*-dibromoolefins **1a**, isocyanate, and terminal alkyne in the presence of Cu/Pd as catalyst to access an N-1 and C-2 functionalized indoles **195** (Scheme 49).[73] These products **195** undergo selective 6-*endo* cyclization, yielding either the *O*-cyclized products **196** in the presence of Au(I)/$AgNO_3$ or the *N*-cyclized products **197** with Au(I)/AgOTf during post-multicomponent reaction modification.

2.5. Indium-catalyzed cyclization

Indium has emerged as an important transition metal in catalytic reactions due to its inert character, high electronegativity,

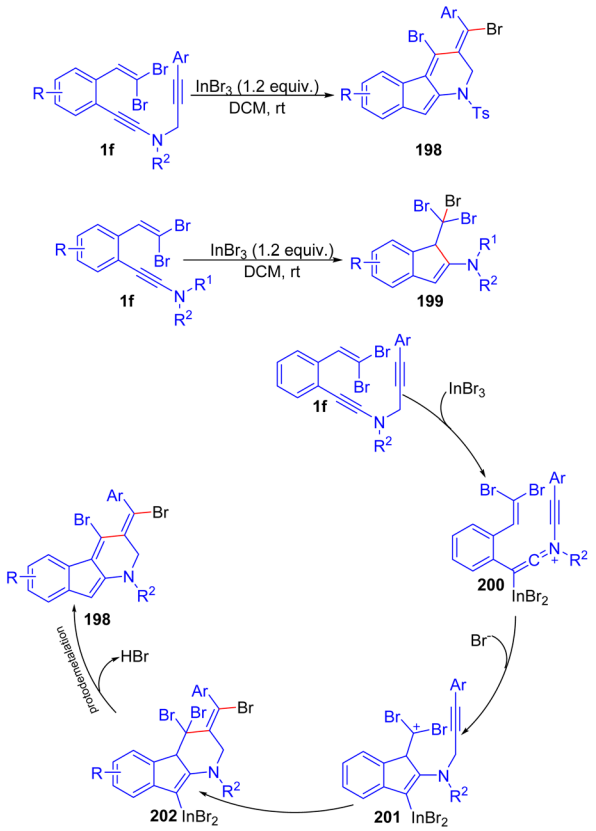


Scheme 49 Annulation of o-*gem*-dibromovinyls, isocyanates, and terminal alkynes.

ease of handling, stability in air and moisture, and greater resistance to oxidation compared to other metals. Moreover, its recyclability and high tolerance toward a wide range of chemical substrates and functional groups have led to its increasing use in organic reactions in recent years.[74]

In 2015, Weng *et al.* reported synthesis of dibrominated 2,3-dihydro-1*H*-indeno[2,1-*b*]pyridine derivatives **198** *via* reaction of *o*-substituted *gem*-dibromoolefins **1f** in the presence of $InBr_3$ at 80 °C under nitrogen for 10 minutes (Scheme 50).[75]

These products **198** show potential in medicinal chemistry, as indeno[2,1-*b*]pyridine-based compounds exhibit pharmacological activities. A series of **1** underwent tandem cyclization and desired products **198** were yielded with moderate to high yields for electron-neutral and electron-deficient substrates, while electron-donating substituents resulted in lower yields. Halogen-substituted substrates were successful, but *n*-butyl substituent formed an unidentifiable mixture. A mechanism was suggested that after the formation of the keteniminium cation **200** from ynamide metalation, **200** undergoes 5-*exo*-*dig* cyclization which leads to formation of cation **201**. An anti-addition of bromide and a carbonium ion across the alkyne generates tribrominated compound **202**. Subsequent dehydrobromination and protodemetalation result in the formation of **198**. In addition, when they performed this reaction at room temperature under nitrogen for 10 minutes, it led to synthesis of 1-tribromomethyl-2-amino-1*H*-indenes **199**.



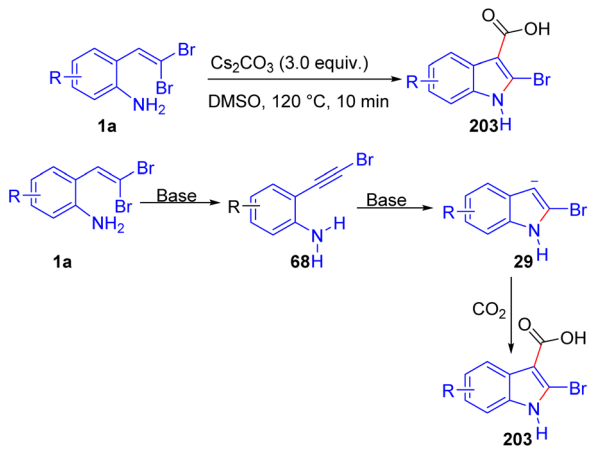
Scheme 50 Synthesis of dibrominated 2,3-dihydro-1*H*-indeno[2,1-*b*] pyridine derivatives.

3. Metal-free cyclization

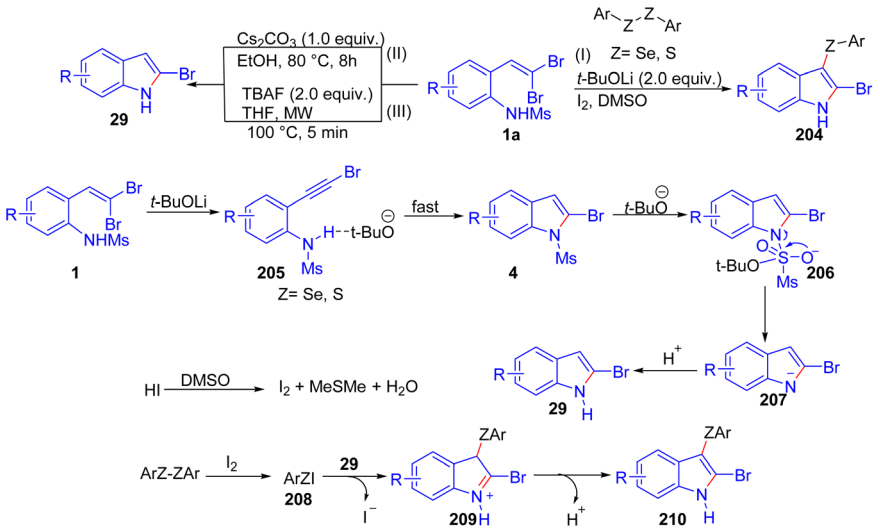
While metal-catalyzed transformations have significantly advanced the utility of *ortho*-substituted *gem*-dibromoolefins, metal-free approaches have also emerged as appealing alternatives due to their inherent environmental benefits and cost-effectiveness.[76] This section discusses recent developments in metal-free cyclization involving *o*-substituted *gem*-dibromoolefins, highlighting their mechanistic pathways, substrate versatility, and synthetic applications.

Kunzer and Wendt introduced a rapid and efficient method for synthesizing 2-halo-3-carboxyindoles **203** from *o*-substituted *gem*-dibromoolefins **1a** using Cs_2CO_3 in DMSO under catalyst-free conditions (Scheme 51).[77] The reaction proceeds optimally at 120 °C, with the formation of an alkynyl bromide intermediate **68**, which undergoes cyclization and CO_2 trapping in a one-pot process, producing the desired indoles **203** cleanly and in high yield after a simple acidic work-up. Electron-donating groups, such as methoxy and methyl substituents, as well as electron-withdrawing groups like nitro and ester functionalities on the aromatic ring, were all well-tolerated, yielding the desired 2-halo-3-carboxyindoles **203** in high purity and yields ranging from moderate to excellent. This wide functional compatibility underscores the method's utility for diverse indole derivatives, including those with sensitive substituents, as the reaction conditions avoid harsh oxidants or transition metals that might otherwise compromise product integrity.

Wang *et al.* developed a novel one-pot method for synthesizing 2-bromo-3-selenyl(sulfenyl)indoles **204** by employing *o*-substituted *gem*-dibromoolefins **1** in tandem reactions with diselenides and disulfides (Scheme 52(I)).[78] Conducted under transition-metal-free conditions, the reaction utilizes *t*-BuOLi and a catalytic amount of I_2 in DMSO, achieving high regioselectivity and efficient yields. The reaction begins with *t*-BuOLi facilitating the elimination of HBr, generating a phenylethynyl intermediate **205** that subsequently undergoes nucleophilic cyclization to form the indole core **4**. For the 3-selenylation step, I_2 and diselenide react to produce an electrophilic PhSeI species **208**, which then undergoes electrophilic addition to the indole



Scheme 51 Synthesis of 2-halo-3-carboxyindoles.

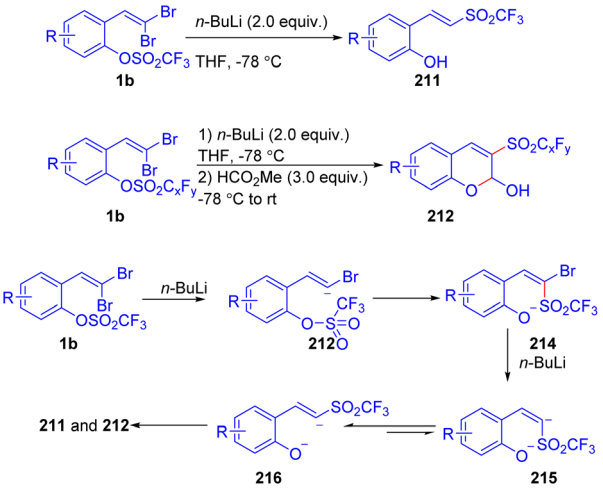


Scheme 52 Synthesis of 2-bromo-3-selenyl(sulfenyl)indoles.

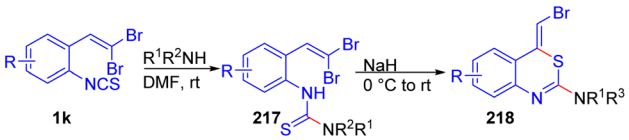
29 at the 3-position, completing the transformation in a sequential manner. Additionally, they demonstrated that this synthetic route also accommodates 2-(*gem*-dichlorovinyl) anilines, which successfully produce 2-chloro-3-selenyl or 3-sulfenyl derivatives. One year later, Wang and colleagues established a streamlined approach for synthesizing 2-bromoindoles **29** through the intramolecular cyclization of *o*-substituted *gem*-dibromoolefins **1a** in the presence of Cs_2CO_3 as base (Scheme 52(II)).[79] This metal-free, environmentally considerate method, carried out in ethanol enables the controlled synthesis of either 2-bromoindoles **4** or their *N*-methylsulfonyl-protected counterparts by adjusting Cs_2CO_3 stoichiometry. In addition, an excellent illustration of TBAF's utility in metal-free cyclization reactions of dibromoolefins **1a** is presented in a method developed by the same group,[80] where they employ TBAF to efficiently synthesize 2-bromoindoles **29** under microwave-assisted conditions. The reaction proceeds optimally in THF at 100 °C within five minutes, leveraging TBAF's dual role as both base and fluoride source for the cyclization process (Scheme 52(III)).

In a 2013 study, Shibata and colleagues presented a stereoselective synthesis of vinyl and heteroaryl triflones **211**/**212** *via* anionic O → C and N → C trifluoromethanesulfonyl migration reactions (Scheme 53).[81] These transformations enabled the efficient preparation of vinyl triflones and heteroaryl triflones under mild reaction conditions. A plausible reaction mechanism was provided by authors, as shown in Scheme 53.

Kobayashi *et al.* developed a one-pot synthesis for (*Z*)-4-(halomethylidene)-4*H*-3,1-benzothiazin-2-amines **218** using *o*-substituted *gem*-dibromoolefins **1k** and secondary amines (Scheme 54).[74] Mechanistic insights suggest that deprotonation of the thiourea intermediate **217** with NaH produces an amide anion, which undergoes cyclization *via* nucleophilic attack on the β-position of the dihalovinyl group, followed by H-transfer and halide elimination to yield the benzothiazine rings **218**. The product **218** configuration was confirmed through NOE



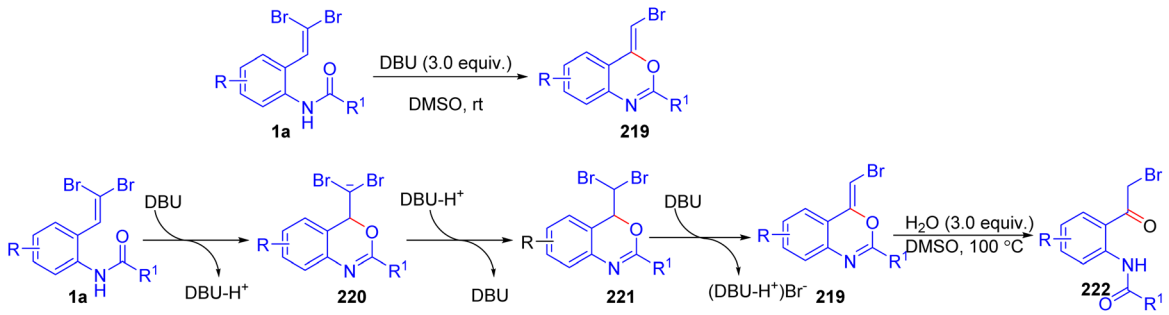
Scheme 53 Synthesis of vinyl and heteroaryl triflones.



Scheme 54 Synthesis for (*Z*)-4-(halomethylidene)-4*H*-3,1-benzothiazin-2-amines.

experiments, which supported the selective formation of the (*Z*)-isomer. Investigations demonstrated that this sequence reliably yields the desired products **218** with high regioselectivity and in generally good yields across a range of secondary amines, although primary amines failed under the reaction conditions.

Garkhedkar *et al.* reported a DBU-promoted regio- and stereoselective synthesis of 1,3-benzoxazines **219** from *o*-substituted *gem*-dibromoolefins **1a**, offering a mild, metal-free alternative for constructing these biologically relevant



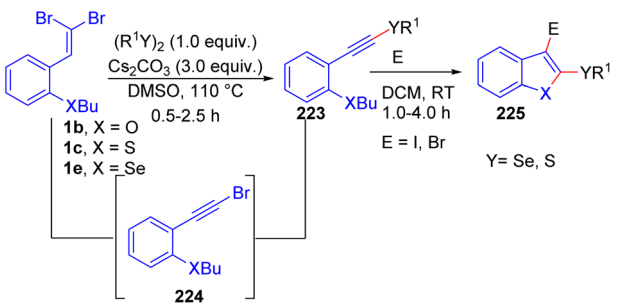
Scheme 55 Regio- and stereoselective synthesis of 1,3-benzoxazines.

heterocycles (Scheme 55).[82] Furthermore, the authors extended their method to generate α-bromomethyl ketones **222** through a ring-opening sequence using water in DMSO. Based on several control experiments, it was proposed that the reaction begins with DBU-mediated deprotonation of the *o*-substituted *gem*-dibromoolefins **1a**, followed by 6-*exo*-*trig* cyclization to deliver intermediate **220**. Subsequent protonation of intermediate **220** generates a stabilized intermediate **221**, which undergoes dehydrohalogenation in the presence of DBU to yield the final 1,3-benzoxazine product **219**. Moreover, this reaction produces benzoxazines **219** with a *Z*-configuration, confirmed by 2D-NMR techniques such as NOESY and HMBC. In the subsequent ring-opening step to synthesize *o*-amido phenacyl bromides **222**, water acts as the nucleophile, attacking the benzoxazine framework. This results in the cleavage of the benzoxazine ring, forming the phenacyl bromide derivatives **222**.

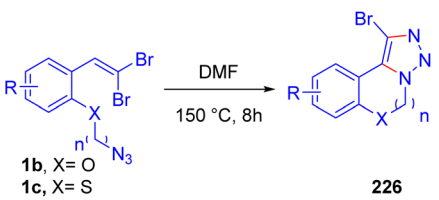
Rampon and co-workers developed a transition-metal-free one-pot synthesis for 3-halo-2-organochalcogenylbenzo[*b*] chalcogenophenes **225**, utilizing reaction between *o*-substituted *gem*-dibromoolefins **1b**/**1c**/**1e** and diorganoyl dichalcogenides (Scheme 56).[83] This method efficiently generates 2,3-disubstituted benzo[*b*]chalcogenophenes **225** with yields ranging from moderate to excellent, aiming to streamline synthetic routes by eliminating separate purification steps typically needed for chalcogenoacetylenes. Initial optimization showed that the use of Cs_2CO_3 in DMSO afforded the 1-bromoalkyne **224** as target intermediate in high efficiency, a finding corroborated by systematic testing with other bases and solvents. The optimized reaction, conducted at 110 °C, consistently produced high yields within a short time. Mechanistically, the authors propose that base-promoted elimination of *o*-substituted *gem*-dibromoolefins **1** generates a 1-bromoalkyne **224**, which further reacts to deliver the chalcogenoacetylene intermediate **223**. This intermediate **223** undergoes a nucleophilic cyclization upon the addition of iodine, leading to the desired product **225** in high yield. The method demonstrated broad substrate compatibility, accommodating a range of electron-donating and withdrawing groups without significant impact on yield, especially for *S*-aryl and Se-aryl substituted compounds. The one-pot synthesis was extended using *N*-bromosuccinimide (NBS) as the electrophile, successfully producing desired products **225**.

Kobayashi *et al.* present a novel synthetic route for halogen-substituted 1,2,3-triazoles **226** *via* an intramolecular Huisgen cycloaddition of *ortho*-substituted *gem*-dibromoolefins **1** (Scheme 57).[84] This method efficiently forms triazole-fused tricyclic benzocompounds **226**, offering a straightforward pathway to functional triazole derivatives, which serve as intermediates in various biologically active compounds. The researchers observed that heating azide precursors in DMF at 150 °C gives the desired bromo-substituted triazoles **226** in high efficiency, with the reaction benefiting from a metal-free environment under optimized conditions. To explore the reaction scope, the authors tested a range of halogen substitutions, including bromo, iodo, and fluoro groups, confirming that various halogens are well tolerated. They also demonstrated the versatility of the method by synthesizing sulfur/oxygen-containing triazoles and extending the reaction to triazoles with both 5- and 7-membered rings. These variations yielded products **226** in moderate to excellent yields.

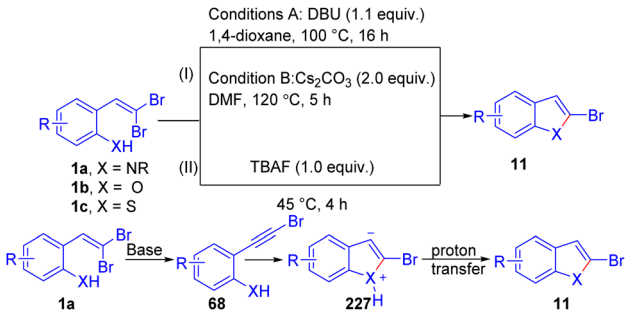
Lautens *et al.* recently proposed a based-mediated and metal-free method for the efficient synthesis of 2-bromobenzoheterocycles **96** from *o*-substituted *gem*-dibromoolefins



Scheme 56 Synthesis of 3-halo-2-organochalcogenylbenzo[*b*] chalcogenophenes.



Scheme 57 Synthesis of halogen-substituted 1,2,3-triazoles.



Scheme 58 Efficient synthesis of 2-bromobenzoheterocycles.

1a/**1b**/**1c**, offering a straightforward and practical route to construct these valuable intermediates in pharmaceutical and material chemistry (Scheme 58(I)).[85] The reaction begins with the base-promoted dehydrohalogenation of the *o*-substituted *gem*-dibromoolefins **1a**/**1b**/**1c**, leading to the formation of a 1-bromoalkyne intermediate **68**. This intermediate **68** undergoes 5-*endo-dig* cyclization, forming the core benzoheterocycle structure **11**. The use of strong bases, such as DBU, was found to be crucial in facilitating the dehydrohalogenation step, allowing the formation of the 1-bromoalkyne intermediate **68**, which then cyclizes under mild conditions. The authors confirmed their hypothesis through several mechanistic studies, which included deuterium-labeling experiments, confirming the presence of a proton exchange at the C3 position of the final benzoheterocycle product. Additionally, the authors conducted a series of control experiments to demonstrate the necessity of both the base and the bromo group in promoting cyclization. These studies confirmed that the 1-bromoalkyne intermediate **68** plays a key role in driving the reaction towards the benzoheterocycle product **11**, highlighting the importance of base-mediated cyclization in this transformation. It should be noted, Chen and associates in 2011, reported a TBAF-promoted intramolecular cyclization of *gem*-dibromoolefins to efficiently synthesize 2-bromobenzofurans and 2-bromobenzothiophenes **11** under metal-free conditions (Scheme 58(II)).[86] This methodology utilizes readily available *o*-substituted *gem*-dibromoolefins **1a**/**1b**/**1c** and addresses challenges associated with traditional halogenation methods, which often require toxic electrophilic halogen sources and yield a mixture of regioisomers. Exploring the reaction scope, they demonstrated that various electron-donating and electron-withdrawing substituents on the benzene ring were well-tolerated, yielding the desired products **11** in high efficiency.

4. Conclusions

This review comprehensively summarizes the advancements made, in a categorical manner, in the field of cyclic compound formation through cyclization reactions of *o*-substituted *gem*-dibromoolefins involving various mechanistic pathways. Two types of cyclization reactions are summarized, based on whether the reactions occur under transition-metal catalysis or under metal-free conditions promoted by a base. The reactions presented and discussed illustrate the versatility of these building blocks for the synthesis of a wide range of carbo- and heterocyclic ring systems using *o*-substituted *gem*-dibromoolefins. As shown in this review, Pd, Cu, Rh, and In have acted as practical and efficient metal catalysts in transformations to access cyclic compounds. Furthermore, the application of other metal catalysts has been less investigated in the field of *o*-substituted *gem*-dibromoolefin chemistry, and it will be an intriguing opportunity to explore their catalytic activity. On the other hand, some transition-metal-free cyclization reactions of *o*-substituted *gem*-dibromoolefins can be employed for the preparation of cyclic compounds with very high efficiency. The environmentally benign nature of the method plays a crucial role in the selection of the approach. While significant progress has been made, key challenges remain in utilizing *o*-substituted *gem*-dibromoolefins, particularly in achieving higher selectivity, milder reaction conditions, and improved scalability. Nevertheless, these challenges provide substantial opportunities for further innovation. We hope that this review will encourage organic chemists, especially those interested in *o*-substituted *gem*-dibromoolefin chemistry, to investigate new reactions in this area.

Conflicts of interest

There are no conflicts to declare.

Data availability

This study is a review article, and no new data were generated or analyzed during the course of this research. All data discussed and referenced are available in the publicly accessible sources cited within the article.

Acknowledgements

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