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REVIEW



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

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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.

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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-metalassisted 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 gemdibromoolefins an appropriate and versatile bidentate electrophile for organometallic reactions, easily undergoing metalcatalyzed cross-coupling reactions.4 Gem-dibromoolefins can be conveniently prepared by a variety of methods such as Wittigtype reactions, elimination-based reactions, and substitution reactions.4,5 For example, in 1962, Ramirez and co-workers

using the reaction of aromatic aldehyde with carbontetrabromide and triphenylphosphine, that is converted to (dibromomethylene)triphenylphosphane (Ph₃P=CBr₂) in situ, in CH₂Cl₂ 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 Br₂PPh₃, 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 Ph₃P=CBr₂, generated from bromoform and PPh3 in the presence of KOt-Bu, reacted with aromatical dehyde 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(NMe₂)₃] in place of PPh₃, 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 MnO2-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,

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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 orthosubstituted 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 (Cu⁰, 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 Culcatalyzed 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). The authors found that using *trans*-1,2-cyclo-hexyldiamine **2** with K₂CO₃ 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

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heteroatoms or sensitive functional groups, such as carbamates, successfully formed five-membered imidazoindolone rings 3 without competing side reactions. A series of electrondonating and electron-withdrawing groups on the aromatic ring had minimal impact on the efficiency, except for the 5methoxy 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 CuIintramolecular cross-coupling bromovinylaniline derivatives 1a (Scheme 3).17 The reaction proceeds smoothly in toluene at room temperature using K₃PO₄ as the base and CuI as the catalyst, affording the desired 2bromoindole 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 2bromoindoles 4.

In 2011, Lan and colleagues developed a one-pot Cu(II)catalyzed reaction to synthesize benzofused heteroaryl azoles 8 (Scheme 4). Two bonds including $C(sp^2)-C(sp^2)$ and $C(sp^2)-O(sp^2)$ bonds were constructed in one synthetic operation in the cross-couplings of ortho-substituted bromoolefins 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 3 Synthesis of 2-bromoindole derivatives.

S-Phos = 2-Dicyclohexylphosphino-2',6'-dimethoxybiphenyl

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 Cu2O-catalyzed domino reaction involving intramolecular C-N coupling and C-Z (Z = O, S, N) bond formation. The optimized conditions included Cu2O as the catalyst, N,N'-dimethylethylenediamine (DMEDA) as the ligand, K₂CO₃ as the base, all in toluene at 70 °C under N₂. 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 electronwithdrawing groups (NO2) 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 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 Cs₂CO₃ 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]

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

quinazolines **16** in excellent yields. The synthesized tetra-hydroindolo[1,2-*a*]quinazolines **16** were then refluxed under basic conditions to yield indolo[1,2-*a*]quinazolines **17**.

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(1)-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 LiClO₄ 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 NaBH₄ 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 E-isomer 46', which is better suited for oxidative addition to the Cu(\mathbb{I}) species, forming

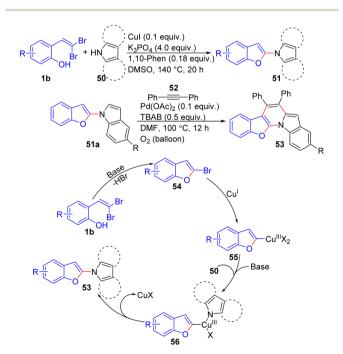
the selenonium intermediate 48. Remarkably, experimental evidence supports this hypothesis, as a control experiment using the pure E-isomer 46 under the reaction conditions resulted in 45% isomerization to the Z-isomer 46′. Subsequently, an Ullmann-type coupling generates intermediate 48, releasing the 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-(2benzofuryl)-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.

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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, K₃PO₄, 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 bisheterocycles 51 in good to excellent yields regardless of the presence of electron-donating or -withdrawing functional groups. The mechanism the authors proposed, involves a basepromoted 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(1), 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 (Pd⁰, 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 Me₄NCl 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

Br
$$+ R^{1}$$
 $+ R^{1}$ $+$

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 $\mathbf{1a}$ were compatible, providing 2-vinylic indoles $\mathbf{62}$ with diverse substitution patterns. The enoate $\mathbf{1}$ was employed in the presence of tris(dibenzylideneacetone)dipalladium (Pd_2dba_3) (4 mol%) with n-Bu₄NCl (1 equiv.) and $NEt_3/K_3PO_4\cdot H_2O$ in toluene at $120 \, ^{\circ}\text{C}$, for this study, and gave the desired tricyclic adduct $\mathbf{63}$ in good yield.

In 2005, Fang and Lautens reported a protocol to generate 2substituted 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 K₃PO₄/H₂O 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-endodig 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 PdCl₂(PPh₃)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 electrondonating (*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(PPh₃)₄ and K₂CO₃ 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 electrondonating 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 PdCl₂/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-

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$$R = R^{1} - B(OH)_{2}$$

$$R^{1} - B(OH)_{2}$$

$$R^{1} - B(OH)_{2}$$

$$R^{1} - A(BV), aryl$$

$$R^{1} = A(BV), aryl$$

$$R^{1} - A(BV), aryl$$

$$R^{1} - A(BV), aryl$$

$$R^{1} - A(BV), aryl$$

$$R^{1} - A(BV), aryl$$

$$R^{2} - A(BV), aryl$$

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, wateraccelerated, 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 Cs2CO3 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-alquinoline 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 palladiumcatalyzed 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 electronwithdrawing 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 osubstituted 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 Pd₂dba₃ as catalysts, and Cs₂CO₃ 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 ${\bf 1g}$ to ${\rm Pd}^0$, followed by transmetalation with a boronate ${\bf 87}$, and reductive elimination of intermediate ${\bf 89}$, regenerating the ${\rm Pd}^0$ species. Then, intermediate ${\bf 89}$ is converted to the alkenylpalladium ${\bf 90}$ in the presence of ${\rm Pd}^0$. Finally, carbopalladation of ${\bf 90}$ followed by β -hydride elimination affords the methyleneindene ${\bf 85}$. In the same year, Wu et~al. published a synthesis of 1-methylene-1H-indenes ${\bf 85}~via$ same starting materials in the presence of ${\rm Pd}({\rm OAc})_2$ (2.5 mol%) and ${\rm PPh}_3$ (5 mol%) as catalyst with KOH (3.0 equiv.) as base in toluene (Scheme ${\bf 20(II)}).^{38}$ 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 R¹ 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 Pd(OAc)₂/2-dicyclohexylphosphino-2',6'-diisopropoxybiphenyl (RuPhos) catalytic system with K₂CO₃ 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 pd⁰ species, resulting in palladium complex 96. Subsequently, base-

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

Base $\frac{S}{100}$ Pd-Ln $\frac{S}{Br'}$ Scheme 22 Synthesis of 2-carbonylbenzo[b]thiophene.

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/PPh₃ 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

Scheme 23 Synthesis of 2-arylbenzofurans(thiophenes).

conditions involved using *o*-substituted *gem*-dibromoolefins **1b**/ **1c** with BiAr₃ **103** in the presence of Pd(PPh₃)₄ and Cs₂CO₃ 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 osubstituted 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 osubstituted gem-dibromoolefins 1f. Following, the intermediate **108** is formed from the oxidative addition of Pd⁰ 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

52

109

Scheme 24 Synthesis of monoannelatedpentalenes

110, followed by zinc-assisted reductive elimination. (c) Twoelectron 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 coworkers also extended this methodology to improve its yield (Scheme 24(II)).44 Better reaction efficiency was achieved by incorporating two equivalents of K₂CO₃, 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 gemdibromoolefins 1f. Meanwhile, very recently, Gazdag et al. also utilized Rivera-Fuentes and their group's method45 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-bromoguinolines 115 via isocyanide 114 insertion/intramolecular cyclization of orthosubstituted 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 Pd⁰ species. The reaction scope covers various o-substituted gem-dibromoolefins 1a with both electrondonating 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

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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

Br
$$Ar^1$$
 Ar^1 Ar^1

Scheme 26 Synthesis of π -extended bispentalene derivatives.

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.

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 $[4n+2]\pi$ -systems by synthesizing bispentalenes possessing $[4n+2]\pi$ -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 2H-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 Pd⁰ 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 Pd⁰. 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 2H-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)CuSCF₃ or with [(bpy)CuSeCF₃]₂ in the presence of Pd₂(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)CuSeCF₃ or with [(bpy)CuSeCF₃]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-(1phenylvinyl)-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-(1phenylvinyl)-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 PPh₃ 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 Pd⁰ 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

$$R = \begin{bmatrix} B_{r} \\ V \\ XH \end{bmatrix} + \begin{bmatrix} (bpy)CuECF_{3} \\ (bpy)CuECF_{3} \end{bmatrix} = \begin{bmatrix} Pd_{2}(dba)_{3} & (5.0 \text{ mol}\%) \\ P(o-Tol)_{3} & Et_{3}N \\ CH_{3}CN, 100 \text{ °C} \\ CH_{3}CN, 100 \text{ °C} \end{bmatrix} + \begin{bmatrix} 131 \\ E = S, Se \\ 11 \end{bmatrix}$$

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

NNHTs PdCl₂(PPh₃)₂

R³ (10 mol%)

t-BuOLi, Dioxane

132 110 °C, N₂, 1h

133 R¹

Pd^IIBi

NNHTs

t-BuOLi

Scheme 33 Monoareno-pentalenes with two olefinic protons.

NNHTs PdCl₂(PPh₃)₂

R³ (10 mol%)

t-BuOLi, Dioxane

132 110 °C, N₂, 1h

133 R¹

R³

Cycle A

R³

Cycle B

R³

R³

R³

R³

Cycle B

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

138

NR1

Scheme 32 Synthesis of phosphorylated heteroaromatics.

palladacycle complex undergoes reductive elimination, producing intermediate 11 and releasing the Pd⁰ 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-Fuentes⁴³ 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 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(PPh₃)₄, K₂CO₃ 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 bisheterocycles. 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 $\it et~al.$ described the synthesis of bisbenzofulvenes $\it 155~$ through a palladium-catalyzed

intramolecular Heck coupling followed by Ni-mediated C(sp²)-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 Nimediated dimerization. Bulky phosphines, like PtBu3, generally led to poor yields, while smaller cone angle ligands such as triphenylphosphine (PPh₃) improved yields, reaching up to 89% for bromobenzofulvene 154. This adaptability highlights the method's potential for creating structurally varied bisbenzofulvenes 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 osubstituted *gem*-dibromoolefins **1g** with allenyl malonates **156**, synthesizing bicyclic compounds 157 via a one-pot cascade reaction (Scheme 36). The reaction proceeds using Pd(OAc)₂ as the catalyst, a phosphine ligand (P[3,5-(CF₃)₂C₆H₃]₃), and K₃PO₄

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

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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 Pdo into the C-Br bond of the osubstituted 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 Pd⁰ 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 PPh₃ (40 mol%) and K₂CO₃ in THF/H₂O (4:1) was crucial for achieving efficient cascade coupling, with water serving as an essential cosolvent to improve K₂CO₃ solubility. Under these conditions, a wide variety of gem-dibromo olefins bearing electron-donating, electron-withdrawing, and heteroaryl substituents 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.

 $esp = \alpha, \alpha, \alpha', \alpha'$ -tetramethyl-1,3-benzenedipropionate

Scheme 38 Synthesize of 2,3-dibromoindoles.

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 Rh₂(esp)₂ as catalyst, giving 2,3dibromoindoles 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, dualmetal 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(2H)-one derivatives 170 through a nucleophilic addition/Cu-catalyzed N-arylation/Pdcatalyzed C-H activation sequence (Scheme 40).64 The methodology employes o-substituted gem-dibromoolefins 1j and Nalkyl-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 K2CO3 as optimal for the N-arylation step, and Pd(dppf)Cl₂ 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(2H)-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-NO₂ and 4-Ac were detrimental, likely due to reduced nucleophilicity. The reaction's versatility extended to N-benzyl and Nnaphthyl 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)Cl₂

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

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

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 6H-isoindolo[2,1-a]indol-6-ones 173 using a similar strategy as their previous works (Scheme 42).66 The reaction employs osubstituted gem-dibromoolefins 1a and benzovl chlorides 172 as starting substrates, and CuBr and Pd(dppf)Cl2 as a dual catalytic system. Optimization studies revealed that CuBr, in combination with DMEDA and K₂CO₃, is the most effective for the initial C-N coupling cyclization, leading to formation (2-bromo-1Hindol-1-yl)(aryl)methanones 174, while Pd(dppf)Cl₂ 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 coppercatalyzed 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 6H-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 42 Synthesis of 6H-isoindolo[2,1-a]indol-6-ones.

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

presence of sodium arylsulfinate 175, TBAF, PdCl₂, Cu(OAc)₂ and NEt₃ (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 SO₂. 180 then reacts with 177, generated *via* oxidative addition of 2-bromobenzofuran 54 to Pd⁰, resulting in intermediate 178 through transmetalation. Reductive elimination of 178 affords the final product 59 and regenerates Pd⁰.

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 NO₂.

Another excellent example of utilizing o-substituted gem-dibromoolefins $\mathbf{1e}$ to construct 2-substituted benzo[b]selenophenes $\mathbf{182}$ 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 $\mathbf{182}$ via sequential cyclization/Sonogashira cross-coupling reactions

Scheme 44 Generation of 2-cvanobenzofurans(thiophenes).

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

(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). 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 Ag₂CO₃ to sequester the halides, resulting in cleaner reactions and enabling a lower ligand/Pd ratio. The reaction demonstrated

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(π)-catalyzed dehydrobromination and Ag(π)-catalyzed activation of the triple bond under mild conditions was reported by Perumal and co-workers (Scheme 47). 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 Cucatalyzed 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

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

high yields without the need for Pd catalysts or CO gas (Scheme 48).72 The optimal reaction conditions involved were 5 mol% CuBr₂ as the catalyst, 5 mol% 2,2'-Bpy as the ligand, 3.0 equiv. of Et₃N 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, COOCH3, 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 2bromobenzofuran 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.

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(ı)/AgNO₃ or the *N*-cyclized products **197** with Au(ı)/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.

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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 antiaddition 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-1H-indenes 199.

Scheme 50 Synthesis of dibrominated 2,3-dihydro-1H-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 Cs₂CO₃ in DMSO under catalystfree conditions (Scheme 51).77 The reaction proceeds optimally at 120 °C, with the formation of an alkynyl bromide intermediate 68, which undergoes cyclization and CO2 trapping in a one-pot process, producing the desired indoles 203 cleanly and in high yield after a simple acidic work-up. Electrondonating 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)). 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 3sulfenyl derivatives. One year later, Wang and colleagues established a streamlined approach for synthesizing 2-bromoindoles 29 through the intramolecular cyclization of osubstituted gem-dibromoolefins 1a in the presence of Cs₂CO₃ 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 Nmethylsulfonyl-protected counterparts by adjusting Cs₂CO₃ 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 \rightarrow C and N \rightarrow C trifluoromethanesulfonyl migration reactions (Scheme 53). 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)-4H-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)-4H-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 1,3benzoxazine 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 ringopening 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

Br Br
$$(R^1Y)_2$$
 (1.0 equiv.)

Cs₂CO₃ (3.0 equiv.)

DMSO, 110 °C

XBu 0.5-2.5 h
1c, X = S
1e, X = Se

Br

XBu 224

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 halogensubstituted 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/oxygencontaining 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 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 1bromoalkyne 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 basemediated 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.

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