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过渡金属催化偕二溴烯烃衍生物的偶联反应

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摘要 偕二溴烯烃衍生物是有机化学中非常重要的合成工具, 已被广泛应用于功能化分子的构建. 在过去几十年中, 金属催化(如铂、铜、银、金、镍)与偕二溴烯烃衍生物的转化已发展成为合成炔烃、色烯、吲哚、苯并吲哚及苯并噻吩等具有重要生理活性的苯并稠合杂环的有力工具. 总结了自 2013 年以来过渡金属催化的偕二溴烯烃衍生物转化的研究进展.

关键词 偕二溴烯烃衍生物; 炔基中间体; 过渡金属催化; 偶联反应

Transition-Metal Catalyzed Coupling Reactions of *gem*-Dibromovinyl Derivatives

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Abstract *gem*-Dibromovinyl derivatives are valuable synthetic tools in organic chemistry, which have been widely applied in the construction of founctionalized molecules. In the past few years, metal-catalyzed (such as Pd, Cu, Ag, Au and Ni) transformations with *gem*-dibromovinyl derivatives have been developed and become a powerful tool for the synthesis of alkynes, chromenes, indoles, benzindole, benzothiophene and other benzo-fused heterocycles with important physiological activity. The progresses in transition-metal-catalyzed transformations of *gem*-dibromoviny derivatives since 2013 are summarized.

Keywords *gem*-dibromovinyl derivative; alkynyl intermediate; transition metal catalysis; coupling reaction

1 Introduction

gem-Dibromovinyl derivatives are important and interesting synthetic building blocks in various chemical transformations.[1] In addition, dihaloethylene functional group is a versatile and attractive bidentate electrophile for organometallic chemistry.[2] Generally, the *gem*-dibromovinyl derivatives could be synthesized via Ramirez olefination using the Corey-Fuchs reaction with aldehyde (or ketone) and CBr_4/PPh_3 conveniently.[3] The two halogen atoms bonded to a vinyl carbon make these molecules more active than the corresponding monohaloolefins in the oxidative addition reaction of metal complexes, leading to the corresponding metals catalyzed cross-coupling reaction easily. In the synthesis of alkynes, carbocyclic compounds, heterocycles, *etc*., *gem*-dibromovinyl derivatives have become attractive units, by judicious selecting starting materials and ligands. During the past years, transition-metal-catalyzed transformations have been developed into one of the most useful and powerful strategy in the furnishing of C—C bonds in the organic reactions. In particular, transition-metal-catalyzed transformations have been used as effective strategies for accessing carbon and heterocycles. To synthesize heterocycle, cascade reactions, which use 1,1-dibromovinyl derivatives as the core substrates, caused much more attention due to their usefulness not only in the first cyclization or alkylation, but also for further one pot processes. In 2012, Chelucci[1] provided an elegant review on the synthesis and metal-catalyzed reactions of *gem*-dihalovinyl systems. During the last 10 years, numerous beautiful works have been reported in this field. So the present review will summarize the recent progresses on transition-metal-catalyzed coupling reactions of *gem*-dibromoviny deriva-

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tives since 2012.

2 Coupling reaction of *gem*-dibromoalkene derivatives

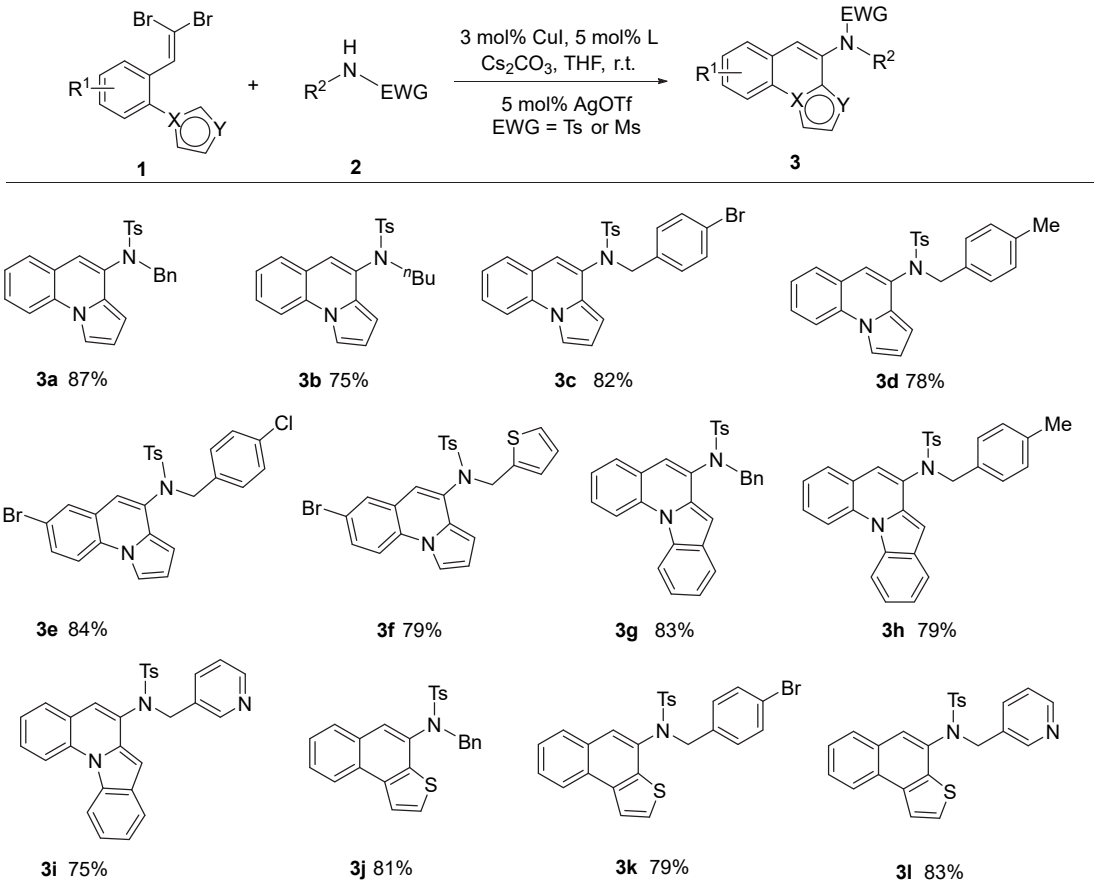
Perumal and co-workers[4] demonstrated the synthesis of pyrrolo-/indolo[1,2-*a*]quinolines and naphtho[2,1-*b*]thiophenes utilizing *gem*-dibromovinyls and sulphonamides in 2014. This methodology proposed a two-step protocol to construct tricyclic and tetracyclic heterocycles in one-pot through the Cu(I)-catalyzed formation of ynamide followed by a Ag(I)-mediated intramolecular hydroarylation. The method has milder reaction conditions, shorter reaction time and better yields, which is economical, practical and reliable.

Perumal *et al*. applied the standard conditions to the synthesis of pyrrolo[1,2-*a*]quinoline derivatives (Scheme 1). The transformation proceeded well for substrates **1** and **2**, especially, the valuable and active bromo could survive under the standard conditions (**3e** and **3f**). Next, the group worked to achieve fused tetracyclic nitrogen analogues by changing the heterocyclic nucleophile on the *gem*-dibromovinyl (Scheme 1, **3g**～**3i**). Furthermore, they applied this methodology to synthesize other indolo[1,2-*a*]quinoline analogues by modifying the substituents on sulphonamides. These compounds were found to have photophysical properties, and a few representative examples of the pyrrolo- and indolo[1,2-*a*]quinolines showed diverse fluorescence in solution, solid and aggregate states. After successful synthesis of tricyclic and tetracyclic quinolines, the team explored the applicability of introducing a thiophene ring to the *ortho*-position of *gem*-vinyldihalide, and the reaction proceeded smoothly to generate naphtho[2,1-*b*]thiophenes with the standard Cu(I)/Ag(I) conditions in excellent yields (Scheme 1, **3j**～**3l**).

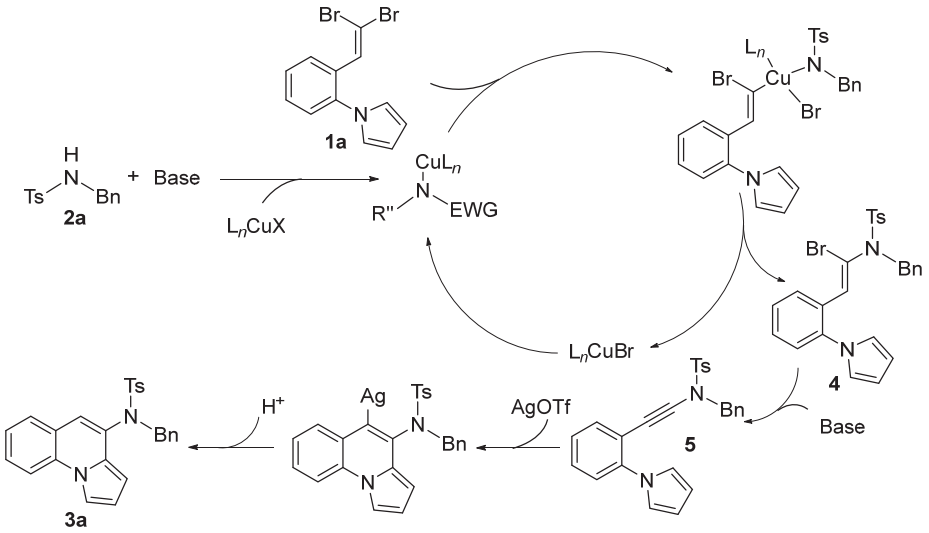
A mechanism for the synthesis of fused nitrogen heterocycle is introduced in Scheme 2. The *trans* C—Br bond of *gem*-dibromovinyl **1a** showed higher reactivity, which can be first oxidized and added to Cu(I). Stereoselective cross-coupling with *N*-benzyl-4-methyl-benzenesulfonamide **4**, followed by dehydrobromination afford alkynylamide **5**. Then, intramolecular hydrogenation reaction can be performed through activating the triple bond via coordination with Ag^+ to provide pyrrolo[1,2-*a*]quinoline **3a**.

Zhang and co-workers[5] demonstrated the construction of *N*-arylsulfonyl-1,2,3-triazole **8** using readily available *gem*-dibromo-2-arylethylenes **6** in the presence of Cs_2CO_3 via a cascade Cu(I)-promoted Huisgen cycloaddition of the resultant alkynes with tosyl azide in 2016 (Scheme 3).

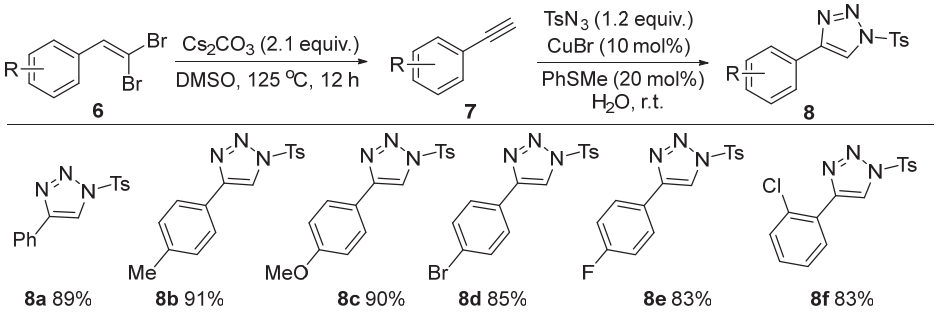
In 2015, Rao and co-workers[6] demonstrated a direct cascade methodology for the development of 2-aryl and 2-styrylbenzofuran scaffold with 1,1-dibromoalkene and phenol catalyzed by palladium (Scheme 4). This elastic and



Scheme 1 Synthesis of pyrrolo-/indolo-/naphtho-[1,2-*a*]quinolines

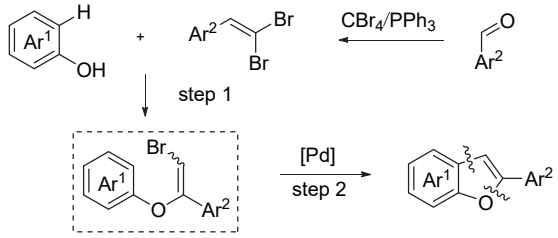


Scheme 2 Mechanism for the synthesis of pyrrolo[1,2-*a*]quinolines



Scheme 3 Synthesis of *N*-arylsulfonyl-1,2,3-triazoles from 1,1-dibromo-2-arylethylenes

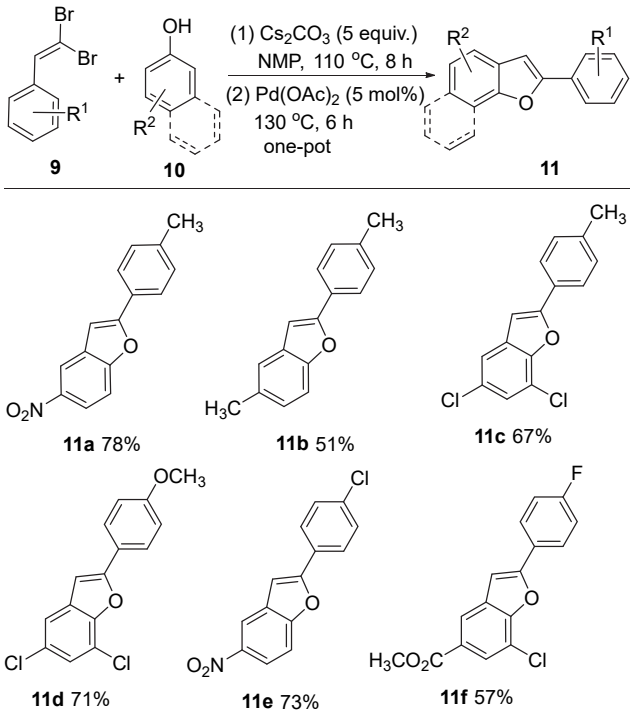
new process makes it facile to obtain multi-substituted benzofurans or benzodifuran in poeqeconomic practical manner. The strategy is a two-step one-pot process, and the cyclization of 2-bromomovinyl phenyl ether can be achieved in the presence of $Pd(OAc)_2$ in high yield.



Scheme 4 Synthesis of 2-arylbenzofuran scaffold through direct involvement of 1,1-dibromoalkene and phenol

As shown in Scheme 5, various 2-arylbenzofurans were synthesized using different functionalized *gem*-dibromides and phenols. Phenols bearing both electron-withdrawing and electron-rich groups afforded the corresponding benzofurans in good to high yields.

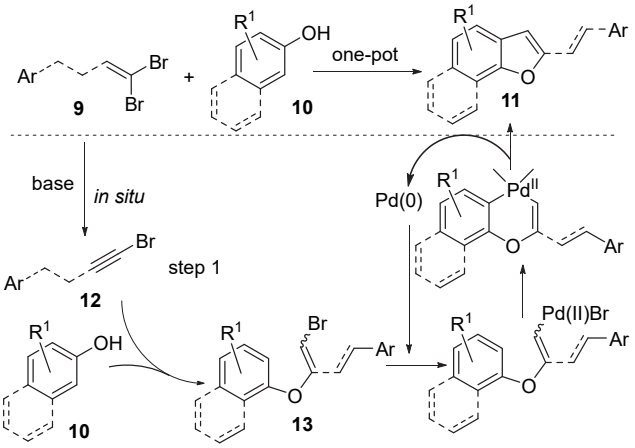
The mechanism for the furnishing of benzofuran from *gem*-dibromide and phenol is illustrated in Scheme 6. In step one, the initial dehydrobromination of 1,1-dibromide **9** would form 1-bromoalkyne **12** with base. Furthermore, the addition with phenol **10** was performed to provide 2-bromovinylphenyl ether **13**. In step two, 2-bromovinyl-



Scheme 5 Two-step one-pot synthesis of benzofurans

phenyl ether **13** might undergo oxidative addition, cycli-

zation and reductive elimination to yield 2-substituted benzofuran **11** in a one-pot process catalyzed by palladium(0).



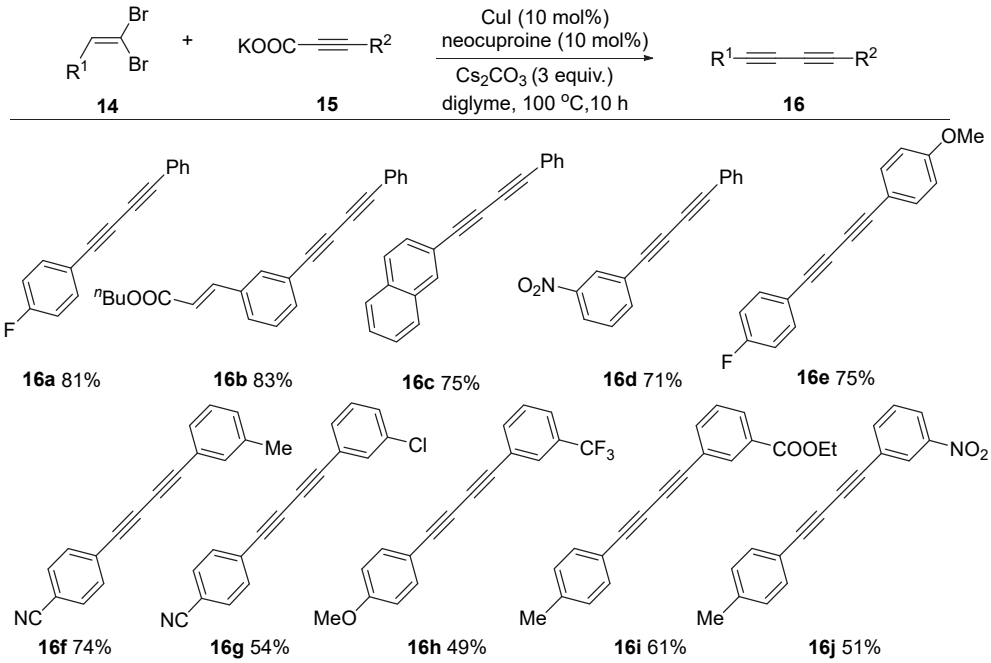
Scheme 6 Mechanistic pathway for the formation of benzofuran from 1,1-dibromide and phenol

In 2013, Cu-promoted decarboxylative cross-coupling of potassium alkynyl carboxylates with *gem*-dibromo-1-alkenes was realized to synthesize unsymmetrical 1,3-diyne derivatives by Fu and co-workers.[7] The method is a novel Cu-catalyzed strategy for 1,3-diyne synthesis, which uses *gem*-dibromo-1-alkenes as alkynyl electrophiles. Various of alkenyl, alkynyl, alkyl and aryl substituted *gem*-dibromo-1-alkenes react with aryl- or alkyl-substituted propionate esters smoothly to generate unsymmetrical 1,3-diynes and 1,3,5-triynes, showing good selectivity and functional group compatibility.

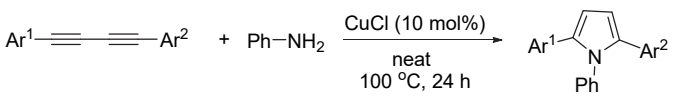
Then, the reaction scope of *gem*-dibromo-1-alkene coupling partners was examined (Scheme 7). The result exhibits that the substrates of 1,1-dibromo-1-alkenes possessing both electron-rich and electron-deficient substitutions could deliver the corresponding products in moderate to good yield (**16a**～**16j**). The range of alkynyl carboxylate was investigated and aryl propiolates bearing electron donating or withdrawing groups such as alkoxy (**16e**), alkyl (**16f**), chloro (**16g**), trifluoromethyl (**16h**), ester (**16i**) and nitro (**16j**) are well tolerated. Although these products could be obtained in moderate yields, the selectivities were very well.

Furthermore, the unsymmetrical 1,3-diyne was applied to the synthesis of substituted pyrrole derivatives efficiently (Scheme 8).

Xi group[8] developed a convenient method to synthesize *gem*-dihaloenynes from 1,1,4,4-tetrahalo-1,3-butadienes by the Fritsch-Buttenberg-Wiechell rearrangement. If 1,1,4,4-tetrabromo-1,3-butadiene was treated with *t*-BuLi in tetrahydrofuran (THF), **18a** and **18b** were isolated in 53% and 54% yield, respectively (Scheme 9). When the reaction was conducted in hexane, the *gem*-dibromoenyne derivatives **18a** and **18b** were isolated in 66% and 61% yields, respec-



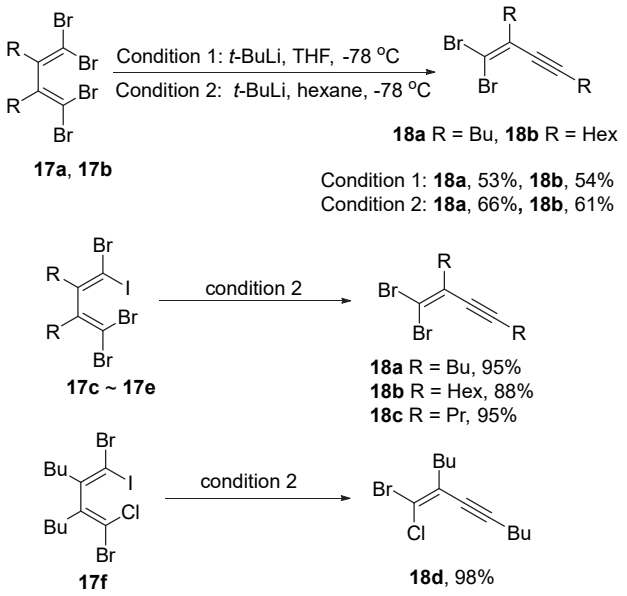
Scheme 7 Scope of potassium alkynyl carboxylates and 1,1-dibromoalkenes



Ar^1 = *p*-anisole, Ar^2 = Ph, 76% yield
Ar^2 = *m*-trifluoromethylphenyl, Ar^2 = Ph, 50% yield

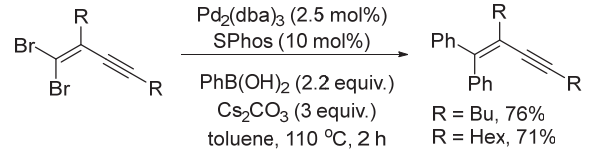
Scheme 8 Synthesis of pyrole derivatives

tively, which might be due to the relatively low reactivity of the C(sp^2)—Br bond. In fact, when *n*-BuLi was used rather than *t*-BuLi, the lithio-bromo exchange in THF or in hexane could not be observed. When the mixed polyhalogenated conjugated butadiene of Cl, Br, I was treated with *n*-BuLi using hexane as solvent, the corresponding *gem*-dihaloenyne could be obtained quantitatively as the unique product.

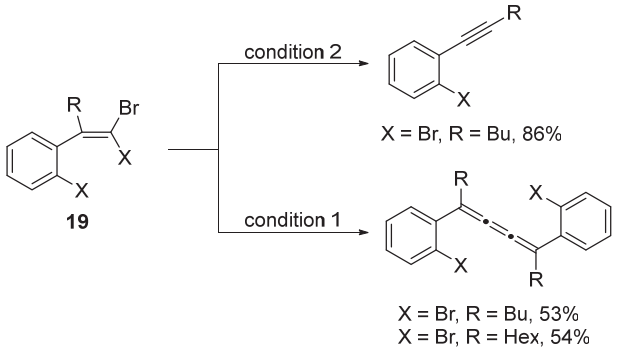


Scheme 9 Synthesis of *gem*-dihaloenynes

Then, they demonstrated the synthetic application of obtained *gem*-dihaloenyne derivatives via Suzuki-coupling (Scheme 10). If the *o*-bromo-(2,2-dibromovinyl)benzene derivative **19** was treated with *n*-BuLi using hexane as solvent, the corresponding Fritsch-Buttenberg-Wiechell rearrangement delivered the *o*-bromophenyl acetylene in 86% isolated yield. Meanwhile, butatrienes derivatives were delivered through organolithium-mediated transformation of *o*-halo-(2,2-dihalopentyl)benzene **19** in THF.



Scheme 10 Suzuki-Miyaura coupling of *gem*-dibromoenynes

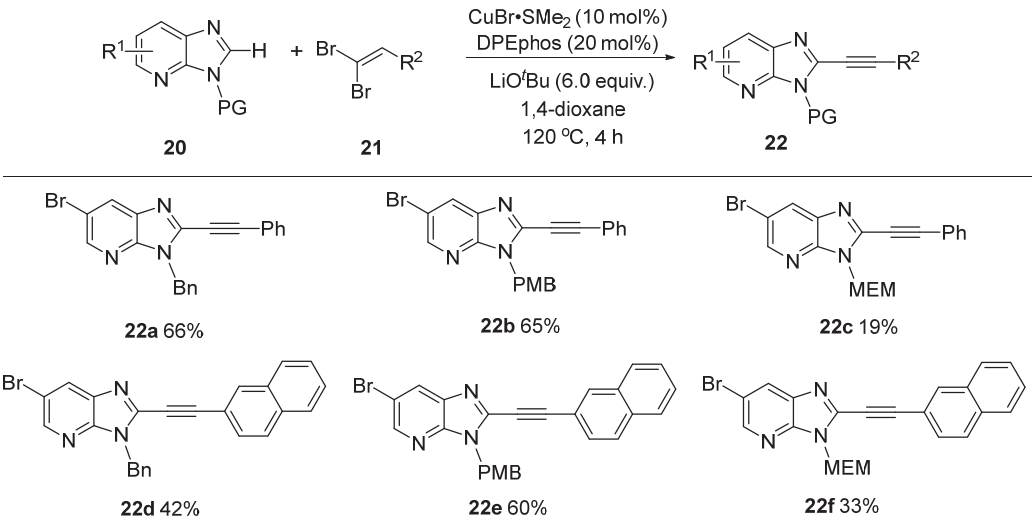


Scheme 11 Synthesis of butatrienes

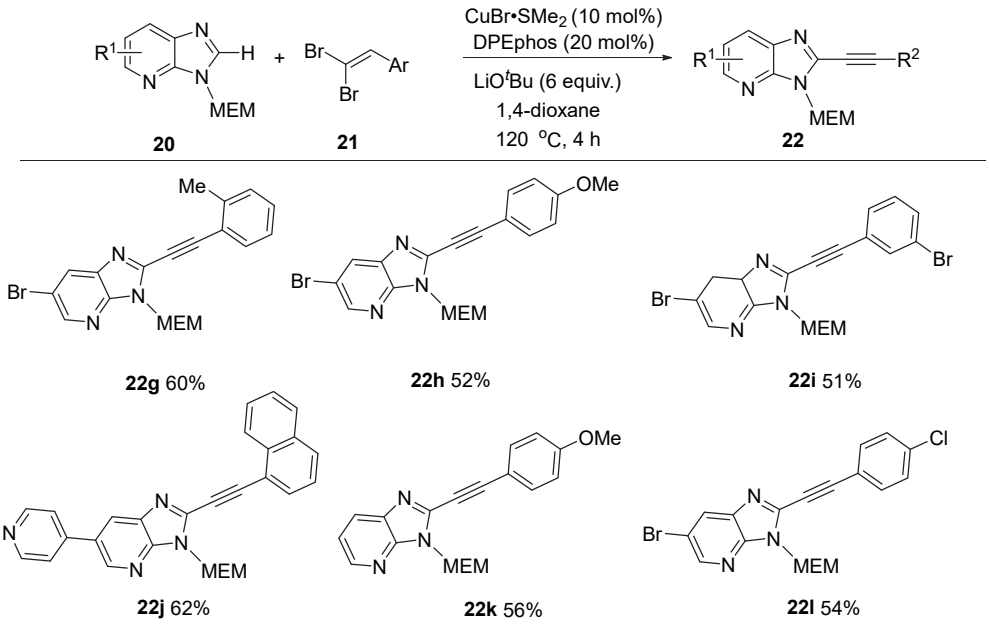
In 2016, Piguel and co-workers[9] reported the direct alkynylation at C(2) position of 3*H*-imidazo[4,5-*b*]pyridines utilizing *gem*-dibromo-1-alkenes in the presence of CuBr•SMe_2/DPEphos/Li*O*-*t*-Bu using 1,4-dioxane as solvent at 120 ℃. Both electron-rich and electron-deficient *gem*-dibromo olefins worked with 6-bromo-3*H*-imidazo[4,5-*b*]pyridine **20** to yield C(2)-alkynyl-3*H*-imidazo[4,5-*b*]-pyridines **22** in medium to good yields (Scheme 12).

Subsequently, the authors explored the direct alkynylation between N(3)-MEM-3*H*-imidazo[4,5-*b*]-pyridines and various *gem*-dibromoalkenes (Scheme 13). Regardless of whether the electron-rich (**22g**, **22h**, **22j** and **22k**) or electron-deficient (**22i** and **22l**) groups on the benzene, *gem*-dibromolefins reacted with N(3)-MEM-3*H*-imidazo[4,5-*b*]-pyridines, providing the desired molecules smoothly.

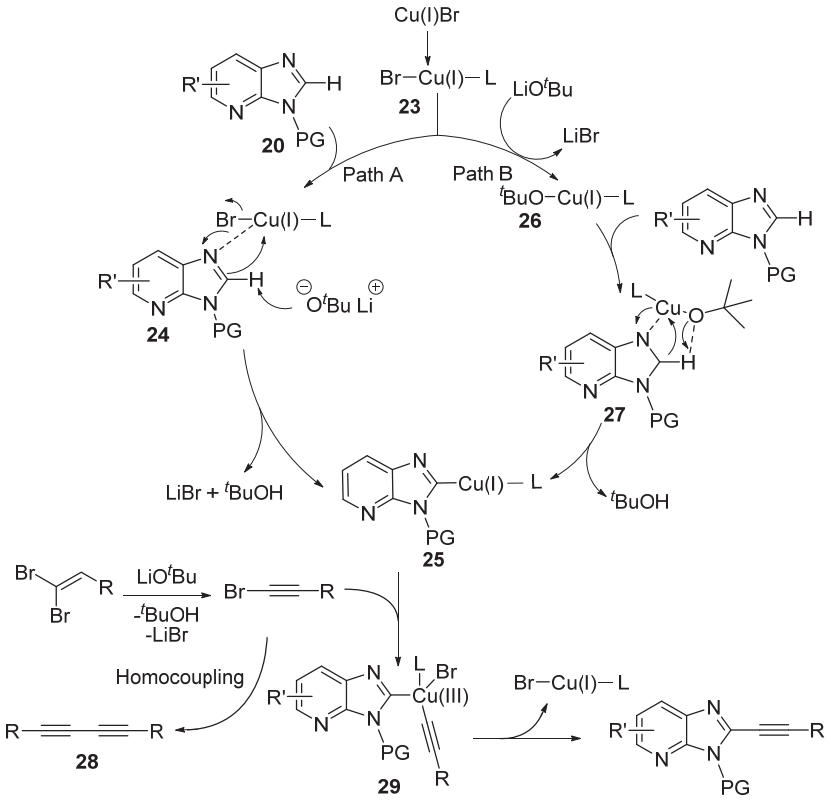
Two possible pathways for direct alkylation of substrate **20** were proposed in Scheme 14. In path A, the sequence



Scheme 12 Direct alkynylation between various *N*(3)-protected-6-bromo-3*H*-imidazo[4,5-*b*]pyridines and dibromoalkenes



Scheme 13 Direct alkynylation between various N(3)-MEM-3*H*-imidazo[4,5-*b*]pyridines and dibromoalkenes



Scheme 14 Mechanism for the direct alkynylation of 3*H*-imidazo[4,5-*b*]pyridines

begins with the coordination of copper complex **23** to the nitrogen adjacent to the activatable C — H bond of 3*H*-imidazo[4,5-*b*]pyridine (N1), resulting in intermediate **24**. Later, deprotonation and rearrangement lead to 2-cuprio-3*H*-imidazo[4,5-*b*]pyridine **25** with a base. On the other hand, it is reasonable according to path B. Alkoxide complex **26** is provided via ligand exchange between intermediate **23** and ^{t}BuOLi. The copper complex **25** is formed via internal deprotonation of 3*H*-imidazo[4,5-*b*]pyridine and intermediate **27**. At the same time, the dehydrobromination of the dibromoolefin produces the corresponding bromoalkyne, which can be coupled to form the diacetylene **28** via homo-coupling. Oxidative addition of bromoalkyne to complex **25** produces a tetracoordinated

copper(III) intermediate **29**. Subsequent reduction elimination steps produce coupled products by reproduction the catalyst.

Yan and Zhao's group[10] reported a Pd-promoted carbon-carbon bond formation strategy of two halides (*gem*-dibromoalkenes and halobenzenes) in 2018. The terminal alkyne was formed *in situ* by a cascade elimination-hydrodebromination process, which then afforded the final internal alkyne in one pot. This transformation was carried out under the classical Cu-free Sonogashira cross-coupling condition. Aryl halides were used to couple with *gem*-dibromoalkenes, rather than relatively expensive arylboronic acids to synthesize internal alkynes.

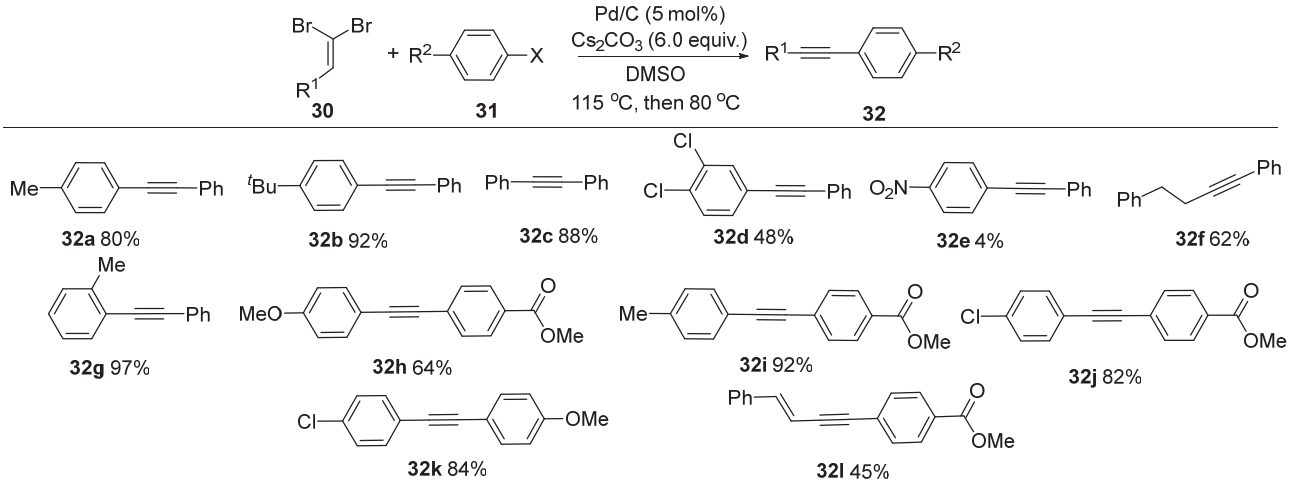
Under the optimized conditions, several *gem*-dibromoalkenes were investigated to couple with iodobenzenes (Scheme 15). Dibromoalkenes bearing electron-donating or non-functionalized aryl were transformed to the corresponding compounds with good yields (**32a**～**32c**). The substrate bearing an *ortho* substituents at the aromatic ring also proceeded efficiently to afford the corresponding product in good yield, indicating that steric congestion did not reduce the yield of the transformation (**32g**). But the nitro-substituted substrate was an adverse reactant, and the yield was only 4% (**32e**). Then, the substrate with an alkyl substitute worked very well under the standard conditions (**32f**).

Based on these results, they tried to apply bromobenzenes for a more challenging but more economical cross-coupling partner to synthesize diarylalkynes and conjugated enynes using $Pd(OAc)_2/PPh_3$. Diaryl alkynes possessing both electron-donating and electron-withdrawing group (**32h**～**32l**) on two phenyl rings were generated in good to high yields.

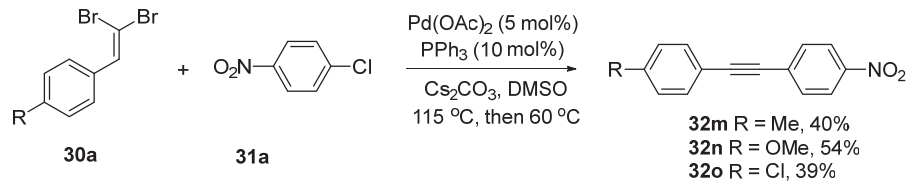
Usually, the reactivity of aryl chlorides is relatively low in transition-metal-promoted cross-coupling reactions. However, aryl chlorides with NO_2 group worked well with the standard conditions, albeit at moderate yields (**32m**～**32o**) (Scheme 16).

In 2019, Shiri and co-workers[11] realized a straightforward method to synthesize 3-(hetero)aryl- propynamides from *gem*-bromo alkenes and isocyanates with $Pd(OAc)_2/Cs_2CO_3$ in *N*,*N*-dimethylformamide (DMF) at 90 ℃ with good selectivity (Scheme 17). Various substituted dibromoalkenes and isocyanides were investigated as shown in Scheme 14. The *gem*-dibromo-1-olefins containing *meta*-, *para*- and *ortho*-electron- donating and/or electron-withdrawing substitutions (**35a**～**35c**) were readily transformed into the corresponding 3-arylpropionamides in good to excellent yields. Then, 2-chloroquinolines containing dibromoalkene were also investigated using the optimized conditions, delivering the corresponding molecule in high yields (**35e**～**35f**).

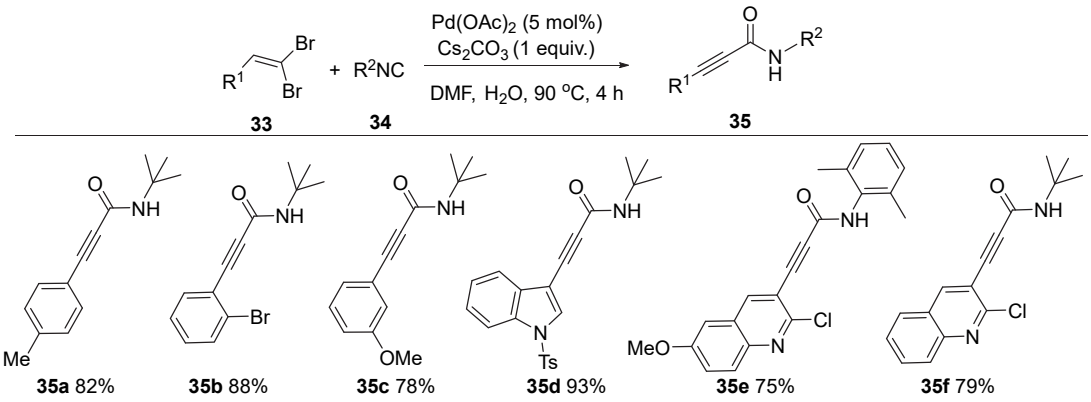
Finally, a possible pathway for palladium-catalyzed coupling reaction of 1,1-dibromo-1-alkenes **33** with isocyanates **34** was proposed (Scheme 18). The presence of palladium(0) under base medium might activate 1,1-dibromo-1-alkenes to form intermediate **36**. And then, isocyanate is inserted into **36** to generate **37**. The base-induced replacement of Br with OH results in the generation of intermediate **38**. The following reductive elimination of palladium(II) give amide **39**. Finally, the elimination of HBr



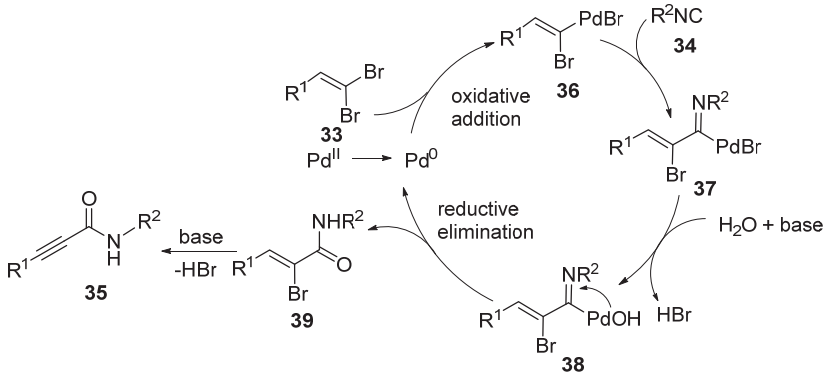
Scheme 15 Synthesis of internal alkynes



Scheme 16 Synthesis of diaryl alkynes from *gem*-dibromoalkenes and 1-chloro-4-nitrobenzene



Scheme 17 Synthesis of various 3-arylpropynamides

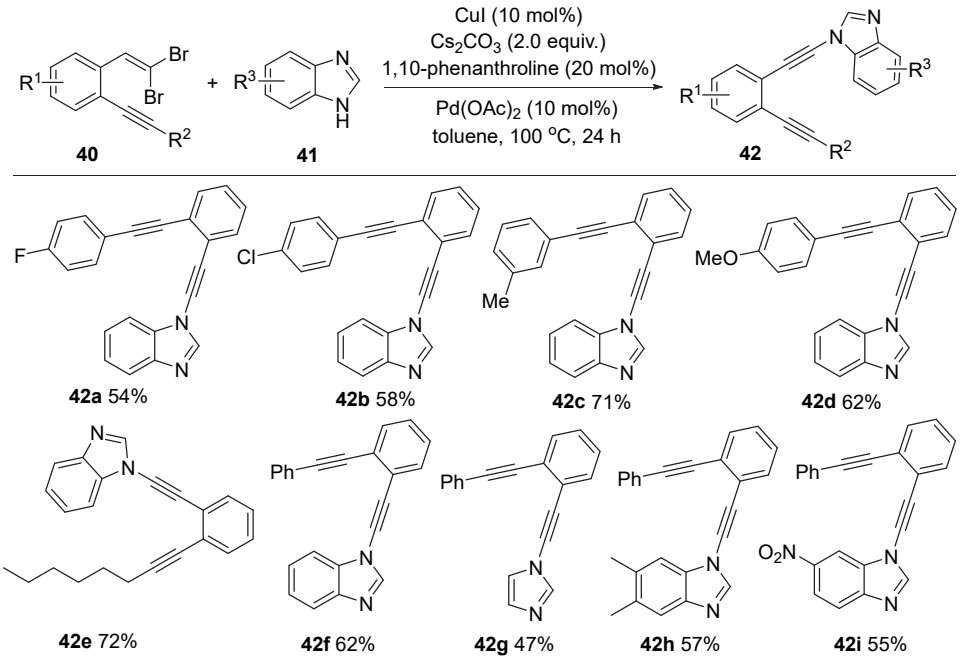


Scheme 18 Pathways involved in the Pd-catalyzed cross-coupling of 1,1-dibromo-1-alkenes with isocyanides

with base can convert **39** to the desired product propynamide **35**.

Bao and co-workers[12] discovered a CuI and $Pd(OAc)_2$ co-catalyzed cascade Ullmann-type C—N coupling in 2014. A large amount of multi-substituted imidazole and benzimidazole diyne derivatives with large steric hindrance were synthesized.

Substrates with different R^2 substituents in the 1-(2,2-dibromovinyl)-2-(phenylethynyl)benzene component were screened (Scheme 19). The electron-donating groups pro-



Scheme 19 Synthesis of diynes from 1-(2,2-dibromovinyl)-2-(phenylethynyl)benzene and imidazole/benzimidazole

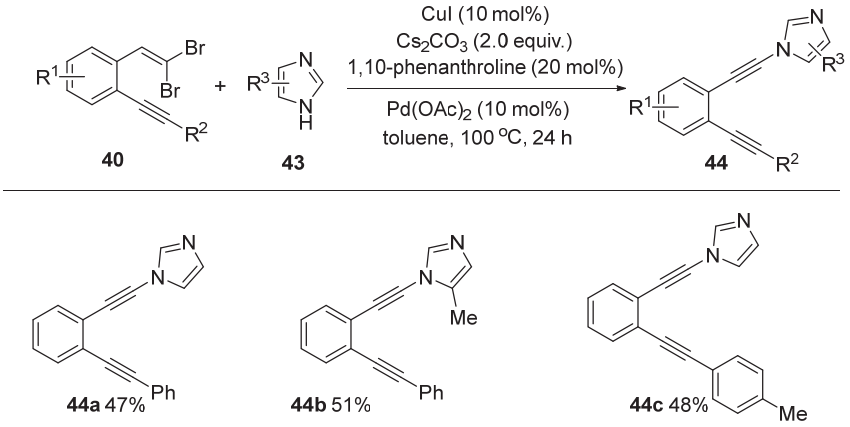
moted the reaction (**42c**, **42d**), however, the electron-withdrawing groups reduced the yield sharply (**42a**, **42b**). Alkyl groups could also work well to afford the target molecules in moderate yield (**42e**).

The range of substituted benzimidazoles used in Cu/Pd co-catalyzed cascades was also explored (Scheme 20). Due to different nucleophilic properties, the yields of the corresponding products of imidazole and benzimidazole are different from each other. Generally, the yield of benzimidazole is higher (**42f**, **42g**). Compared with the electron-withdrawing substitutent, the electron-donating substitutent could promote the tandem reactions (**42h**, **42i**).

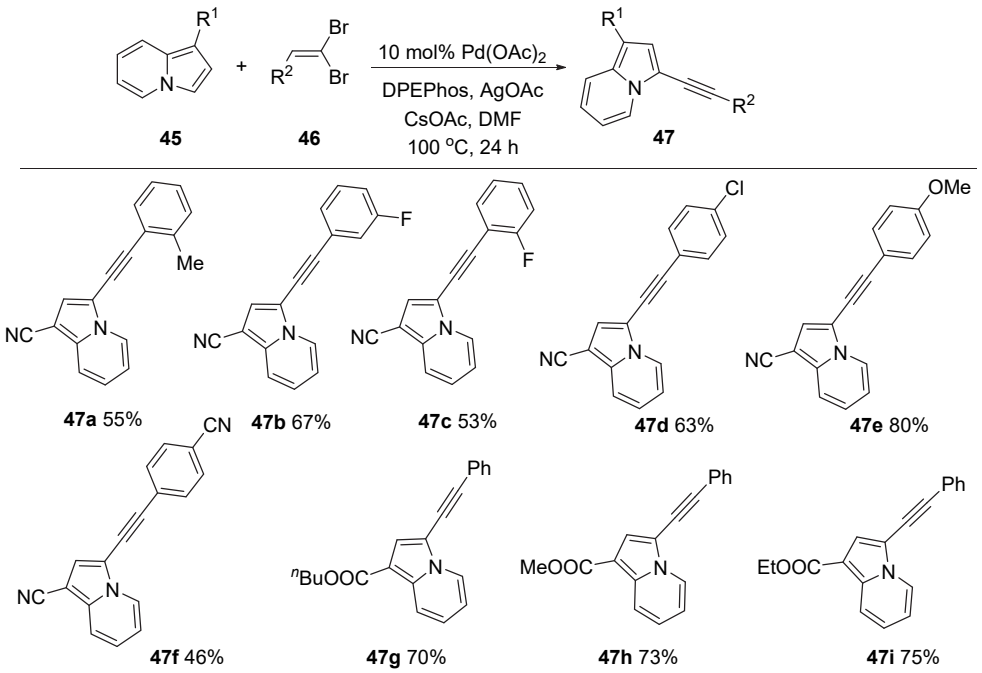
Furthermore, various functionalized imidazole derivatives were applied in the copper/palladium co-catalyzed transformations, providing the corresponding molecules with good yields (Scheme 20). Compared with imidazole (**44a**, **44c**), 4-methylimidazole was more reactive, which indicated that the nucleophilic of imidazoles were favour the Ullmann coupling (**44b**).

In 2014, Zhang group[13] demonstrated a direct C-3 alkynylation reaction of indolizines with (2,2-dibromovinyl)arenes using $Pd(OAc)_2$ (10 mol%) and DPEPhos (20 mol%). This protocol showed high efficiency and good tolerance to various functional groups.

Then the substrate scope and generality of the alkynylation of alkynindoles and *gem*-dibromo-1-olefins were screened. Various indolazine derivatives **45** were investigated with (2,2-dibromovinyl)benzene as shown in Scheme 21. Indoxazines with electron withdrawing groups **47a**～**47i** at the C-1 position could be well alkynylated to the desired molecules with good yield. The reaction of various (2,2-dibromovinyl)arenes with indolizine-1-carbonitrile was also investigated, generating the corresponding functionalized indoxazines with good to high yields.



Scheme 20 Scope of substituted imidazoles used in the Cu/Pd-co-catalysed cascade reaction

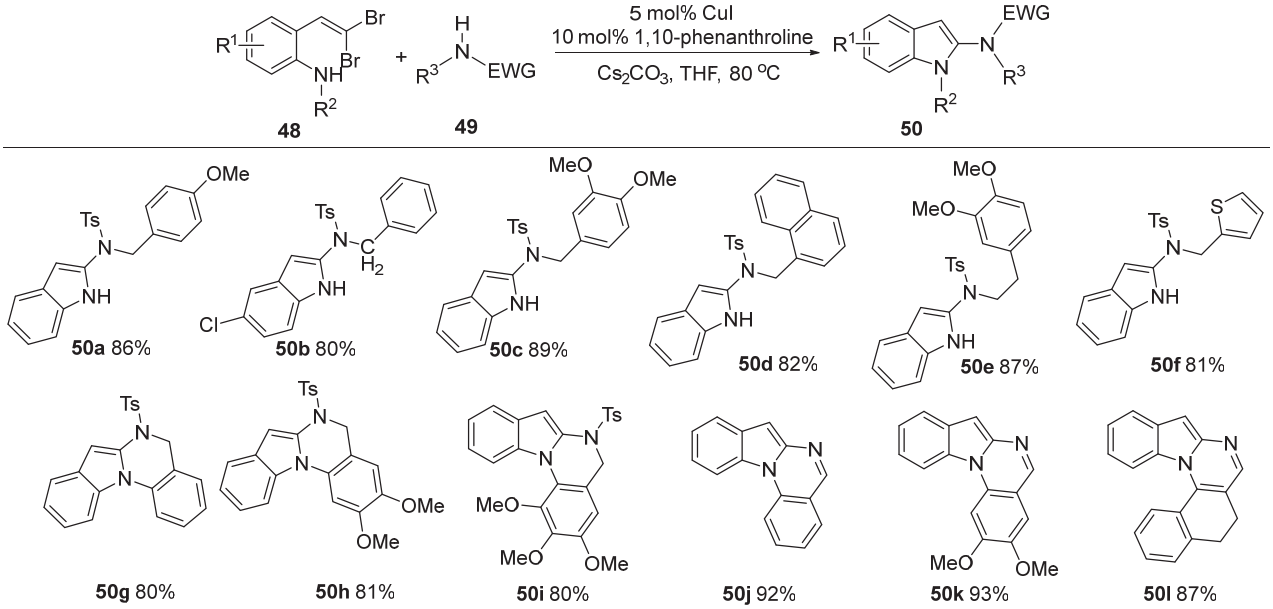


Scheme 21 Direct C-3 alkynylation of indolizines with (2,2-dibromovinyl)arenes[14]

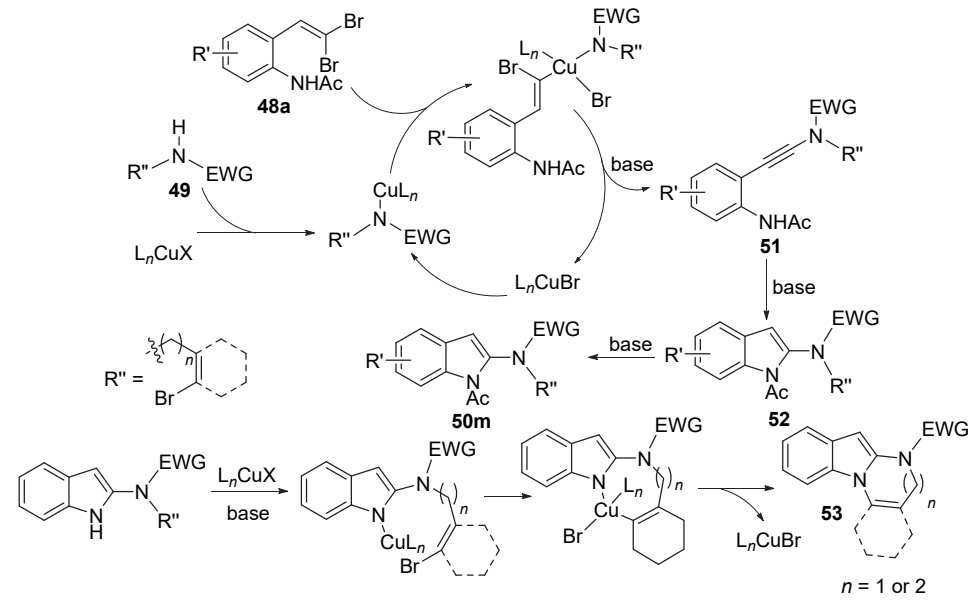
In 2014, Peiuma's group[14] reported a copper-catalyzed fast and efficient construction of 2-amidoindoles and tetrahydroindolo[1,2-*a*]quinazolines with *gem*-dibromovinylanilides and sulfonamides, which is economical and practical.

The substrate ranges of various sulfonamides and *gem*-dibromovinylanilines were screened as shown in Scheme 22. Substrates possessing electron-rich groups, halogen substituents or heterocyclic motifs (**50a**～**50f**), provided the indole derivatives with excellent yields. The intramolecular *N*-arylation of 2-amidoindole with a proximal aryl halide was confirmed to construct a tetrahydroindolo[1,2-*a*]-quinazoline with excellent yields. Then, the Ts group of tetrahydroindolo[1,2-*a*]quinazolines could be removed via refluxing in the presence of bases to give indolo[1,2-*a*]-quinazolines **50j**～**50l** efficiently.

The possible mechanism for the construction of 2-amidoindoles and tetrahydroindolo[1,2-*a*]quinazolines was proposed in Scheme 23. The *trans* carbon-bromo bond of *gem*-dibromovinylanilide **48** undergos oxidative addition to copper readily, which then couples with sulfonamide **49**. Then the following dehydrobromination reaction produces a yamide **51**. Finally, the base-induced intramolecular hydroamidation of ynamide leads to the formation of 2-amidoindoles **52**. With a near-end aryl halide, the intramolecular *N*-arylation would perform to generate tetrahydroindolo-[1,2-*a*]quinazoline or polycyclic indole **53**.

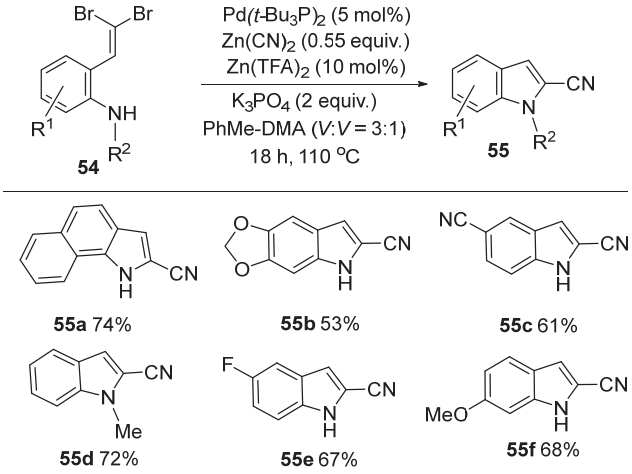


Scheme 22 Synthesis of various derivatives of 2-amidoindoles



Scheme 23 Mechanism for the formation of 2-amidoindoles and tetrahydroindolo[1,2-*a*]quinazolines

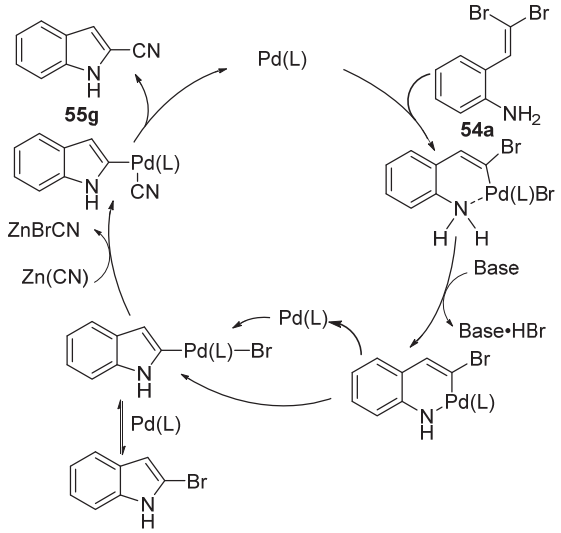
In 2017, Lautens's group[15] reported an elegant palladium(0)-catalyzed construction of 2-cyanoindoles from 2-*gem*-dihalovinylaniline (Scheme 24). A strong catalyst system of $Zn(TFA)_2$ was used to extend the reaction activity. In addition, the usage of cyanide could be minimized by benefiting the good solubility of $Zn(CN)_2$ in a mixture of two solvents.



Scheme 24 Scope of the Pd(0)-catalyzed synthesis of 2-cyanoindoles from *gem*-dibromides

The author tried to survey the order of coupling reactions and the possibility that cyanation occurred before cyclization, while no these products were detected in reactions with partial conversion. This transformation remains a possible pathway since oxidative addition of palladium across the (*E*)-C—Br bond would produce the kinetically favored structure.

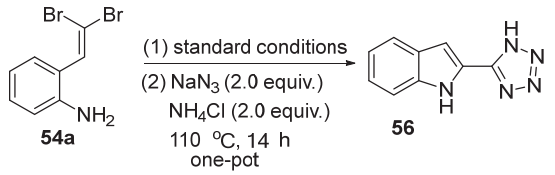
The possible reaction mechanism was proposed in Scheme 25. The oxidative addition in the C—Br bond of 2-(2,2-dibromovinyl)aniline **54a** provides a stable palladacycle. Deprotonation and reductive elimination of aniline affords 2-bromo-1*H*-indole. Notably, oxidative addition into the other C—Br bond is reversible. Transmetalation



Scheme 25 Mechanism for the reaction

with $Zn(CN)_2$ and reductive elimination could produce 1*H*-indole-2-carbonitrile **55g** and regenerate catalyst.

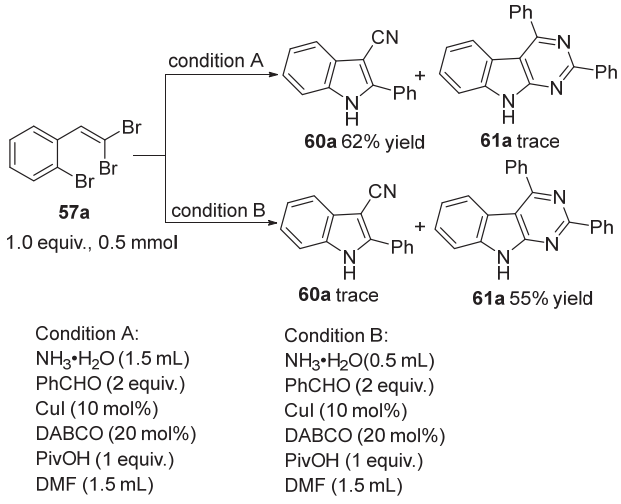
In order to prove the synthetic utility of this methodology, the one-pot derivatization was conducted after completing the palladium-catalyzed step. Then the mixture was treated with NaN_3 and NH_4Cl. After heated for 14 h, tetrazole **56** was isolated in 65% yield (Scheme 26).



Scheme 26 One-pot derivatization to afford the corresponding tetrazole

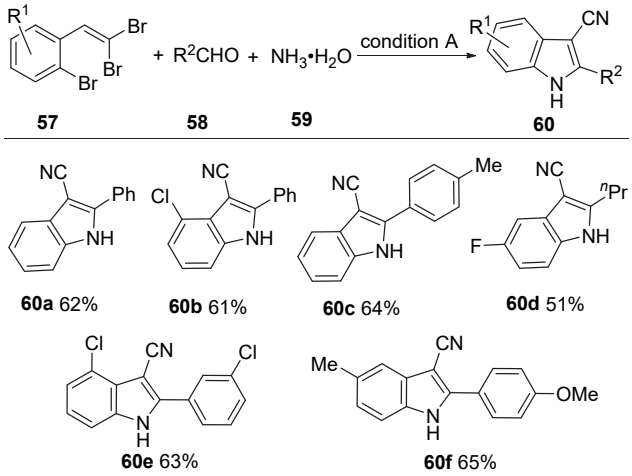
In 2015, Zhang and Fan's group[16] developed an approach for the synthesis of indole-related heterocycles, including 1*H*-indole-3-carbonitrile, 9*H*-pyrimido[4,5-*b*]indole and 9*H*-pyrido[2,3-*b*]indole derivatives. The method shows attractive superiority such as easily achieved starting materials, mild reaction conditions and different reaction modes towards different target molecules with easy-to-adjust selectivity.

The optimization to the synthesis of 3-cyano-1*H*-indole and 9*H*-pyrimido[4,5-*b*]indole was explored as shown in Scheme 27. Condition A using 1-bromo-2-(2,2-dibromovinyl)benzene (1.0 equiv., 5 mmol), benzaldehyde (2.0 equiv.), aqueous ammonia (1.5 mL), 1,4-diazabicyclo-[2.2.2]octane (DABCO) (20 mol%) and PivOH (1.0 equiv.) with CuI (10 mol%) in DMF (1.5 mL) at 80 ℃ for 24 h yielded 2-phenyl-1*H*-indole-3-carbonitrile in 62% yield. On the other hand, condition B using 1-bromo-2-(2,2-dibromovinyl)benzene (1.0 equiv., 0.5 mmol), benzaldehyde (3.0 equiv.), aqueous ammonia (0.5 mL), DABCO (20 mol%) and PivOH (1.0 equiv.) with CuI (10 mol%) in DMF (3 mL) at 80 ℃ for 30 h provided 2,4-diphenyl-9*H*-pyrimido-[4,5-*b*]indole **61a** in 55% yield.



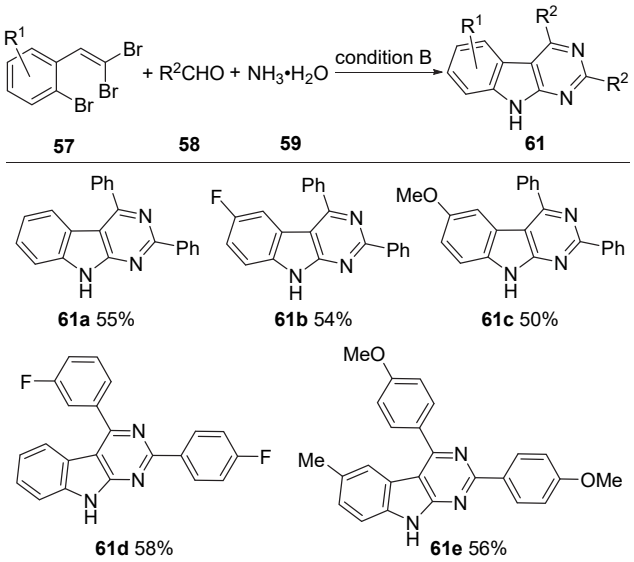
Scheme 27 Optimization study on the formation of 3-cyano-1*H*-indole and 9*H*-pyrimido[4,5-*b*]indole

Under the above condition A, the substrate scope for the construction of 3-cyanoindole derivatives was explored (Scheme 28). The substituent on the aryl ring (**60a**～**60f**) exhibited low effect on the reaction efficiency, which were compatible well in this transformation.



Scheme 28 Substrate scope for the synthesis of 3-cyanoindoles

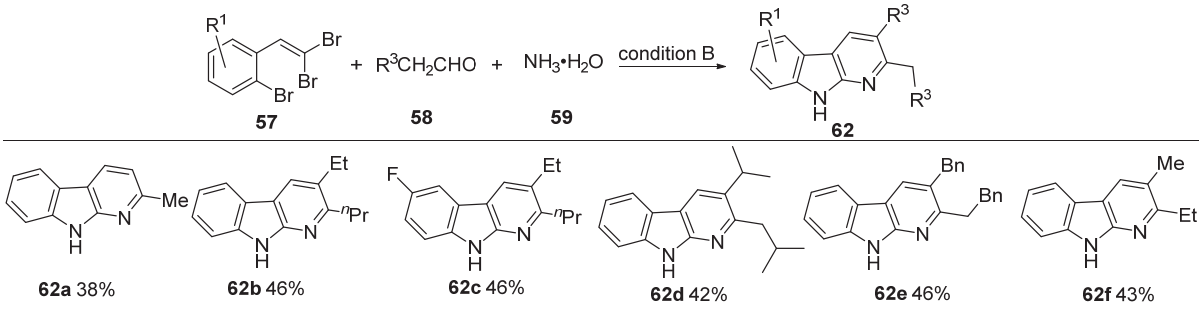
Then, the scope for the furnish of 9*H*-pyrimido[4,5-*b*]indole derivatives was also tested (Scheme 29). The results showed that different substituted 1-bromo-2-(2,2-dibromovinyl)benzene substrates worked with different kinds of aryl aldehydes and aqueous ammonia smoothly, providing lots of 9*H*-pyrimido[4,5-*b*]indoles regardless of either electronic or spatial nature of the substituents (**61a**～**60e**).



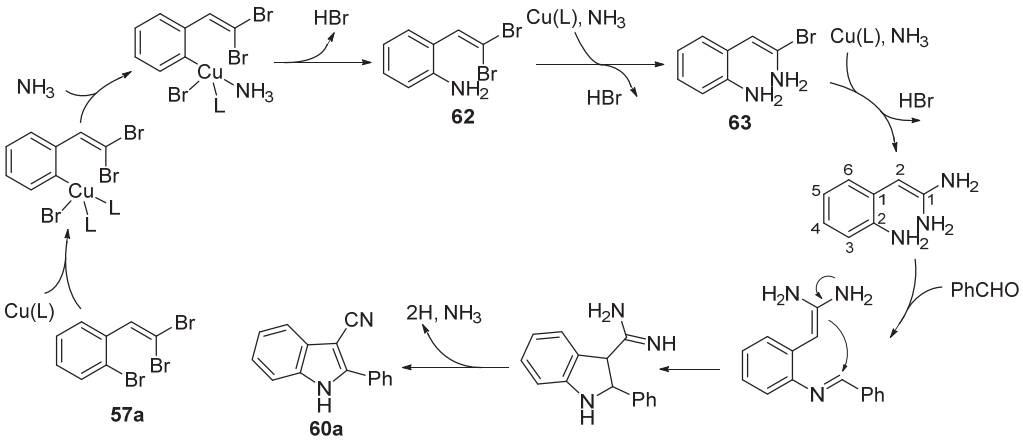
Scheme 29 Substrate scope for the synthesis of 9*H*-pyrimido[4,5-*b*]indoles

Furthermore, aliphatic aldehydes (**58a**) was subjected to the standard conditions, delivering various 9*H*-pyrido[2,3-*b*]indoles smoothly (Scheme 30). It was found that acetaldehyde, butyraldehyde, propionaldehyde, 3-methylbutanal and 3-phenylpropanal (**62a**～**62f**) were compatible substrates to this transformation, giving *α*-carbolines in moderate yields.

A possible pathway for the construction of 2-phenyl-1*H*-indole-3-carbonitrile was proposed (Scheme 31). First, in



Scheme 30 Substrate scope for the synthesis of 9*H*-pyrido[2,3-*b*]indoles



Scheme 31 Mechanism for the formation of 3-cyano-1*H*-indole

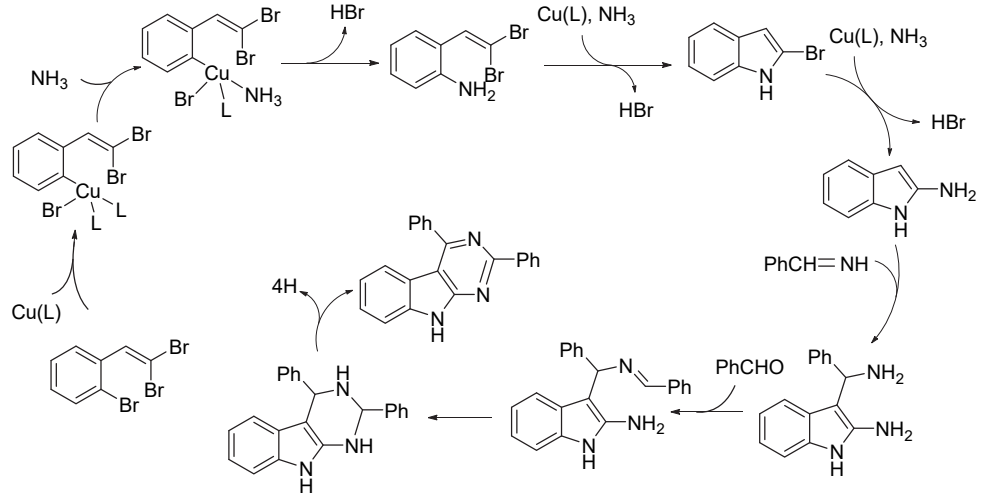
the presence of DABCO and PivOH, the aryl amination of 1-bromo-2-(2,2-dibromovinyl)benzene (**57a**) catalyzed by Cu(I) in aqueous ammonia gave 2-(2,2-dibromovinyl)-aniline (**62**). Under high-concentrated ammonia (Condition A), 2-(2,2-dibromovinyl)aniline undergoes two consecutive intermolecular vinyl amination reactions to provide intermediate 2-(2-aminophenyl)ethylene-1,1-diamine (**63**). Then, 2-(2-aminophenyl)ethylene-1,1-diamine is condensed with benzaldehyde to form an imine intermediate, which undergoes nucleophilic addition, oxidative dehydrogenation and elimination of NH_3 to produce 2-phenyl-1*H*-indole-3-carbonitrile (**60a**). Thereafter, possible pathways for the formation of 2,4-diphenyl-9*H*-pyrimido[4,5-*b*]indole and 2-methyl-9*H*-pyrido[2,3-*b*]indole was also proposed (Schemes 32 and 33).

In Scheme 32, the nucleophilic addition of indole derivatives to enamine is the crucial step for the cyclization of pyrimidine ring. In Scheme 33, the Michael addition of amine to *α*,*β*-unsaturated aldehyde is the key step for the formation of pyridine ring.

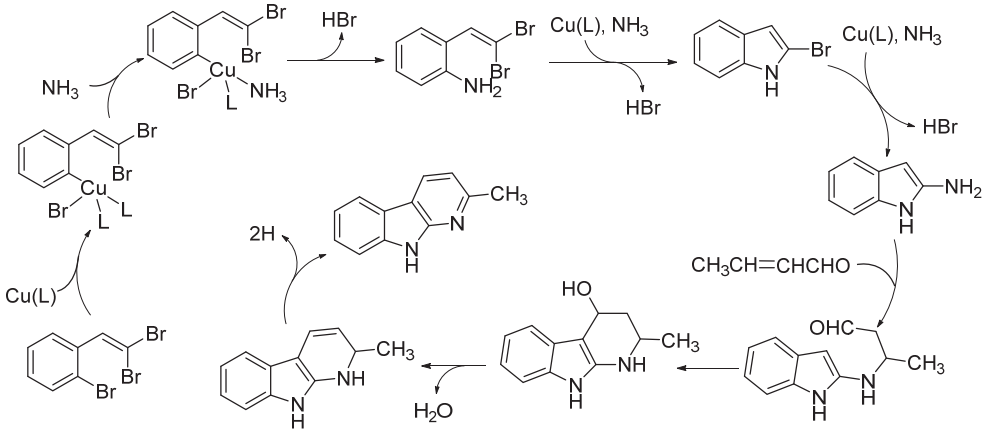
In 2013, Kundu and co-workers[17] realized a Pd/Cu and Au/Ag catalyzed two-step strategy for the fast and efficient construction of multi-functionalized indole based tricyclic heteroaromatic derivatives. The author used *gem*-dibromovinylanilines **64**, aryl or alkyl isocyanates **65** and terminal aryl or alkyl alkynes **66**, providing various bifunctionalized indole derivatives **67** efficiently (Scheme 34).

Under the optimized catalyst set A, the enyne-urea derivatives delivered *O*-cyclized derivatives in good yields. The electric property of substituents on any aromatic ring showed less effect on the yields and chemoselectivities. With condition of catalyst set B, the *N*-cyclized derivatives could be produced in good yields. However, substrates with aliphatic substituents at the alkynyl furnished the cyclized molecules in very good yield with a nonchemoselectivity, and the 6-*endo*-*dig*-*O*-cyclized product was isolated. The positive inductive effect of the aliphatic groups which reduced the electrophilicity of the cationic gold intermediate, might be responsible for the loss of the chemoselectivity.

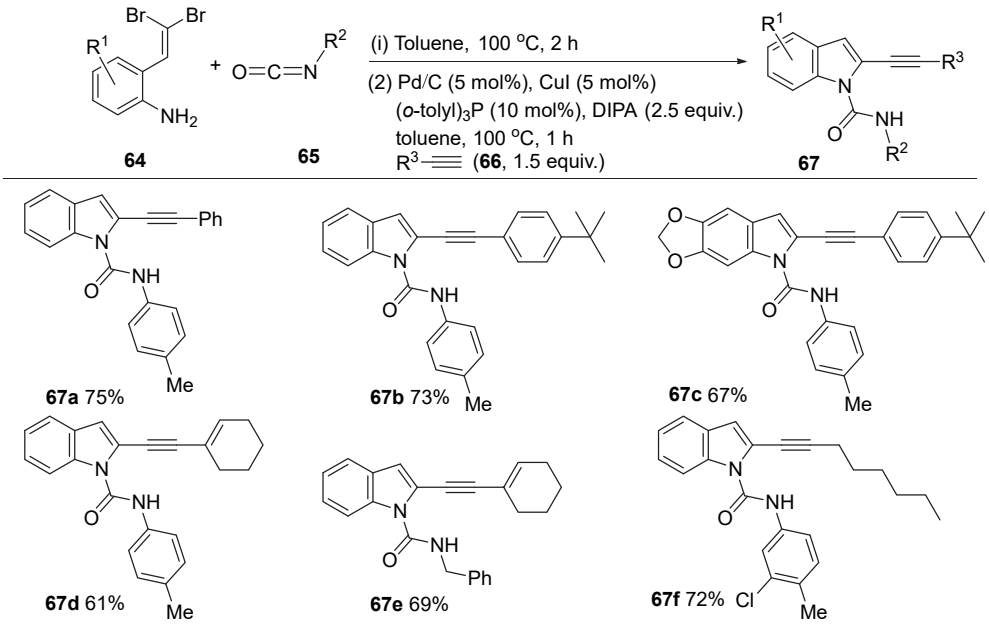
Subsequently, the author explored the scope of 6-*endo*-*dig*-*O*-cyclized products using $AuClPPh_3/AgNO_3$ (catalyst set A) as additives and 6-*endo*-*dig*-*N*-cyclized products using $AuClPPh_3/AgOTf$ (catalyst set B) as additives (Scheme 35).



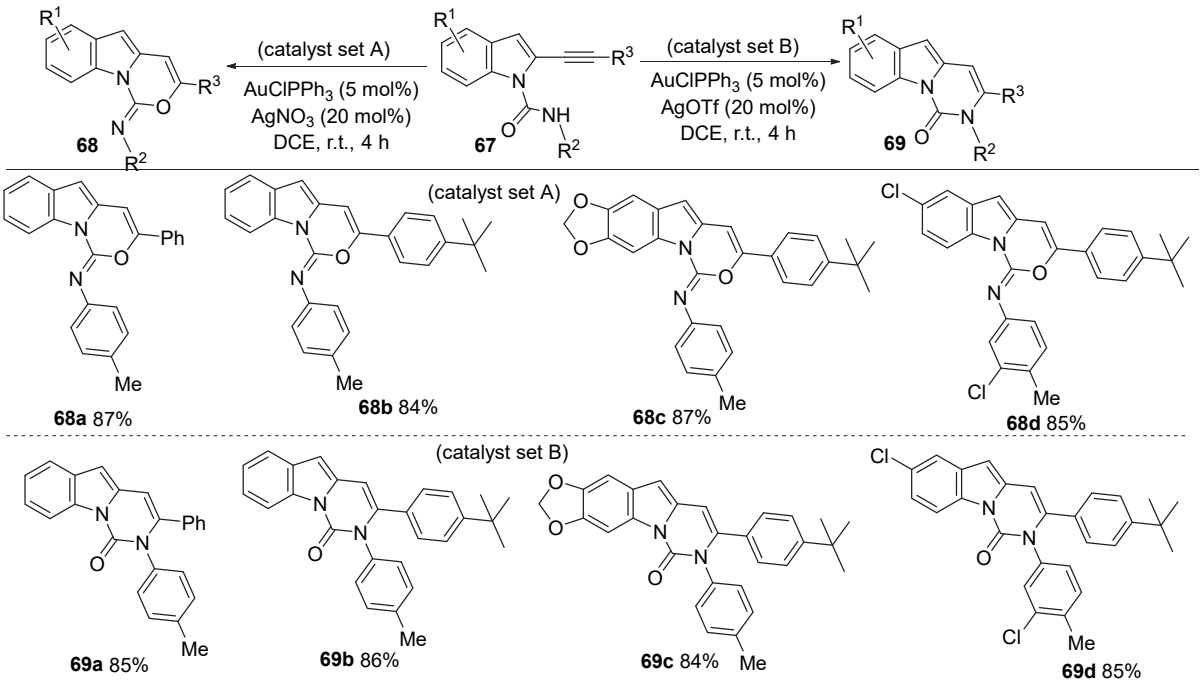
Scheme 32 Mechanism for the formation of 2,4-diphenyl-9*H*-pyrimido[4,5-*b*]indole



Scheme 33 Mechanism for the formation of 2-methyl-9*H*-pyrido[2,3-*b*]indole



Scheme 34 Three-component sequential synthesis of synthon in one pot



Scheme 35 Scope for chemoselective O- and N-cyclization

Then the author proposed a mechanism for the chemoselectivity (Scheme 36). According to catalyst set B, the $[Ph_3P\text{-}Au]^+TfO^-$ complex formed *in situ* activates the triple bond by AgOTf to provide a soft electrophilic complex **70**. The nitrogen atom of urea has less negative electricity than oxygen atom, and it favorably attacks electron-deficient alkynes with relatively soft nucleophiles, thereby delivering *N*-cyclization products. According to the catalyst set A, the *O*-cyclization promoted by $AuClPPh_3$/$AgNO_3$ may involve the activation of alkynes by the Au catalyst and the coordination of Ag to the oxygen of urea to deliver complex **73**, which upon cyclization and proto-deauration delivers the *O*-cyclized product **68e**. The mechanistic exploration indicates the importance of choosing right counterion for Au-catalyzed transformations, becasue it might play an essential role in identifying new region-divergence pathways, leading to diversity-oriented synthesis.

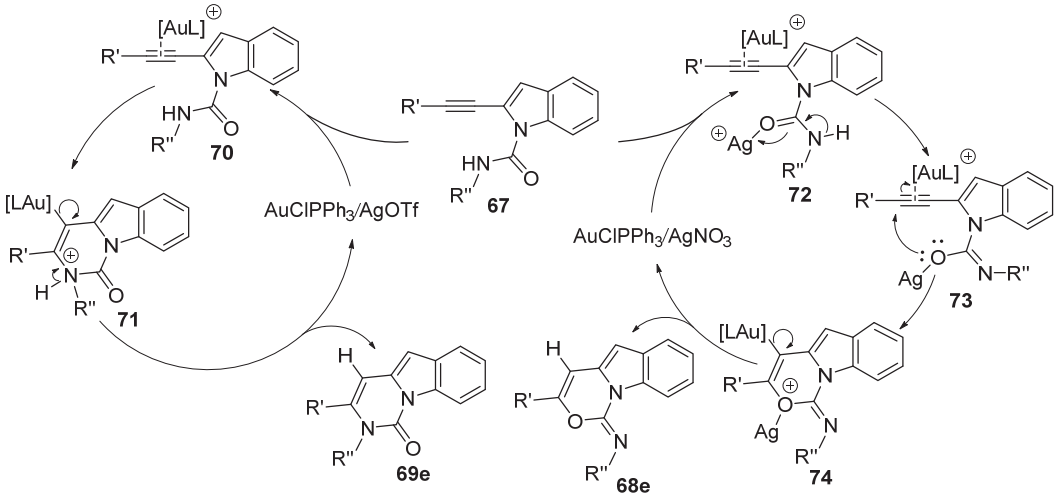
In 2019, Liu group[18] demonstrated a method to synthesize 2-(1-phenylvinyl)-indoles, using 2-*gem*-dibromovinylanilines and hydrazones, which can be completed in one pot within 1 h. With the standard conditions, a series of *N*-tosylhydrazones and 2-*gem*-dibromovinylaniline **75** were examined as shown in Scheme 37. Both electron-

donating and electron-withdrawing substitutents on the phenyl group of *N*-toluenesulfonyl hydrazone (**77b**～**77d**) showed good tolerance, delivering corresponding molecules in medium to good yields. The 2-*gem*-dibromovinylaniline derivatives (**77g**, **77h**) also showed good compatibility to this transformation.

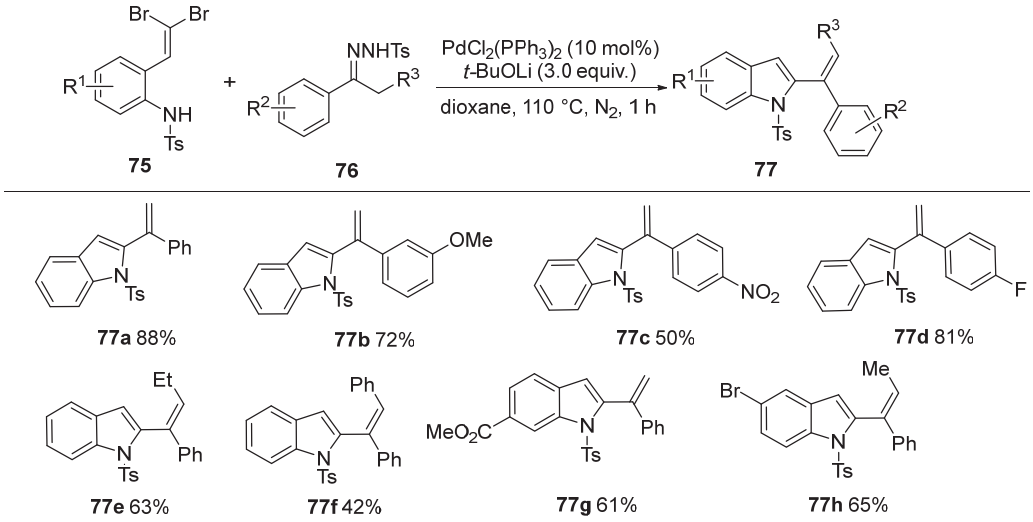
A possible route including two catalytic cycles is illustrated in Scheme 38. According to cycle A, palladium(0) complex oxidized addition to *gem*-dibromovinylaniline **75a**, providing the stable palladacycle **78**. The following deprotonation gave palladium(II) complex **79**, which subsequntly formed indole derivative **80** through reductive elimination. If the transformation was interrupted before the conversion completed, compound **80** could be isolated easily. Then it could be converted to **77a** in high yield under the standard conditions. According to cycle B, the second oxidative addition of indole derivative **80** to Pd(0) produced Pd(II) complex **81**, which then generated alkylpalladium complex **83** with carbene intermediate which was produced from diazo intermediate **82**. In the end, the *β*-H elimination of compound **83** provided the corresponding motif 2-(1-phenylvinyl)-indole **77a**.

In 2005, Lautens and co-workers[19] demonstrated a strategy to synthesize 2-substituted indoles from readily prepared *ortho*-*gem*-dihalovinylanilines through a palladium-catalyzed cascade C—N/Suzuki-Miyaura coupling (Scheme 39). Different kinds of commercial available aryl and heteroarylboronic acids bearing diverse electronic and steric feature were investigated. Various substituted *ortho*-*gem*-dibromovinylanilines such as Me, OBn, CF_3 and COOMe, were evaluated with arylboronic acid, providing the desired products in good to high yield (**86a**～**86d**).

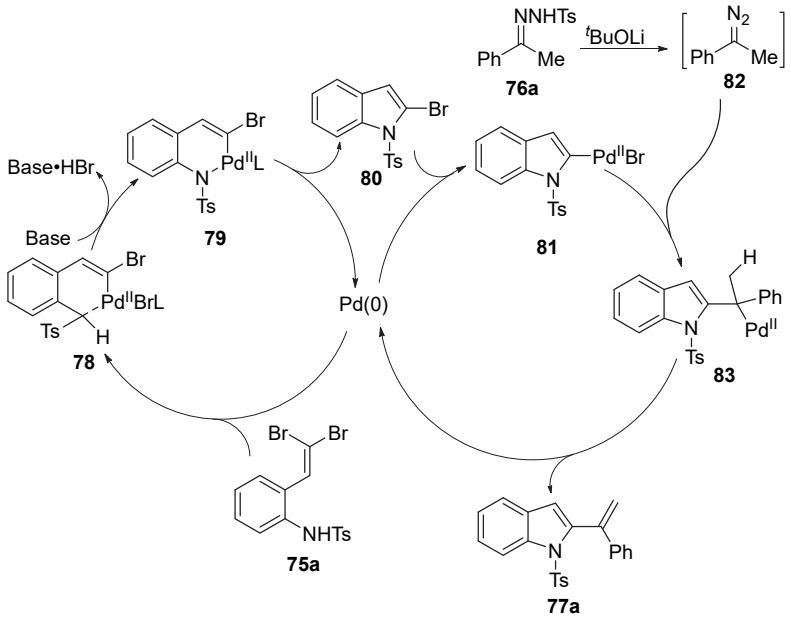
Furthermore, this reaction could also be utilized to synthesize 1,2-disubstituted indoles efficiently (**86e**, **86f**). The *N*-arylated substrates could provide indole products with good to excellent yields through the palladium-catalyzed tandem cross-coupling reaction. Notably, both alkenyl boronic acid and alkenyl catechol boronate ester could work well using this strategy.



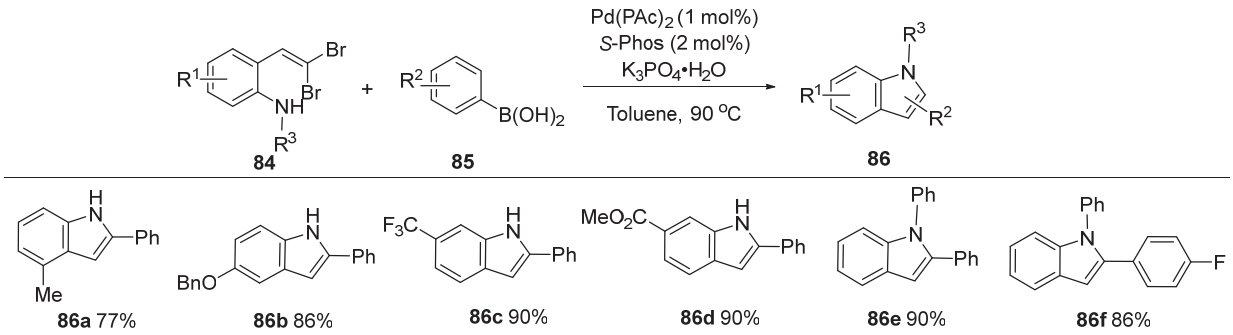
Scheme 36 Mechanism for the chemoselectivity



Scheme 37 Scope of *N*-tosylhydrazones selenophenes and *gem*-dibromovinylaniline derivatives



Scheme 38 Possible mechanism of tandem reaction



Scheme 39 Synthesis of 2-substituted indoles and 1,2-disubstituted indoles

In 2019, Weng and co-worker[20] reported an efficeint strategy to 2-trifluoromethylthio-(seleno)-substituted benzofurans catalyzed by palladium. This methodology also allowed the synthesis of 2-trifluoromethylthio-(seleno)-substituted benzo-fused heterocycles.

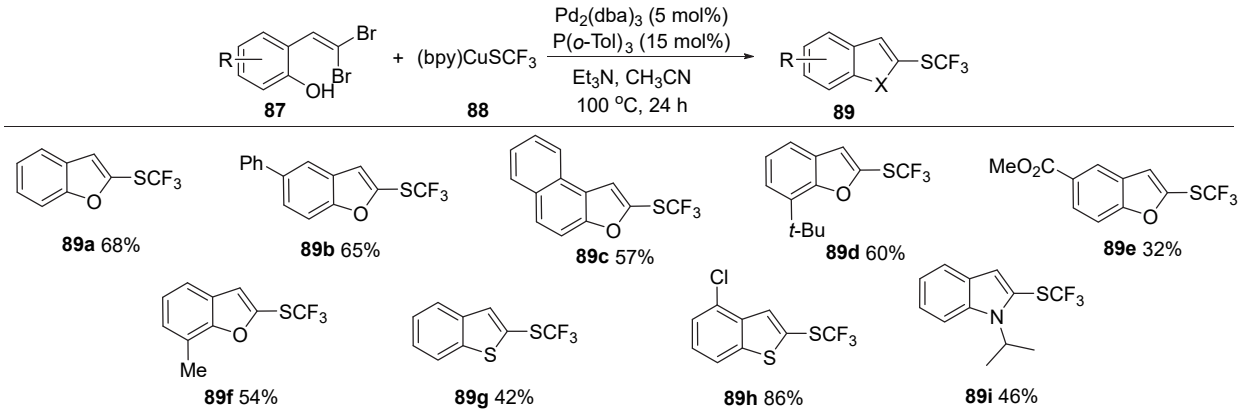
In order to investigate the substrate scope of this trifluoromethylthiolation, a lot of 2-(2,2-dibromovinyl)-phenols were examined with the optimized conditions as shown in Scheme 40. The reaction worked very well with a series of 2-(2,2-dibromovinyl)phenols to deliver functionalized 2-trifluoromethylthiobenzofurans in moderate yields. Then this method was successfully applied into the synthesis of trifluoromethylthiolated benzothiophenes and indoles (**89g**～**89i**).

Furthermore, this methodology was utilized in the furnish of 2-trifluoromethylselenobenzo-fused heterocycles which were found to be biological significance (Scheme 41). The trifluoromethylselenolation of different 2-(2,2-dibromovinyl)phenols proceeded smoothly with [(bpy)-CuSeCF$_3$], and the desired trifluoromethylselenolated benzofurans were isolated in good or excellent yields. Meanwhile, 2-(*gem*-dibromovinyl)anilines could also work very well in the trifluoromethylselenization to produce the corresponding indole derivatives (**91g**～**91i**) with low yields.

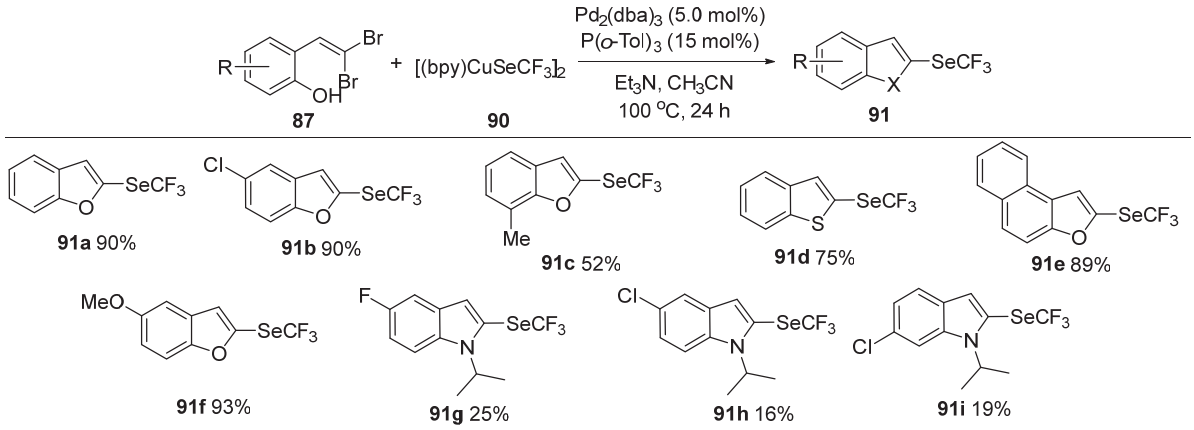
In 2017, Zeni *et al*.[21] explored a copper/palladium catalyzed multicomponent cyclization to construct 2-substituted benzo[*b*]selenophenes using 2-*gem*-dibromovinyl aryl selenides with a nucleophilic reagent (Scheme 42). The co-catalyzed action between Cu and Pd was important to obtain the desired products with good yields and avoided the production of hydrogenated benzo[*b*]selenobenzene.

Substrates with both electron-donating and electron-withdrawing groups (**93b**～**93d**) provided products in good yields, indicating that the electronic influences of substituents on the aromatic ring of selenophenols were relative low. Then a 2-(2,2-dibromovinyl)phenyl) ethylsulfide was also examined, which provided the corresponding 2-bromobenzo[*b*]thiophene **93e** in 60% yield.

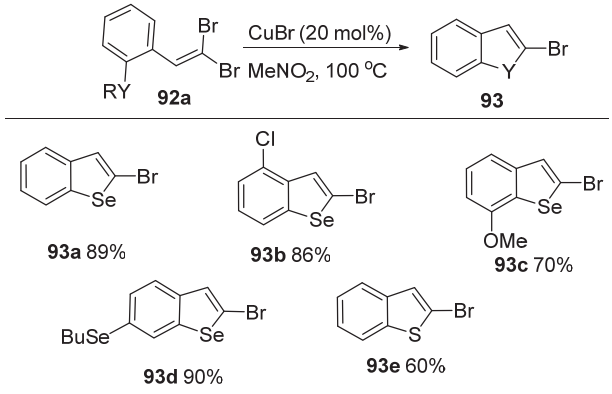
Furthermore, this methodology was applied into the coupling of *gem*-dibromovinyl selenides with terminal



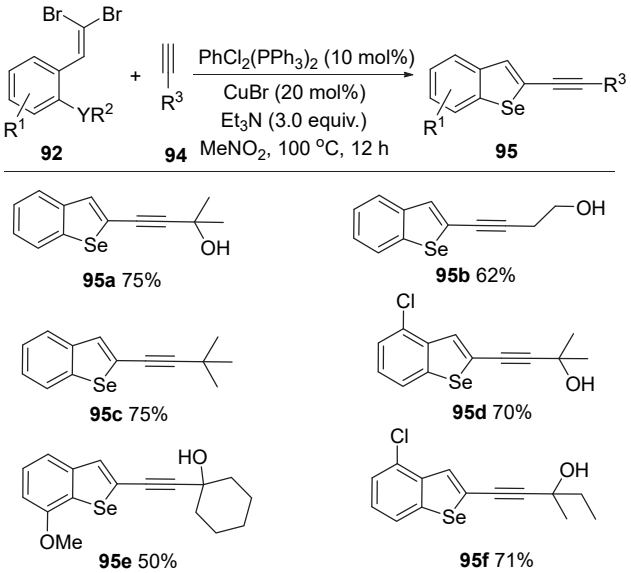
Scheme 40 Scope of the trifluoromethylthiolation of dibromovinyl phenols, thiophenols and anilines with (bpy)$CuSCF_3$



Scheme 41 Scope of the trifluoromethylselenolation of dibromovinyl phenols, thiophenols and anilines with [(bpy)$CuSeCF_3$]



Scheme 42 Synthesis of 2-bromobenzo[*b*]chalcogenophenes



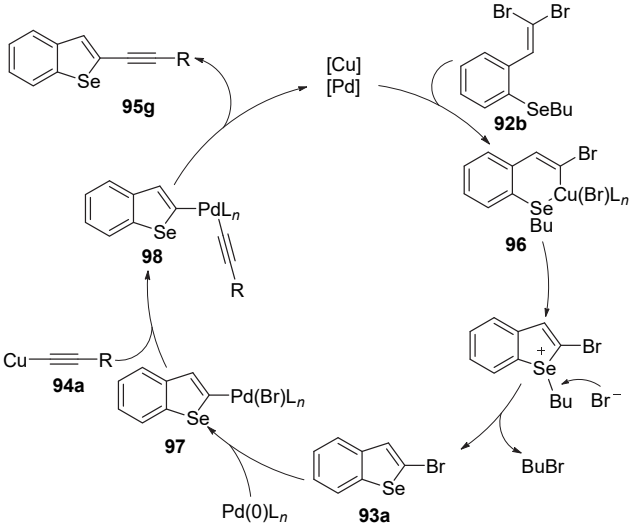
Scheme 43 Synthesis of 2-alkynyl-benzo[*b*]selenophenes

alkynes (Scheme 43). First, the author investigated the influence of dibromovinyl selenide on different terminal alkynes. The results indicated that the esteric effects on the alkynes influenced the yields slightly (**95a**～**95c**). Electron-rich aryl groups (**95e**) of the dibromovinyl selenides produced the corresponding compounds in good yields, while better yields were obtained using electron-deficient aryl groups chloro (**95d** and **95f**).

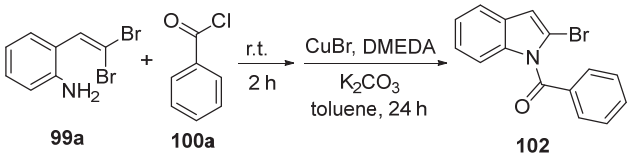
A cyclization route is outlined in Scheme 44. Firstly, the copper catalyst oxidizes the addition to vinyl bromide **92b** to form intermediate **96**, which then provides the 2-bromobenzo[*b*]selenophene **93a** via intramolecular Ullmann reaction process followed by the nucleophilic substitution on the selenium atom. Then another oxidative addition of palladium(0) to 2-bromobenzo[*b*]selenophene **93a** forms a

palladium(II) species, which then reacts with the copper activated alkyne to give intermediate **98**. Finally, the reductive elimination of coomplex **98** affords the desired product **95g** along with releasing palladium(0) for the next cycle.

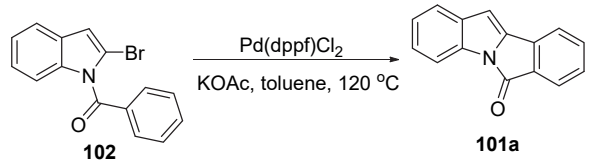
In 2012, Bao and co-workers[22] established a strategy for the direct construction of 6*H*-isoindolo[2,1-*a*]indol-6-one derivatives from the readily available benzoyl chlorides and *o*-*gem*-dibromovinyl anilines (Scheme 45). Based on the optimized conditions of the first step, they achieved palladium-catalyzed C—H bond activation to produce 6*H*-isoindolo[2,1-*a*]indol-6-one derivatives with Pd(dppf)Cl_2 and KOAc (Scheme 46).



Scheme 44 Mechanism for the forming 2-alkynyl-benzo[*b*]-selenophenes



Scheme 45 Optimization of copper-catalyzed intramolecular coupling



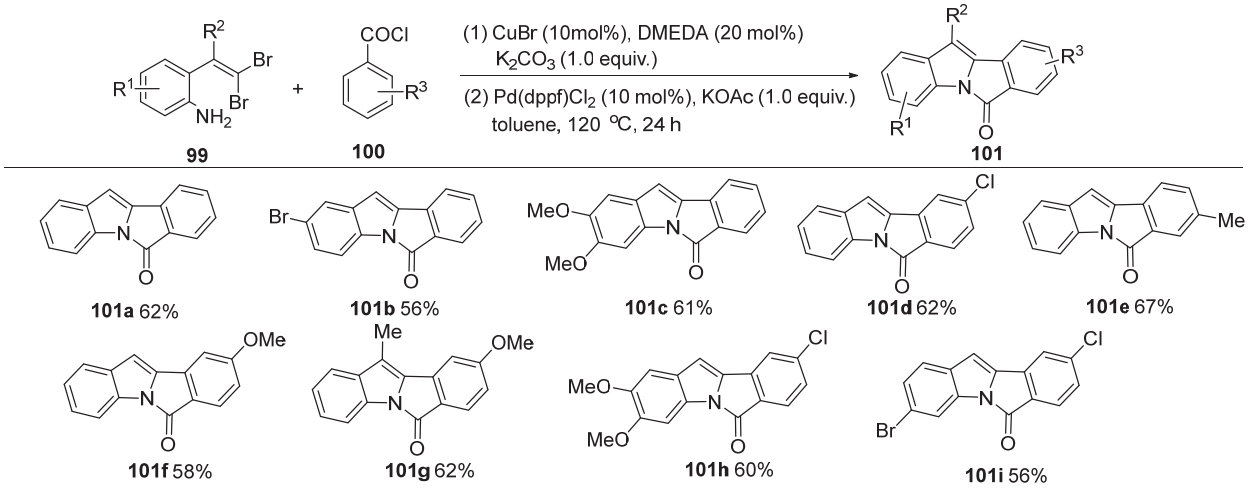
Scheme 46 Optimization of palladium-catalyzed C—H activation

Subsequently, the group performed the two conversions in one-pot. And the substrate scope is listed in Scheme 47. This transformation proceeded smoothly to deliver the corresponding 6*H*-isoindolo[2,1-*a*]indol-6-one derivatives in moderate yields. Notably, the active bromo could survive very well under the standard conditions, which was potential to be applied in further cross-coupling reactions.

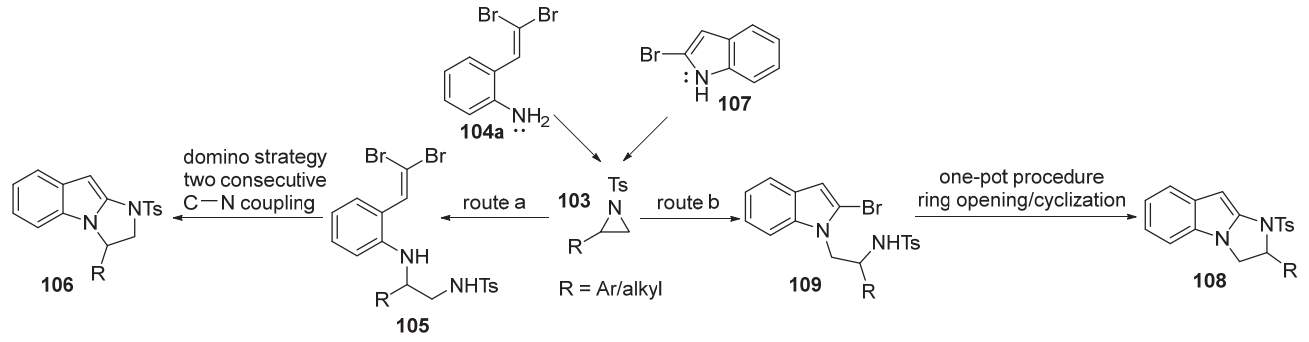
In 2017, Ghorai *et al*.[23] reported a Cu-catalyzed domino/one-pot processes for synthesizing isomers of imidazolium from racemic and enantiomerically pure forms of activated aziridine. The reactions underwent ring opening of Ts protected aziridines with 2,2-dibromovinylaniline or 2-bromoindole derivatives, and then proceeded double C—N bond formation or a C—N coupling under Cu-catalyzed respectively.

In order to investigate the S_N2 nucleophilic ring-opening reaction for activating aziridines and azetidines, the authors proposed two routes for synthesizing two different regioisomers of the same imidazoindoles, involving ring opening and cyclization using 2-bromoindoles **109** and 2,2-dibromovinylanilines **105** as nucleophiles (Scheme 48). In route a, the ring opening step was achieved in the presence of Lewis acid $LiClO_4$, which formed intermediate **105**. On the other hand, the ring opening step happened to the less steric position of **103**, which then gave the cyclization product **108** in one pot.

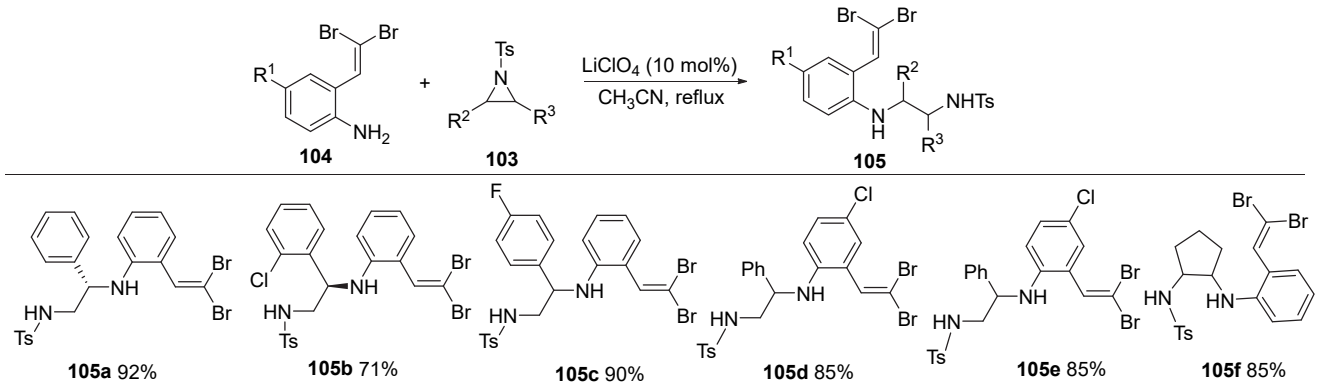
Utilizing $LiClO_4$ (10 mol%) as a Lewis acid, adduct **105** was synthesized by ring opening of **103** and **104** (Scheme 49). Then the cyclization of **105** provided the corresponding product in excellent yield with CuI/*trans*-1,2-diamino cyclohexane (Scheme 50). Halogen substituents on aryl



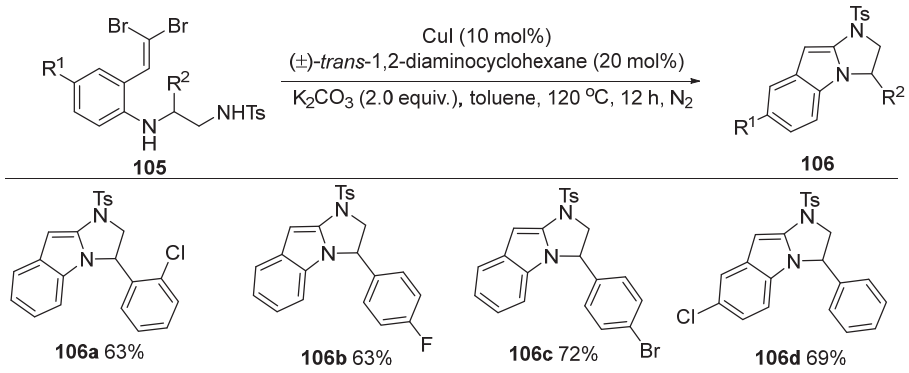
Scheme 47 Synthesis of 6*H*-isoindolo[2,1-*a*]indol-6-ones



Scheme 48 Synthetic routes to regioisomeric imidazoindoles



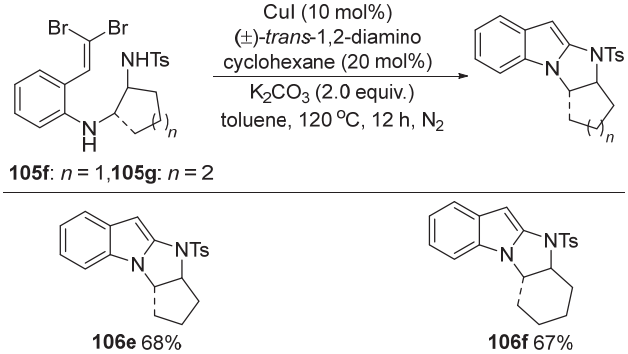
Scheme 49 Substrate scope for the formation of **105**



Scheme 50 Synthesis of racemic imidazoindoles **106** by domino C—N, C—N cyclization

groups showed good tolerance. The tetracyclic indole scaffolds **106e** and **106f** could be furnitured efficiently with the corresponding racemic cyclopentyl- and cyclohexyl-substituted 2,2-dibromovinylanilines **105f** and **105g** (Scheme 51).

To further generalize the methods of different substitutions, the author synthesized the regioisomers **108** of imidazoindole derivatives **106**. The 2-bromoindole was considered to be a cumbersome nucleophile, which would attack aziridine **107** at sites with smaller steric hindrance during the ring opening step and formed the ring opening product **109**. The intermediate **109** could then readily undergo Cu-catalyzed C—N bond formation in a two-step one-pot reaction to form the desired regioisomeric imidazoindoles **108** (Scheme 52).

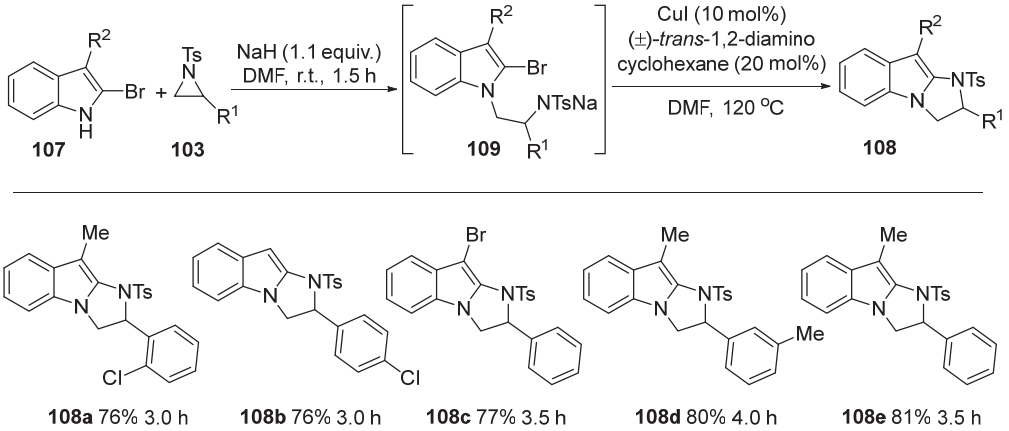


Scheme 51 Synthesis of tetracyclic imidazoindoles

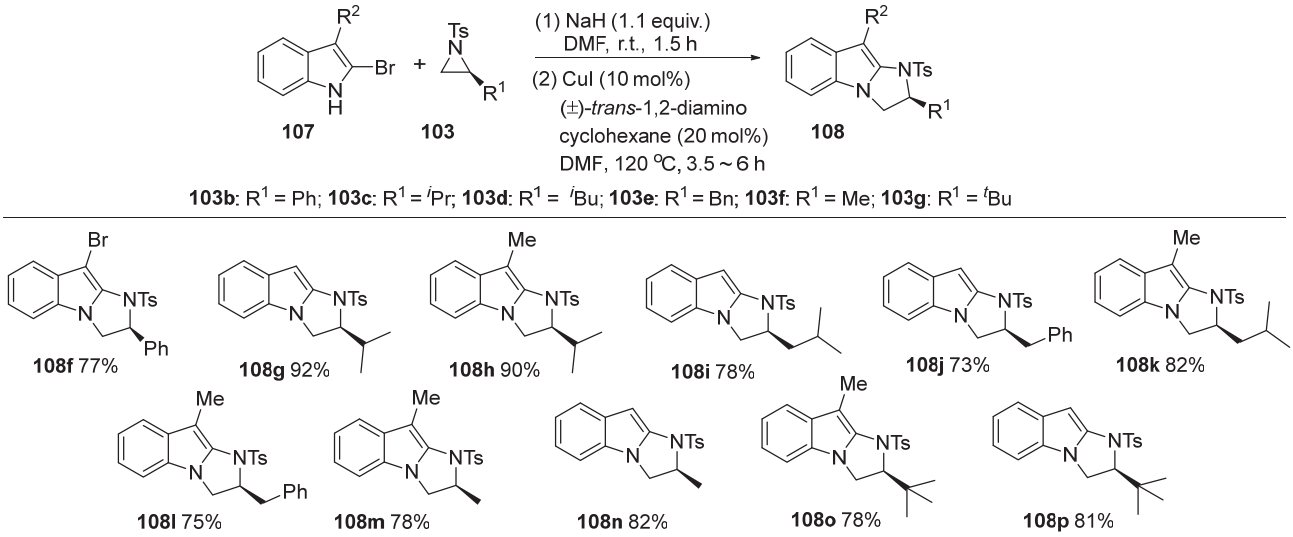
The author found that when enantiopure aziridines **103** were used as the substrate, the corresponding imidazo-

indoles **108** were obtained in enantiopure style (Scheme 53). The same to all examples, the chiral centre remained fully in the ring-opening step, thus obtaining the imidazolium derivative **108** in enantiomerically pure form.

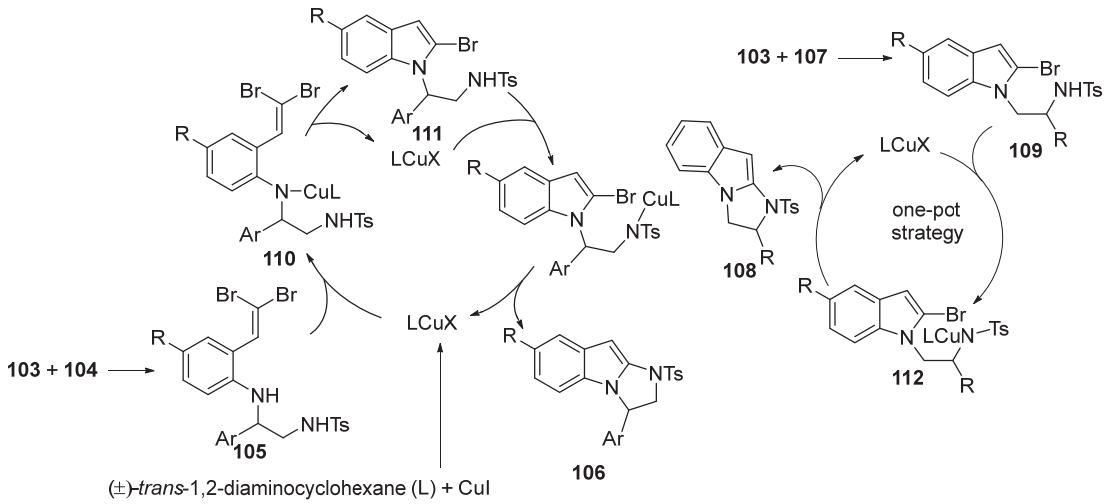
The possible mechanism the synthesis of imidazoindoles is shown in Scheme 54 . With lewis acid $LiClO_4$ to active



Scheme 52 Two-step one-pot strategy for the synthesis of racemic regioisomeric imidazolindoles **108**



Scheme 53 Two-step one-pot strategy for the synthesis of nonracemic regioisomeric imidazolindole **108**



Scheme 54 Mechanisms for the synthesis of imidazoindoles

aziridines, the intermediate **105** is generated. The nitrogen group with lower acidity (NH) coordinate with the copper(I) to form the Cu-complex **110**, which subsequently undergoes oxidative addition with one of the bromo atoms on the *gem*-dibromide followed by reductive elimination to deliver indole compound **111** through a favorable six-membered cyclic intermediate. Subsequently, the same cascade process (coordination, oxidative addition and reduction elimination) provides the final molecule **106**.

According to the synthesis of nonracemic regioisomeric imidazolindoles, the two-step one-pot strategy is shown in Scheme 54. The highly regioselective ring-opened product **109** was formed with strong base NaH in the first step, which then cyclized through the intermediate **112** in the next step to generate the desired product **108**.

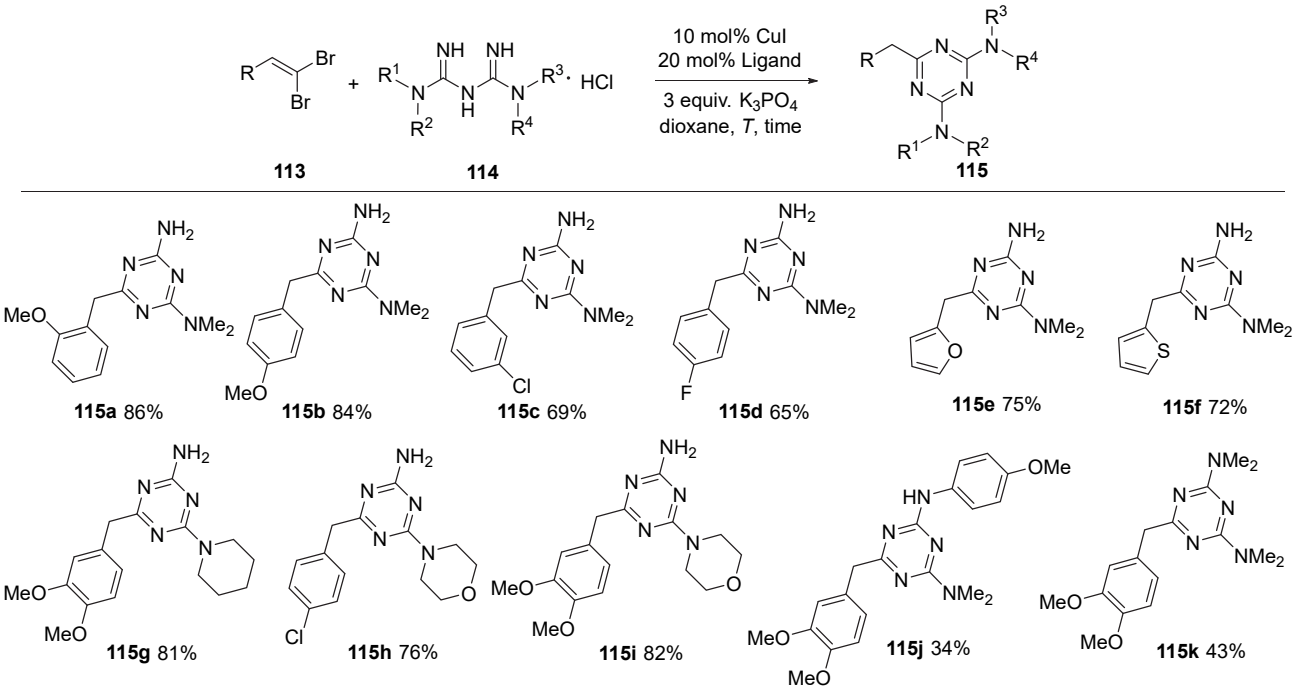
In 2017, Zhang and Cui's group[24] developed a Cu-catalyzed construction of multi-substituted 2,4-diamino-1,3,5-triazines from *gem*-dibromoalkenes and biguanide derivatives under mild reaction conditions (Scheme 55). This method used readily available starting materials, which exhibited a wide range and good functional group tolerance. Based on a large number of biologically active triazines, the developed methodology would become a quite useful tool for effectively constructing functionalized triazine derivatives fused in drug discovery.

The method showed good compatibility to aryl-substituted *gem*-dibromoalkenes. Substrates bearing electron-withdrawing substituents (**115c** and **115d**) provided lower yields than electron-donating examples (**115a** and **115b**). It has also been found that heterocyclic substituted *gem*-dibromo olefins were efficient substrates for oxygen- and sulfur-involving aromatic hydrocarbons and afforded the desired structures with high yield (**115e** and **115f**). This transformation also proceeded smoothly with *gem*-dibromoalkenes and cyclic amino-substituted diguanidines, monosubstituted diguanidine (**115g**～**115i**), trisubstituted diguanidine, or tetrasubstituted diguanidine. However, the trisubstituted **115j** and tetrasubstituted **115k** diguanidine showed low reactivity, resulting in low yields.

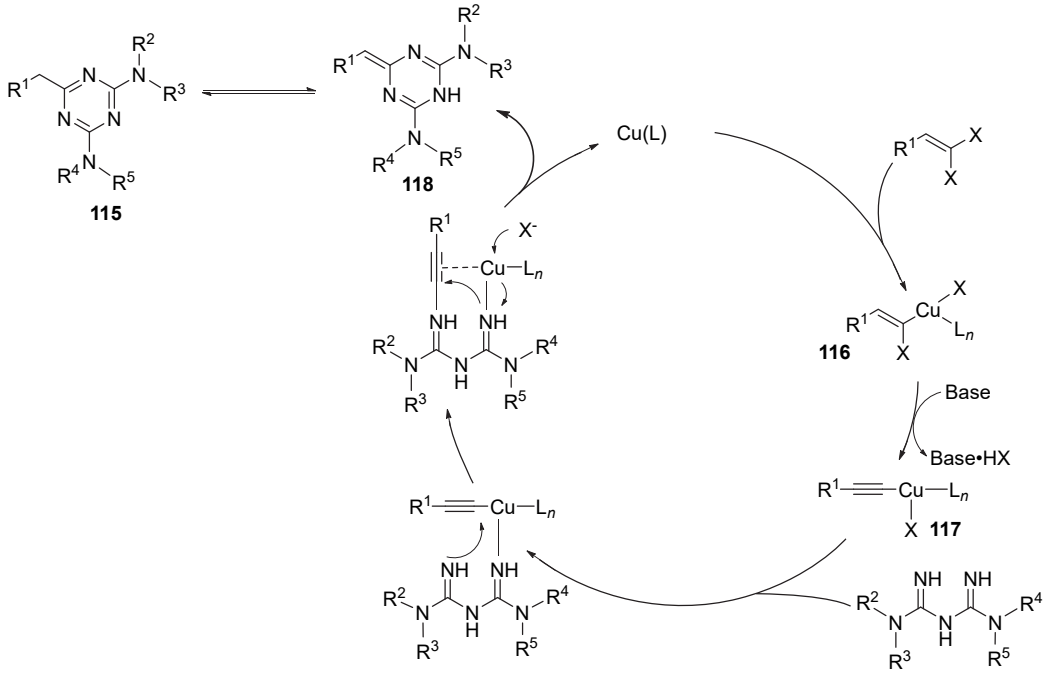
Based on the obtained results, a plausible catalytic pathway was proposed (Scheme 56). The alkenes intermediate **116** could be generated via the insertion of [Cu]-ligand complex to the C—X bond of 1,1-dibromoalkenes, and then the alkyne intermediate **117** was produced from the alkenes intermediate via dehalogenation in the presence of base. A two-step intramolecular nucleophilic attack formed an aza-cyclic intermediate **118**, which immediately isomerized to the aromatic product **115**.

In 2013, Lautens and co-workers[25] realized a palladium-catalyzed cascade protocol for the construction of multi-substituted *N*-fused benzo[*c*]carbazoles through C—H functionalization reaction of *gem*-dibromoolefin derivatives (Scheme 57). An unique feature of this reaction is that both bromides are involved in the C—H functionalization processes.

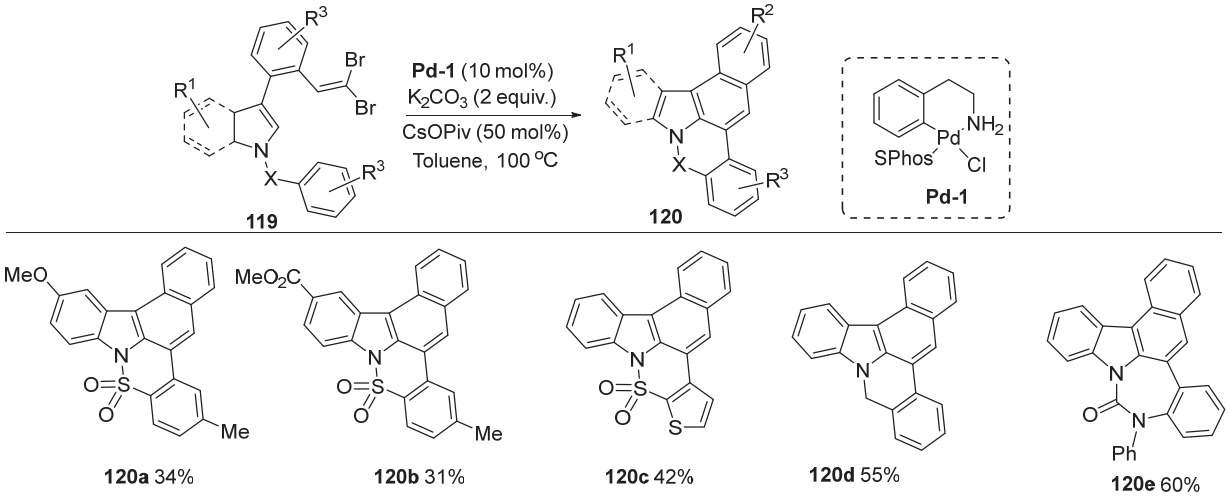
Substrates bearing electron-donating or electron-withdrawing substituents (**120a** and **120b**) could provide the desired product with relative low yields, even far from the reactive sites, indicating that the reaction was sensitive to the electronic effects on indole motif. The sulfonyl-containing arene containing a thiophene substitution could deliver the desired product in a moderate yield (**120c**). This reaction can also occur based on non-sulfonyl based N-substituents (**120d** and **120e**).



Scheme 55 Scope of the synthesis of trisubstituted 1,3,5-triazines



Scheme 56 Mechanism of formation 2,4-diamino-1,3,5-triazines

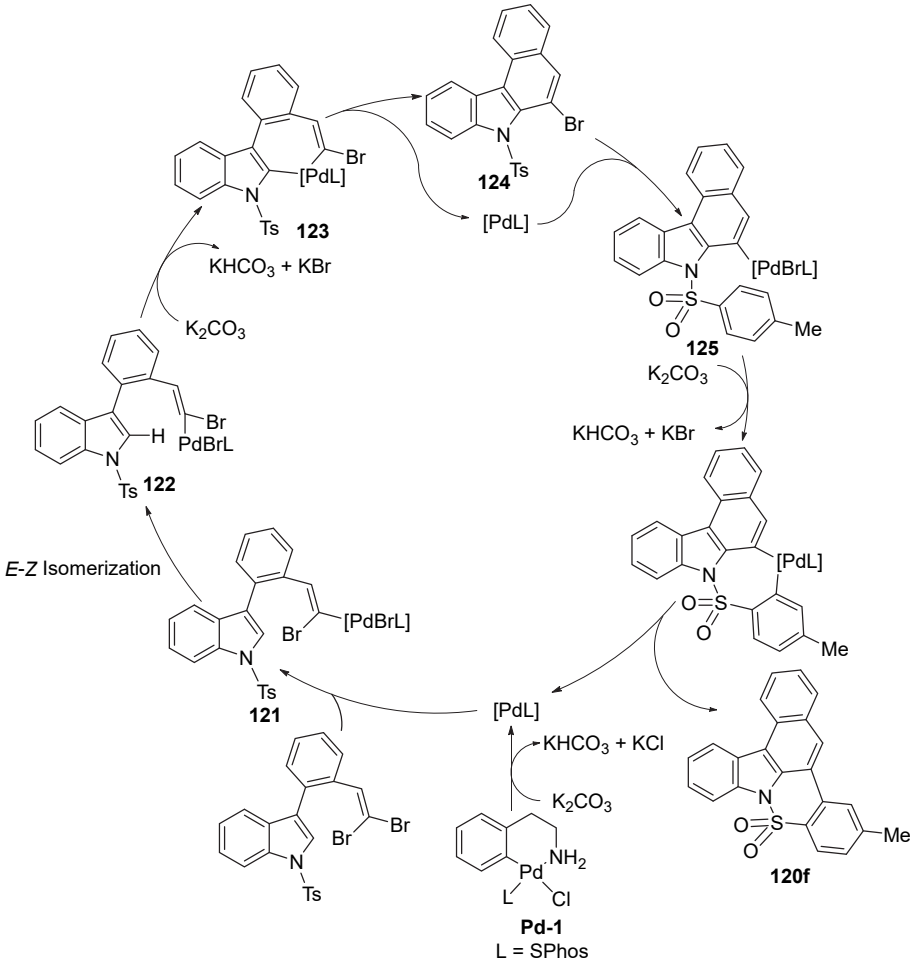


Scheme 57 Substrates scope of the domino reaction

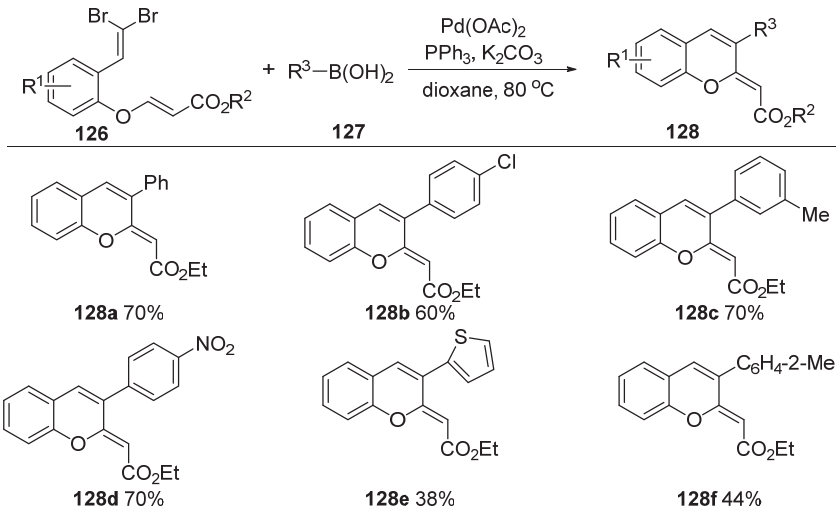
Although it could not exclude the isomerization process during this transformation, a reasonable catalytic cycle is suggested in Scheme 58. The cycle begins with the formation of active palladium(0) complex, which forms (*E*)-complex **121** via the oxidative addition of palladium(0) to (*E*)-Br of *gem*-dibromoolefins. A possible *E*-*Z* isomerization through the vinylidene intermediate provides (*Z*) palladium complex **122**, then affording palladacycle **123** via the C—H bond activation. After reductive elimination, benzo[*c*]carbazole derivative **124** is generated, which then produces arylpalladium(II) species **125** through the second oxidative addition. The second C—H bond activation of the tethered Ts group delivers a seven-membered palladium cycle, which subsequently undergoes reductive elimination to provide the final functionalized benzo[*c*]carbazoles **120f**.

In 2018, Zhang and Fan's group[26] developed a highly efficient and practical method for the construction of (2*H*-chromen-2-ylidene)acetate and (2*H*-chromen-2-ylidene)ethanone derivatives. Interestingly, this cascade reaction could distinguish between electron-withdrawing abilities and subtle differences in individual functional groups, resulting in different chemoselectivities.

The substrate scope and versatility of this tandem strategy was investigated (Scheme 59). Multi-substituted arylboronic acids **127** worked with (*E*)-3-(2-(2,2-dibromovinyl)phenoxy)acrylate **126** smoothly to produce (2*H*-chromen-2-ylidene)acetate **128** with acceptable yields. Different functional groups on the arylboronic acids such as



Scheme 58 Catalytic cycle for the domino reaction



Scheme 59 Substrate scope for the preparation of (2*H*-chromen-2-ylidene)-acetates

aryl, halides, alkyl and NO_2, *etc*., were well tolerated (**128c**, **128b**, **128d**). The reaction did not show significant electronic or spatial effects, and the active Br could survive very well with the optimized conditions.

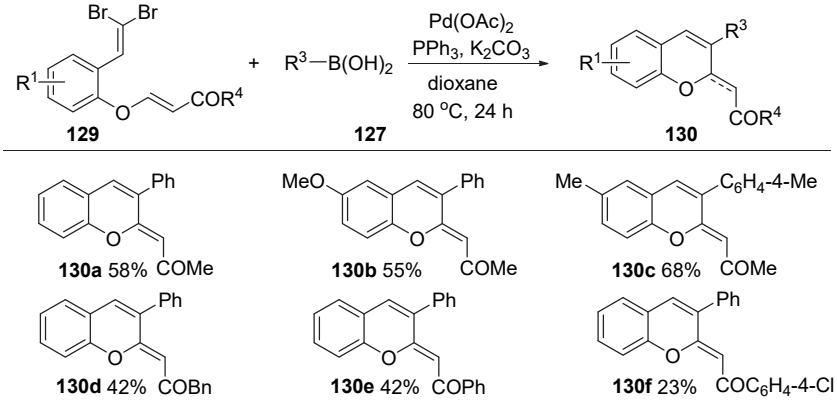
Furthermore, the substrates with ketone were utilized to synthesize (*Z*)-1-(3-phenyl-2*H*-chromen-2-ylidene)propan-2-one (**130a**) (Scheme 60).

A mechanism was proposed to explain the (*Z*)-2-(3-phenyl-2*H*-chromium-2-methylene) subunit from (*E*)-3-(2-(2,2-dibromovinyl)phenoxy)acrylate and arylboronic acid

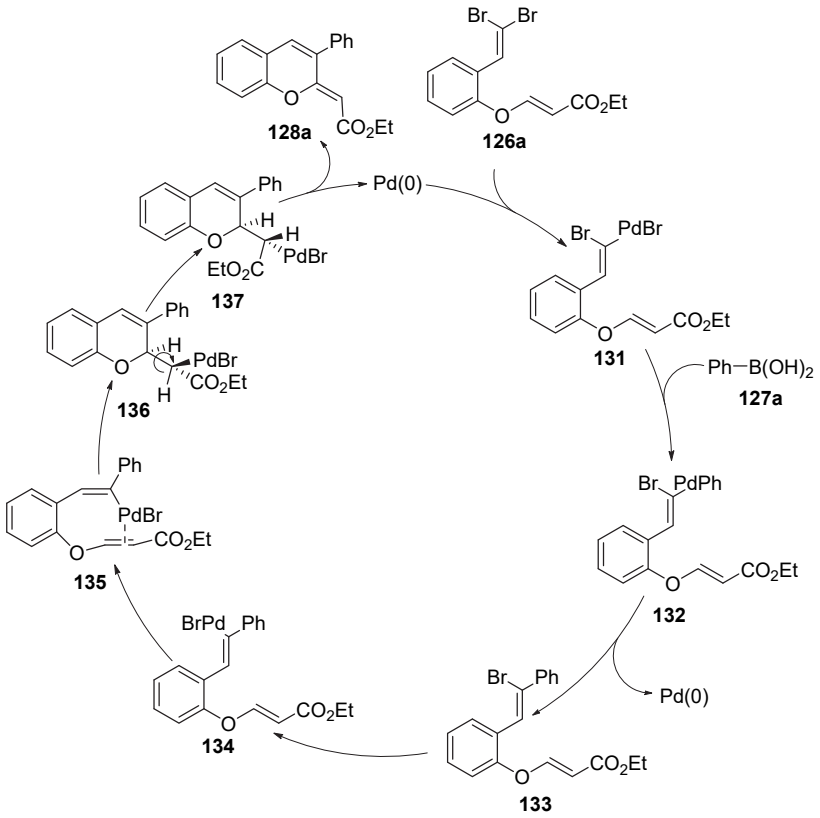
(Scheme 61). Firstly, oxidative addition of palladium(0) to the carbon-bromo bond of (*E*)-3-(2-(2,2-dibromovinyl)-phenoxy)acrylate gives intermediate **131**, which undergoes transmetalation with (*E*)-3-(2-(2,2-dibromovinyl)phenoxy)-acrylate to afford **132**. Then reductive elimination provides intermediate **133** followed by the concurrent release of palladium(0) catalyst. Furthermore, the oxidative addition of Pd(0) into the C—Br bond in **133** gives intermediate **134**. Subsequently, the following isomerization/coordination and insertion to double bond produces the palladium(II) complexes **135** and **136**, respectively. Then, the rotation of C—C σ-bond forms a key *syn* complex **137**, which then undergoes *syn* *β*-H elimination to afford (*Z*)-2-(3-phenyl-2*H*-chromen-2-ylidene)acetate (**128a**) and regenerates palladium(0) catalyst.

In 2018, Chen and co-workers[27] successfully achieved Ni/Ag-catalyzed cascade C — H bond activation and cyclization with dibromoalkenes, resulting in a 3-methyl-eneisoindolin-1-one scaffold. This protocol is easy to handle and has good resistance to various aromatic amides and dibromoalkenes.

The reaction of *N*-(quinolin-8-yl)benzamide with (2,2-dibromovinyl)-benzene derivatives delivered kinds of multi-substituted 3-methyleneisoindolin-1-one motifs with good to excellent yields. *N*-(Quinolin-8-yl)benzamides bearing diverse substituents (*eg*., F, Cl, NO_2 and CF_3) proceeded smoothly, providing the corresponding products (**140b**～**140e**) in moderate yields. Subsequently, different



Scheme 60 Substrate scope for the preparation of (2*H*-chromen-2-ylidene)ethanones

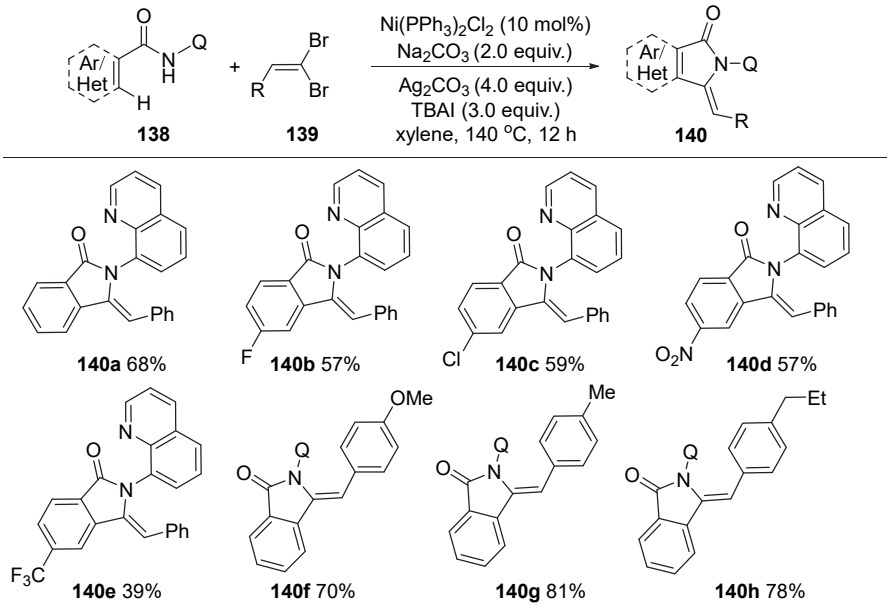


Scheme 61 Reaction pathway accounting for the formation of (*Z*)-2-(3-phenyl-2H-chromen-2-ylidene)acetate

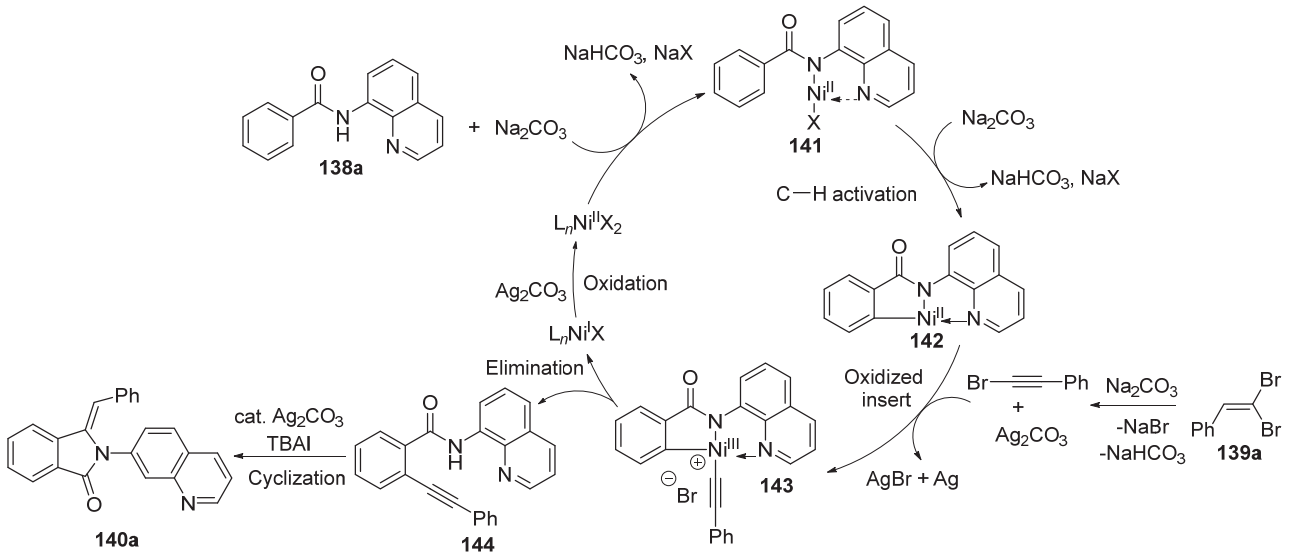
dibromoalkenes were screened with standard conditions as shown in Scheme 62. Dibromoalkene derivatives containing electron-rich substituents (such as Me, OMe and *N*-propyl *etc*.) provide the alkynylation and cyclization products (**140f**～**140h**) ranging from 54% to 81%. The substitutions on the *ortho*-position of aromatic ring show steric hindrance, which exhibit a significant influence to this transformation, and the yield of *gem*-bromo olefin with *ortho*-substituted group is lower than that with a substituent at the *para*-position (**140f**).

Based on the above experimental results, a Ni(I)/Ni(III) catalytic process was tooken into consideration as shown in Scheme 63. This mechanism begins with the activation of inert C(sp^2)—H bond of *N*-(quinolin-8-yl)benzamide to form the key intermediate **142**, and then Ni(II) is oxidized by Ag_2CO_3 to afford Ni(III) complex. Then, the Ni(II) complex **142** could be oxidized insert to the bromoalkyne formed *in situ* to provide intermediate **143**. Then the reductive elimination forms alkylated product **144** and release Ni(II) complex. The silver salts oxidize Ni(II) to Ni(III) to continue the cycle. In the presence of Ag_2CO_3 and tetrabutylammonium iodide (TBAI), the *ortho*-alkynyl amide **144** undergoes a rapid intramolecular cyclization reaction to produce 3-methylene isoindolin-1-one **140a**.

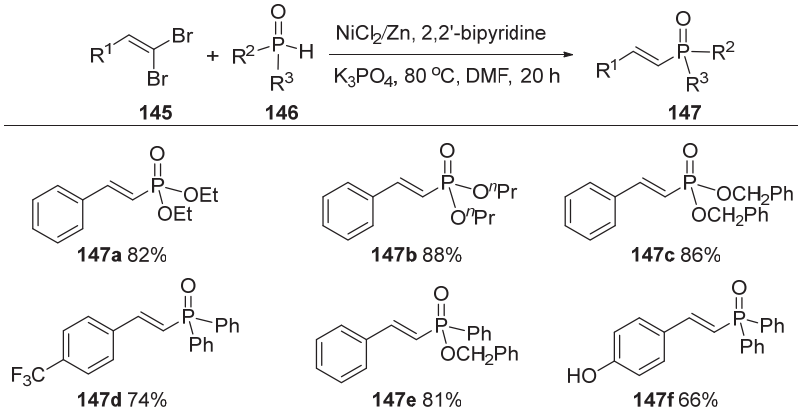
In 2014, Tang *et al*.[28] explored a stereoselective one-pot strategy for the synthesis of *E*-alkenyl-phosphorus compounds with the nickel-zinc catalyst systems. Kinds of P(O)H substrates reacted with 2,2-dibromovinylbenzene efficiently as shown in Scheme 64. This Ni(II)/Zn-catalyzed cross-coupling is a versatile and practical strategy for the



Scheme 62 Scope of *N*-(quinolin-8-yl) benzamides and dibromoalkenes



Scheme 63 Mechanism for the forming 3-methylene isoindolin-1-one product



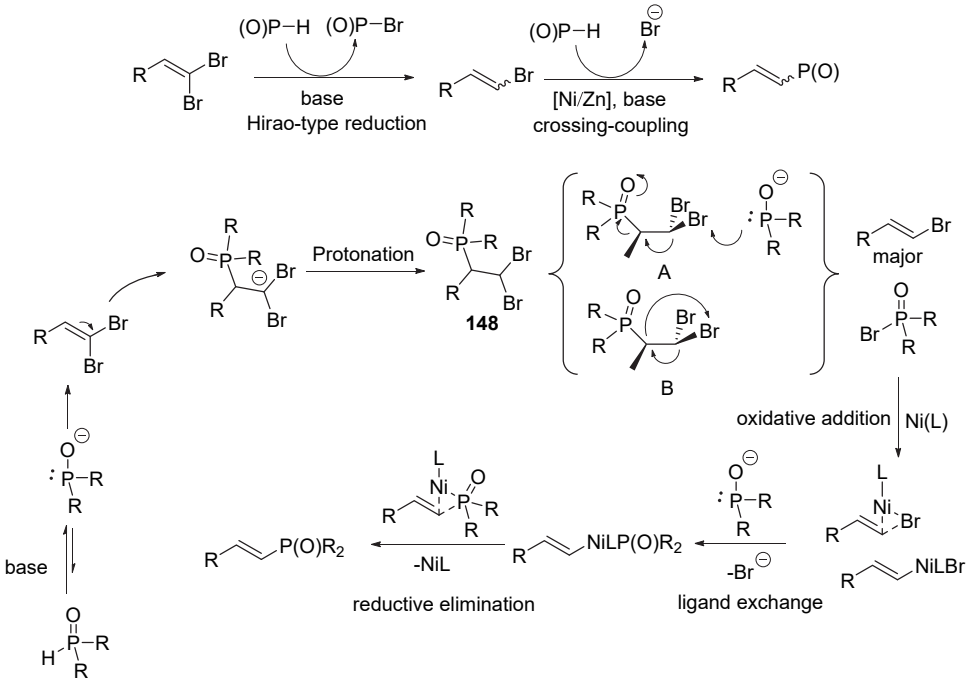
Scheme 64 Reaction of *gem*-dibromoalkenes with P(O)H compounds

furnish of *E*-1-alkenylphosphonates or *E*-1-alkenylphosphine oxides.

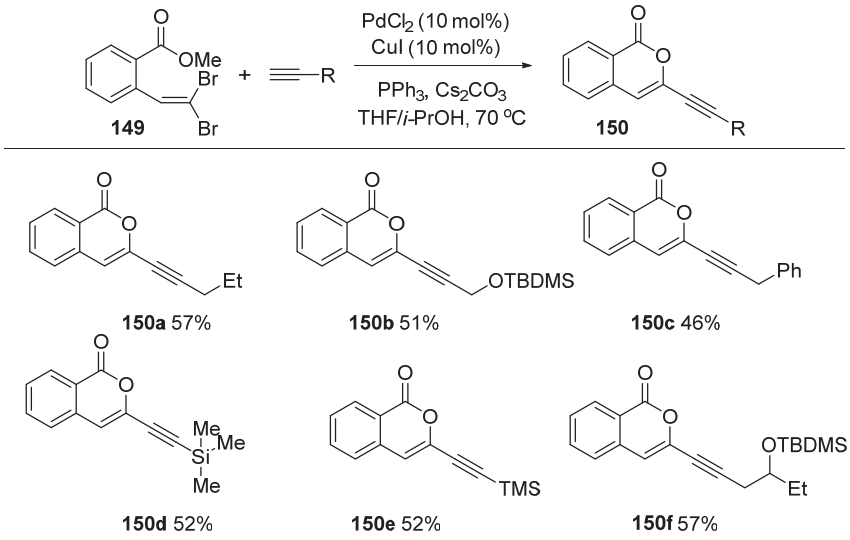
A possible mechanism based on the above analysis and previous reports was proposed (Scheme 65). First, the tetracoordinated $R_2P(O)H$ could form a three-coordinated $R_2P(O)^-$ in the presence of base, which would add to the olenic bond of *gem*-dibromoalkenes and followed by protonation to give the intermediate **148**. Next, both of the routes involve elimination of the $R_2P(O)Br$ species, which results in the Hirao-type reduction products.

In 2018, Liu and co-workers[29] developed an effective methodology to synthesize 3-alkynyl isocoumarin derivatives through a Pd/Cu-catalyzed cascade Sonogashira coupling and lactonization of methyl 2-(2',2'-dibromovinyl)benzoate with various terminal alkynes (Scheme 66). The scope and limitations of terminal alkynes were explored. Various terminal alkynes bearing different founctional groups provided the corresponding 3-alkynylcoumarins in moderate to good yields.

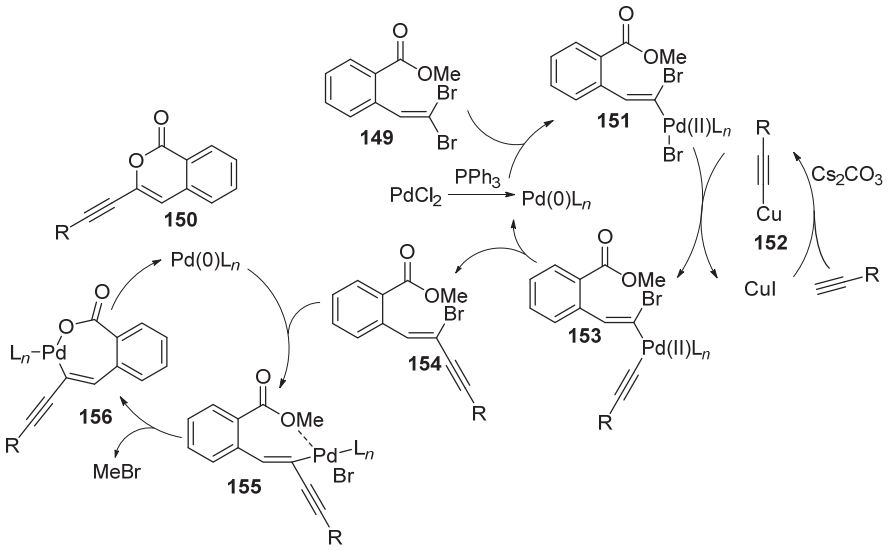
A plausible pathway is illustrated in Scheme 67. First, oxidative addition of Pd(0) species to the (*E*)-bromide of 2-(20,20-dibromovinyl)benzoate **149** occurs to produce Pd(II) intermediate **151**, and the following transmetallation with the copper(I)-acetylide **152** forms intermediate **153**. The subsequent reductive elimination provides the monobromovinyl intermediate **154** accompanying the regeneration of the palladiumd(0) catalyst. Secondly, the oxidative addition of Pd(0) into (*Z*)-bromide **154** could form intermediate **155**. Subsequently, palladium(II) coordinates with the oxygen of ester in complex **155** to promote the elimination of methyl bromide and generates the palladium(II) species **156**. In the end, the reductive elimination liberates the corresponding 3-alkynyl isocoumarin **150** and palladium(0) catalyst.



Scheme 65 Mechanistic pathway



Scheme 66 Tandem Sonogashira coupling/lactonization of 2-(2',2'-dibromovinyl)benzoate with terminal alkynes



Scheme 67 Reaction mechanism of forming 3-alkynyl isocoum

3 Conclusions

The progresses on transition-metal-catalyzed coupling reactions of *gem*-dibromoviny derivatives using 1,1-dibromovinyl derivatives as substrates since 2012 is summarized. We have a wide overview of transition-metal-catalyzed transformations that result in the formation of various C—C, C—H, C—O, C—N, C—S, *etc*., bonds by effectively replacing one or two halogen atoms with other atoms. Through this strategy, 1,1-dibromoviny derivatives can undergo selective monosubstitution and stepwise cross-couplings with multiple reagents to provide numerous valuable molecules, such as stereodefined functionalized alkene, polyene, alkyne, polyyne and carboxylic acid derivatives. Through the regulation of starting materials and reaction conditions, alkynes, chromenes, indoles, benzindole, benzothiophene and other benzo-fused heterocycles with important physiological activity or synthetic value were synthesized. There is no doubt that these elegant strategies have set impressively high standards for future synthetic efforts aimed at a growing number of valuable natural products, pharmaceuticals and organic smart materials.

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