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Recent developments in palladium-catalyzed C–S bond formation
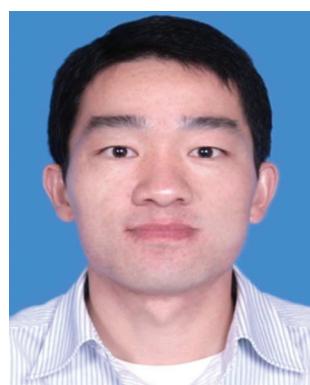
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Transition metal-catalyzed C–S bond formation reactions have attracted considerable attention in the recent years. In this regard, palladium-catalyzed C–S bond formation is typically attractive because it can effectively assemble structurally diverse unsymmetrical aryl sulfides and functionalized sulfones under mild conditions with high regioselectivities. In this review, palladium-catalyzed C–S bond formation reactions are summarized and discussed in detail with the focus on sulfenylation and sulfonylation reactions involving aryl/heteroaryl C–H bonds, alkynes, aryl halides, electron-rich benzoic acid derivatives, arylhydrazines, and organosilicon reagents. Some representative synthetic strategies and their transformation application along with reaction mechanisms are also highlighted.

## 1 Introduction

Organosulfurs are ubiquitous structural frameworks present in a number of natural products, pharmaceutically and biologically active molecules and functional materials,[1] as well as for applications in food industries.[2] These motifs also play important roles in the field of photoelectric materials because of the sulfur atom's higher resonance energy than other heteroatoms.[3] According to the results of a survey in 2014,

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more than 25% of top 200 U.S. prescription drugs are sulfur-containing pharmaceuticals.[4] In the past few years, various novel synthetic strategies have been extensively established for the assembly of structurally diverse functionalized sulfur-containing architectures. Since Migita and co-workers disclosed the first palladium-catalyzed intermolecular coupling of aryl halides with thiols for the construction of structurally complex thioethers,[5] transition metal-catalyzed sulfenylation reactions have been proven to be the straightforward and flexible synthetic methodologies for the preparation of valuable polyfunctionalized organosulfur motifs in contemporary sulfur chemistry. In this regard, several transition metal catalysts such as copper,[6] cobalt,[7] nickel,[8] gold,[9] rhodium,[10] and other metal

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catalysts[11] have been identified as extremely efficient catalysts for this type of chemical transformation. Correspondingly, various practical sulfenylating agents, thiols, disulfides, N-thioarylphthalimides, arylsulfonyl chlorides, and sulfonyl hydrazides have been typically investigated as the sulfur species. However, the above-mentioned sulfenylating reagents have certain disadvantages such as repulsive odor, expensive sulfur sources, air or water instability, and toxicity. From the perspective of environmentally friendly and green chemistry, transition metal-free strategies have been well established for the synthesis of organosulfur skeletons with highly atom- and step-economical manners. Moreover, alternative inorganic sulfenylating reagents such as S_8, Na_2S, K_2S, sodium sulfinates, sodium thiosulfate, and sulfourea, have also been exploited in recent years.[12]
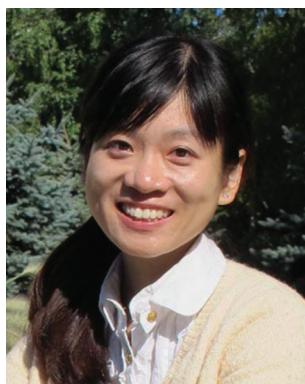
In addition, a palladium-catalyzed cross-coupling reaction has emerged as the most fascinating and powerful tool for the rapid and straightforward preparation of value-added functionalized molecules.[13] However, the palladium catalyst may be poisonous because of the strong coordination of sulfenylating reagents with palladium catalytic species in the chemical transformation process. As a result, palladium-catalyzed sulfenylation transformation has been less reported compared to other metal catalysts. Despite all this, palladium-catalyzed sulfenylation reactions are especially attractive, which can assemble structurally flexible sulfur-containing skeletons. Furthermore, there are several related reviews reported based on transition metal-catalyzed sulfenylation reactions.[14] For instance, in 2014, Lee and co-workers reviewed the transition metal-catalyzed C–S bond coupling reaction.[15] The transition metal catalysts including palladium, copper, nickel, cobalt, indium, gold, rhodium, iron and others were mainly summarized for the coupling of thiols with aryl halides and pseudo halides. After that, Ghaderi also elucidated the transition metal-catalyzed thioetherification reactions of aromatic compounds in 2016.[16] Recently, the application of different sulfe-

nylating reagents for the synthesis of structurally diverse organosulfur frameworks *via* an eco-friendly approach has also been demonstrated by Jiang and co-workers.[17] To the best of our knowledge, no palladium-catalyzed sulfenylation was especially and exclusively reviewed in recent years. Developing efficient and green synthetic methods of palladium-catalyzed coupling reactions for the synthesis of polyfunctionalized fine chemicals is a long-term objective of our group.[18] Recently, we have summarized palladium-catalyzed cascade cyclization/alkynylation reactions for the assembly of structurally diverse alkyne derivatives with excellent chemoselectivities.[19] Additionally, we also made some important achievements in transition metal-catalyzed coupling reactions for the synthesis of a wide range of organosulfur frameworks.[20] In this minireview, we highlight the significant and representative achievements in palladium-catalyzed sulfenylation and sulfonylation from 2010 to the beginning of 2020, including our recent contributions. It is noteworthy that this review will cover some selected examples, which have been recently reviewed elsewhere and will not be discussed in detail.

2 Sulfenylation reactions

2.1 Sulfenylation of aryl/heteroaryl C–H bonds

In the past two decades, transition metal-catalyzed straightforward sulfenylation of unactivated aryl/heteroaryl C–H bonds would be an economic and benign synthetic strategy, allowing direct and concise construction of diversiform sulfur-containing skeletons from the ready availability of starting materials. For instance, Anbarasan and co-workers discovered a palladium-catalyzed aryl(alkyl)thiolation of arenes (**1**) with electrophilic sulfenylating reagents (**2**) for the direct construction of diverse unsymmetrical diaryl or arylalkyl sulfides (**3**) in good yields with highly selectivity (Scheme 1).[21] Optimization conditions indicated that 2 mol% Pd(OAc)$_2$ as the catalyst and TFA

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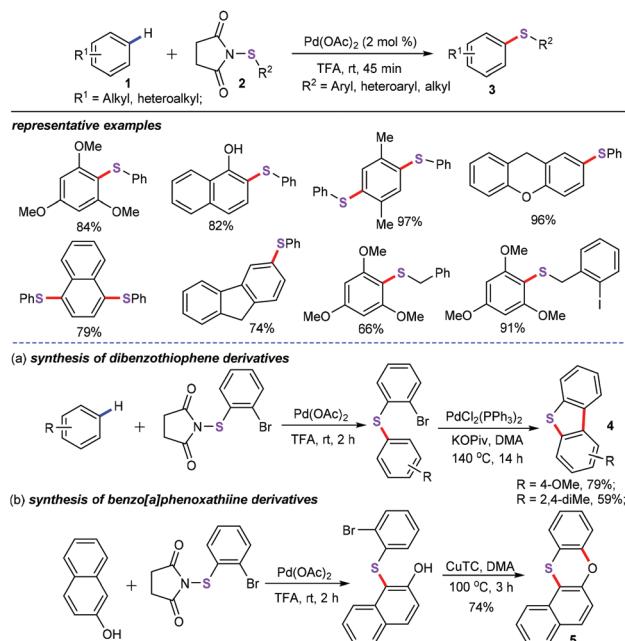
Scheme 1 Palladium-catalyzed aryl(alkyl)thiolation of arenes with *N*-thioaryl(alkyl)phthalimides.

Scheme 3 Palladium-catalyzed trifluoromethylthiolation of aryl C–H bonds.

(trifluoroacetic acid) as the solvent were essential for this protocol. Moreover, under the optimized arylthiolation conditions, various aryl, alkyl, and heteroaryl substituted sulfenylating reagents **2** were confirmed as good coupling partners. Most importantly, using the obtained diaryl sulfides as the synthetic intermediates, dibenzothiophene (**4**) and benzo[*a*]phenoxathiine (**5**) derivatives can be effectively assembled by intramolecular cyclization of the C–H bond (Scheme 1a and b), which can be widely used in materials sciences.[22]

A detailed catalytic mechanism is described in Scheme 2. Initially, the palladium complex reacts with arenes **1** to generate the arylpalladium species **Int-1** *via* C–H functionali-

zation.[23] Then, oxidative addition of the **N–S** bond of **2** with intermediate **Int-1** produces the Pd[IV] species **Int-2**. Consequently, reductive elimination of Pd[IV] intermediate leads to the target products **3** and Pd[II] species **Int-3**. Finally, ligand exchange of **Int-3** with TFA gives the active palladium species to complete the catalytic cycle.

The trifluoromethylthio group represents the privileged structures in pharmaceuticals and biological activities of molecules.[24] For this reason, several transition metal-catalyzed practical and atom economical methods have been investigated in detail in the past few years.[25] In this respect, Shen and co-workers demonstrated elegant palladium-catalyzed intermolecular highly selective C–H monotrifluoromethylthiolation of arenes (**6**) for the first time (Scheme 3).[26] In the presence of 10 mol% of Pd(CH$_3$CN)$_4$(OTf)$_2$ in AcOH at 110 °C for 24 h, this approach provided a facile and environmentally benign way to access trifluoromethylthiolated products (**8**) in moderate to good yields with exceptional functional group tolerance. Both internal and external competition KIE studies disclosed that the C–H activation process is not the limiting step for this catalytic cycle. As a result, the plausible mechanism for this chemical transformation was proposed as follows: (i) cyclopalladation of 2-pyridylbenzene (**6**) with Pd[II] produces palladacycle intermediates **Int-4**; (ii) oxidative addition of the N-SCF$_3$ bond of **7** affords the trifluoromethylthio-substituted Pd[III] or Pd[IV] intermediate **Int-5**; and (iii) reductive-elimination generates the final products.

Meanwhile, Nishihara group successfully accomplished a palladium and copper co-catalyzed direct thiolation of aryl C–H bonds with disulfides or thiols (Scheme 4).[27] In the presence of 10 mol% of PdCl$_2$(PhCN)$_2$ and 10 mol% of CuCl$_2$ as the co-catalyst, 20 mol% of trimesitylphosphine as the optimized

Scheme 2 Plausible mechanism for palladium-catalyzed aryl(alkyl) thiolation.

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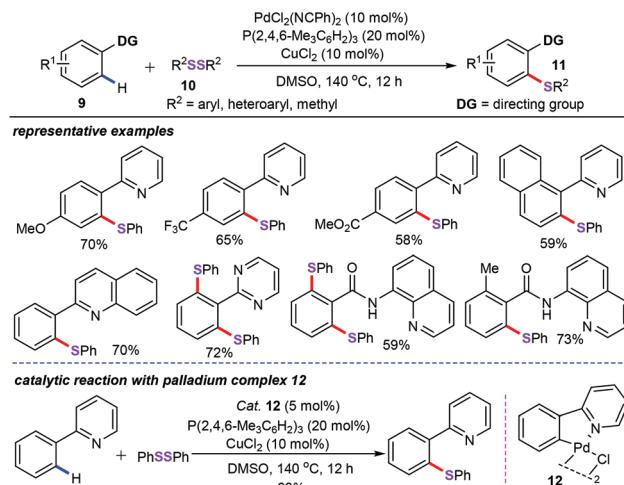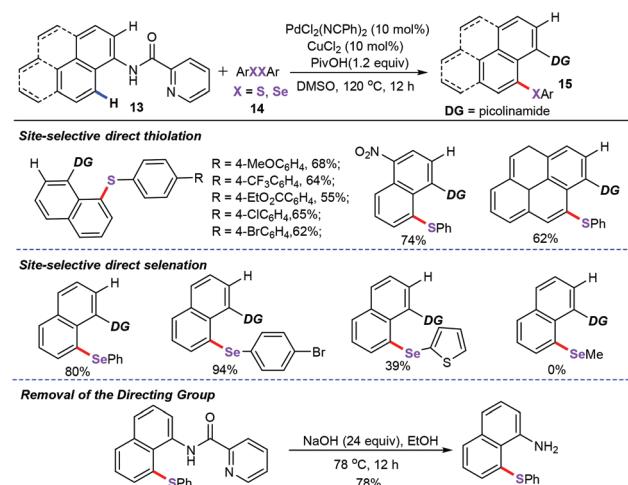
Scheme 4 Palladium and copper co-catalyzed thiolation of aryl C−H bonds with disulfides.

**Scheme 5** Palladium and copper co-catalyzed chalcogenation of naphthylamine derivatives.
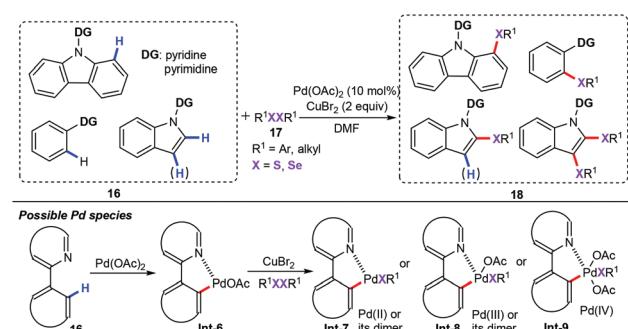
ligand, DMSO as the solvent at 140 °C for 12 h, both the arenes (**9**) bearing directing groups such as pyridyl, 2-quinolyl, 2-pyrimidyl, and the bidentate 8-aminoquinoline groups and diaryl disulfides (**10**) proved to be the suitable substrates for preparing highly functionalized aryl sulfides (**11**) in moderate to excellent yields. However, a lower yield was obtained with aliphatic disulfides, such as dibenzyl disulfide, under the optimized catalytic system. The mechanism studies indicated that the dimeric chloro(2-pyridylphenyl)palladium(II) (**12**) could participate in oxidative addition of the disulfide to form a palladium(IV) intermediate. As a result, the authors also proposed that this chemical transformation may involve a Pd(II)/Pd(IV) catalytic cycle.

Subsequently, Nishihara and co-workers have extended the above-mentioned method to the palladium-catalyzed, picolinamide-directed C−H thiolation of naphthylamine derivatives (**13**) with diaryl disulfides and diaryl diselenides (**14**) for the assembly of 8-chalcogen-1-naphthylamines derivatives (**15**) (Scheme 5).[28] Additional investigation of the acid additives revealed that the PivOH was essential for this chemical transformation, while other acids such as AcOH, p-TsOH, CF₃CO₂H, and CF₃SO₃H did not improve the yields. From the combination of PdCl₂(PhCN)₂ (10 mol%) as the catalyst, CuCl₂ (10 mol%) as the co-catalyst, and PivOH (1.2 equiv.) as the additives, a wide range of functional groups such as –CF₃, –CO₂Et, –Cl, –Br, and –NO₂ were well tolerated under the reaction conditions. Of note, the directing group picolinamide was readily removable after the chalcogenation. However, unlike the previous ortho-functionalization, this chalcogenation of naphthylamine derivatives exclusively yields peri-position products. The control experiments suggested that this protocol proceeds via a thermodynamically stable five-membered palladacycle intermediate process.

In 2015, Kambe and co-workers described a palladium-catalyzed intermolecular C−H chalcogenation process for the formation of various synthetically useful diaryl or alkyl aryl sulfides and selenides (**18**) (Scheme 6).[29] This chalcogenation process can be performed with 10 mol% Pd(OAc)₂ in DMF in the presence of 2 equiv. of CuBr₂ as the oxidant under air atmospheric conditions. With a pyrimidyl or pyridyl group as the directing group, the ortho-C–H functionalization of arenes and heteroarenes (**16**) including carbazole, 2-phenylpyridine, benzoquinoline, and indole derivatives was compatible with the present catalytic system, giving the corresponding products in good yields with excellent regioselectivities. Notably, CuBr₂ plays an important role in the conversion of C–Pd bonds into C–S bonds in the presence of disulfides, which may transfer ArS groups to Pd (**Int-7**) and/or by generating Pd intermediates with a higher oxidation state (**Int-8** or **Int-9**).[30]

Different from the usually used thiolation reagent such as disulfides or thiols, Zhang and co-workers used N-arylthiobenzamides (**20**) as both the thiolation reagent and oxidant for palladium-catalyzed sulfenylation of arenes (**19**) (Scheme 7).[31] It was found that Pd(MeCN)₂Cl₂ could efficiently catalyze this sulfenylation protocol in the absence of phosphine ligands or any other additives. Under optimized conditions, arenes bearing a direction group were allowed to react

Scheme 6 Palladium-catalyzed intermolecular C−H chalcogenation of arenes and heteroarenes.

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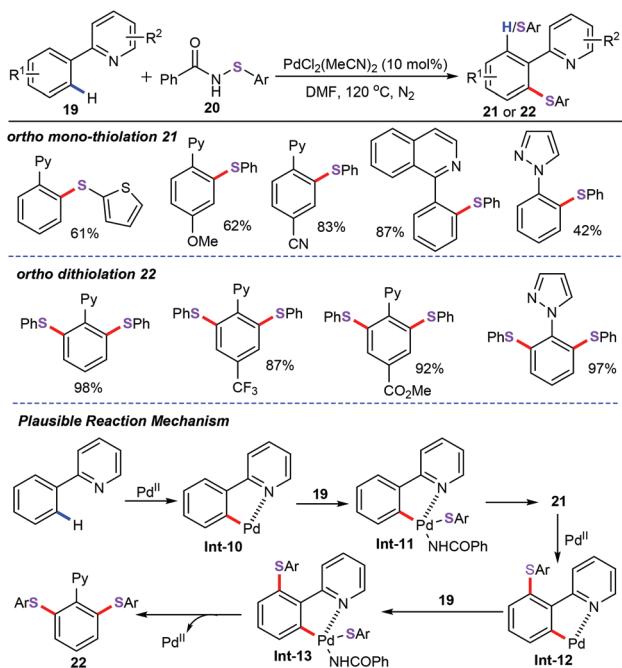
Scheme 7 Palladium-catalyzed sulfenylation using *N*-arylthiobenzamides as a thiolation reagent.

with various *N*-arylthiobenzamides, affording the corresponding aryl thioethers (**21**) or dithioethers (**22**) in moderate to good yields. A variety of functional groups, such as cyano, trifluoromethyl, methoxyl, and ester groups were perfectly tolerated. The authors proposed that this approach may involve a Pd(II)/Pd(IV) catalytic cycle process. As shown in Scheme 8, cyclopalladation of 2-phenylpyridine (**19**) affords the vinyl palladacycle complex **Int-10**. Afterwards, oxidative addition of palladacycle complex **Int-10** with *N*-(phenylthio)benzamide (**19**) gives Pd(IV) intermediate **Int-11**. Reductive elimination followed by another C–H cyclopalladation produces the five-membered palladacycle species **Int-12**. Finally, subsequent oxidative addition and reductive elimination delivers the desired products **22** and Pd(II) catalytic species.
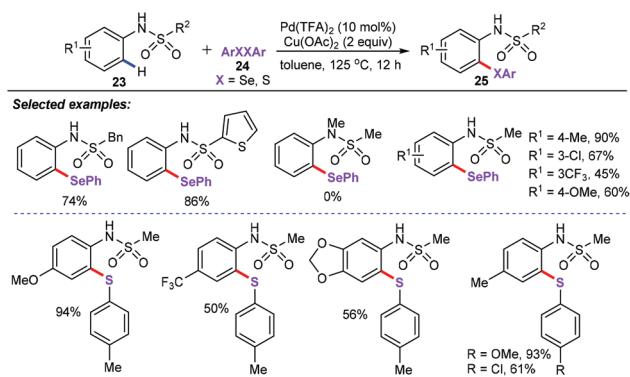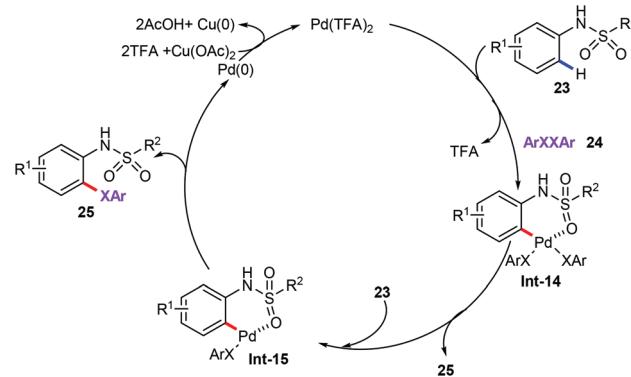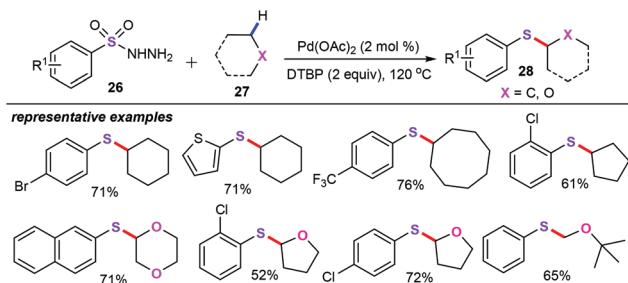
More importantly, the above-mentioned achievements are accomplished mainly through the strong coordination of *N*-containing directing groups such as pyrimidine, pyridine, and bidentate directing groups. On the contrary, the directing groups with the weak coordination have been rarely reported. Recently, Ma and co-workers have disclosed the first ligand-free palladium-catalyzed *ortho*-C–H chalcogenation reactions of sulfonamides (**23**) *via* weak coordination (Scheme 8).[32] The limitations and scope of the sulfonamide substrates bearing diverse substituents at sulfonyl moiety were then comprehensively investigated. The *N*-alkylsulfonyl- and *N*-arylsulfonyl-substituted substrates were good candidates in this chalcogenation reaction. However, tertiary amide was not compatible with this catalytic system. The substrates scope showed that electron-donating substituents of diaryl disulfides (**24**) gave the best results. In addition, the intermolecular competitions in KIE experiments ($k_H/k_D = 1.1$) indicated that the C–H activation is unlikely involved in the rate-limiting step.

From the mechanistic point of view, the six-membered palladacycle intermediate **Int-14** was obtained by subsequent coordination of the palladium catalyst to the weakly coordinated O-atom of the sulfonamide, *ortho*-C–H bond activation, and oxidative addition process. Then, reductive elimination affords the target products **25** and the Pd(II) catalytic species. The authors also proposed another plausible catalytic mechanism. The cyclopalladation of Pd(II) catalytic species with sulfonamides forms palladacycle species **Int-15**, which underwent reductive elimination to generate the final products **25** and Pd(0) species. Finally, the resulting Pd(0) is additionally oxidized by external oxidant Cu(OAc)$_2$ to the palladium(II) active species to complete this catalytic cycle (Scheme 9).
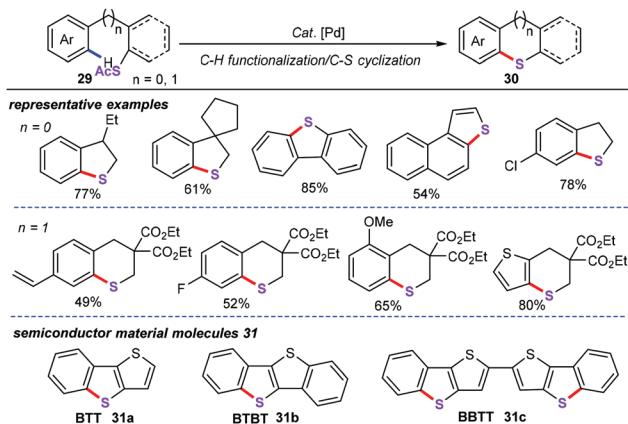
In particular, Yuan and Xiang group developed an elegant strategy of palladium-catalyzed oxidative arylthiolation of alkanes and ethers (**27**) with arylsulfonyl hydrazides (**26**) for the preparation of alkyl aryl sulfides (**28**) (Scheme 10).[33] Using Pd(OAc)$_2$ (2 mol%) as the catalyst and DTBP (di-*tert*-butyl peroxide, 2 equiv.) as the oxidant, a library of functional groups such as alkyl, alkoxyl, halide, and trifluoromethyl, even five-, six-, or eight-membered rings, were perfectly tolerated under

Scheme 8 Palladium-catalyzed chalcogenation reactions of sulfonamides.

Scheme 9 Proposed mechanism of the palladium-catalyzed chalcogenation reactions of sulfonamides.

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Scheme 10 Palladium-catalyzed radical coupling reaction for the synthesis of alkyl aryl sulfides.

Scheme 11 Palladium-catalyzed C−S cyclization reaction.

Scheme 12 Proposed mechanism for the palladium-catalyzed C−S cyclization.

the reaction condition, delivering the desired products **28** in moderate to good yields with excellent regioselectivity. Mechanistically, the oxidant DTBP plays an important role for the formation of the corresponding alkyl radical intermediates by abstract hydrogen from alkanes and ethers.

In 2018, Jiang and co-workers developed a nice protocol of palladium-catalyzed C–S cyclization for the straightforward synthesis of sulfur-containing benzoheterocyclic motifs (**40**) from thioacetates (**39**) (Scheme 11).[34] The optimal conditions were obtained in toluene solvent at 120 °C in the presence of 10 mol% Pd(OAc)$_2$, 2.0 equiv. PtBu$_3$·HBF$_4$, and 2.0 equiv. Ag$_2$CO$_3$ in a N$_2$ atmosphere. This transformation allowed for a range of C–H functionalization and carbon–sulfur cyclization cascade reactions, thereby delivering a series of structurally diverse sulfur-containing conjugated heterocyclic molecules in moderate yields. Notably, these obtained benzoheterocyclic derivatives are more useful intermediates, which can allow for the assembly of semiconductor materials such as BTBT (**31a**), BTT (**31b**), and BBTT (**31c**). The kinetic isotope effect (KIE) value of k_H/k_D 5.3 was obtained under optimal conditions, thus suggesting that the rate-determining step involves the cleavage of the C$_{Ar}$–H bond.
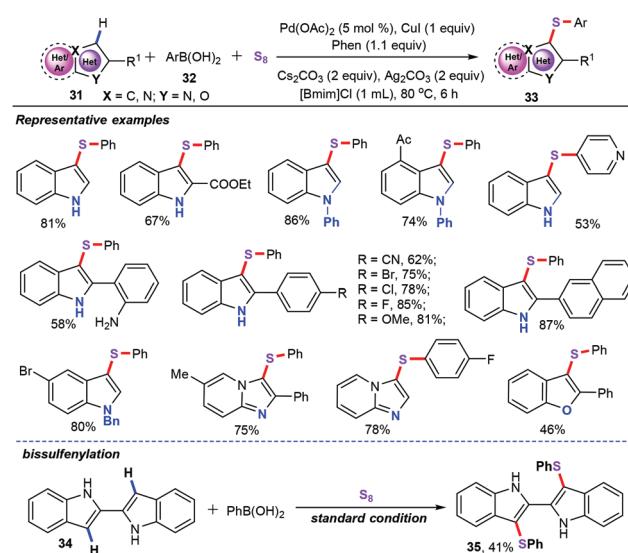
Based on the above-mentioned results, a plausible pathway of this reaction is described in Scheme 12. The palladium species coordinated to thioacetates to from palladacycle species **Int-16**. Subsequently, palladium intermediate **Int-16**

underwent metalation-deprotonation to generate palladium complex **Int-17**, which was confirmed as the rate-determining step in this chemical transformation. Then, reductive elimination of intermediate **Int-17** produces target products **30** and Pd(0) species. Finally, the oxidation of Pd(0) to Pd(II) by silver completes the catalytic cycle.

In recent contributions, our group also successfully accomplished palladium-catalyzed three-component cascade oxidative sulfenylation using elemental sulfur (S$_8$) as a sulfenylation reagent in ionic liquids (Scheme 13).[35] The scope of electron-rich heteroarenes (**31**) as substrates was then evaluated with a variety of electron-rich and electron-deficient substituents even with some sensitive functional groups such as amino groups, ketones, halogens, cyano groups, and esters, which were well accommodated under optimized conditions.

Scheme 13 Palladium-catalyzed oxidative sulfenylation of electron-rich heteroarenes.

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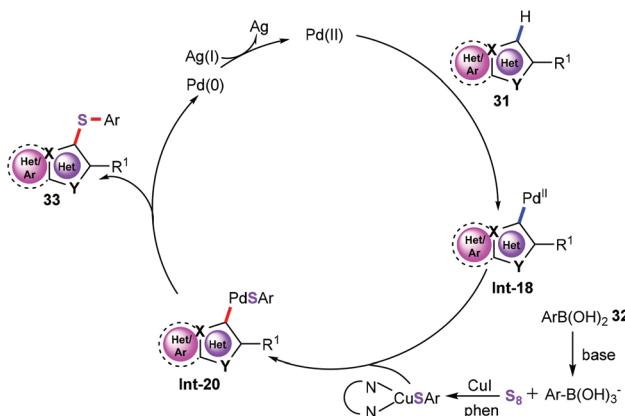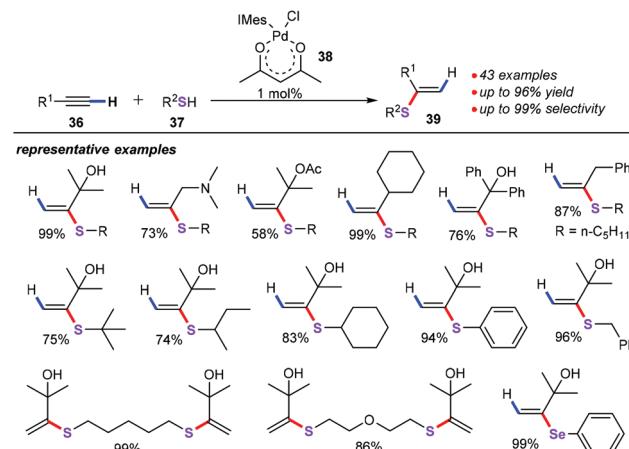
Scheme 14 Plausible mechanism for palladium-catalyzed oxidative sulfenylation.

Scheme 15 Palladium-catalyzed regioselective addition of thiols to alkynes.

As for aryl boronic acids (**32**), various functional groups such as alkyls, halogens, heteroaryls, and cyano groups were also compatible with these reaction conditions. As a result, this approach provides an effective and green pathway for the synthesis of a range of 3-sulfenylheteroarenes (**33**) in moderate to excellent yields. Remarkably, the bissulfenylation reaction for the assembly of 3,3′-bis(phenylthio)biindole (**35**) under optimized conditions was also well performed.

We then suggested a plausible mechanism for this oxidative sulfenylation (Scheme 14). The first step is the electrophilic palladation of heteroarenes, which generates vinyl-palladium intermediate **Int-18**.[36] Meanwhile, using CuI as the catalyst, aryl boronic acid reacts with S_8, affording organocopper thiolate complex **Int-19**.[37] Subsequently, transmetalation of intermediate **Int-19** with **Int-18** produces vinyl-palladium intermediate **Int-20**. Finally, reductive elimination of intermediate **Int-20** gives the target products **33**. Then, Ag_2CO_3 was used as the oxidant for the regeneration of Pd(ɪɪ) from Pd(0).
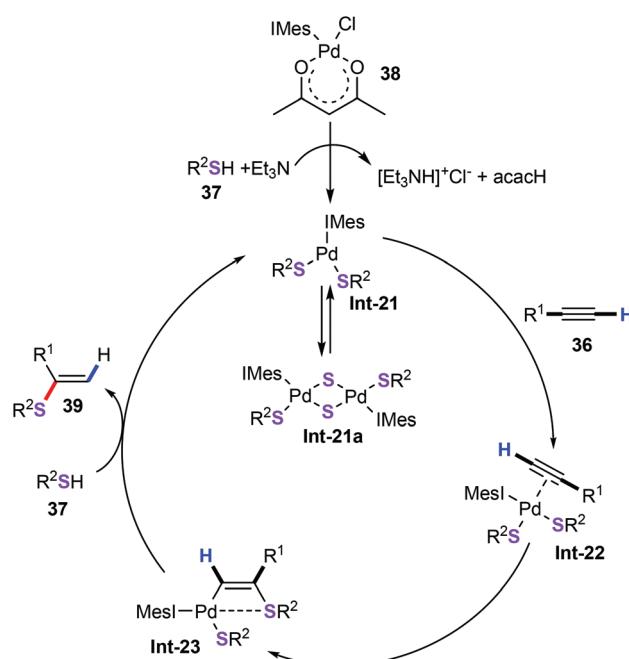
2.2 Sulfenylation of alkynes

Alkynes served as important chemical participants, displaying high reactivity in transition metal-catalyzed sulfenylation. For example, Ananikov and co-workers described a remarkable and highly efficient approach for the preparation of Markovnikov-type vinyl sulfides (**39**) starting from readily available thiols (**37**) with alkynes (**36**) (Scheme 15).[38] Air and moisture stable Pd-NHC complex [(IMes)Pd(acac)Cl] (**38**) can be easily synthesized by the reaction of Pd(acac)₂ and the IMes·HCl imidazolium salt. With 1 mol% Pd-NHC complex as the catalyst and 1 equiv. γ-terpinene as the additive and under solvent-free conditions, a variety of thiols including tertiary, secondary, and primary aliphatic thiols, as well as benzylic and aromatic thiols, could be excellently tolerated, furnishing the desired products **39** in moderate to good yields with excellent selectivity. Additionally, this approach did not require additional ligands and solvents, and avoided the use of complicated experimental techniques.

The mechanism was subsequently postulated (Scheme 16). First, the activation of the precatalyst **38** by replacement of the Cl and acac ligands with SR ligands forms monomeric (**Int-21**) or dimeric (**Int-21a**) Pd complexes. Particularly noteworthy was that dimeric complexes **Int-21a** were established by X-ray analysis. Then, three-coordinated monomeric complex activated alkynes to give π complex **Int-22**, which further undergoes alkyne insertion and affords vinyl palladium species **Int-23**. Finally, the vinyl palladium complex **Int-23** with thiols **37** generates the target products. Notably, the authors also gave some evidence from the DFT calculations for this catalytic mechanism.
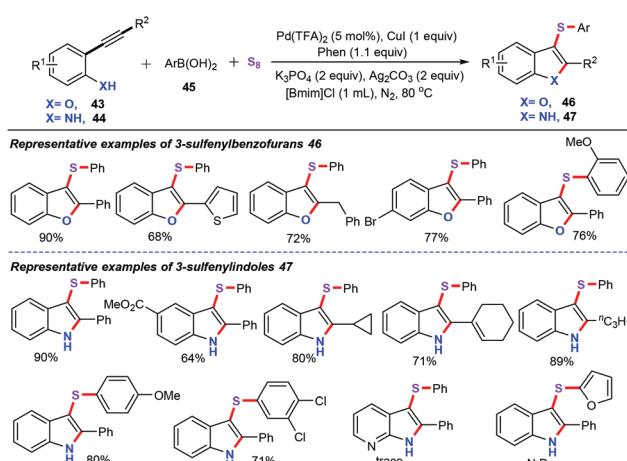
Scheme 16 Plausible mechanism for palladium-catalyzed hydrothiolation of alkynes.

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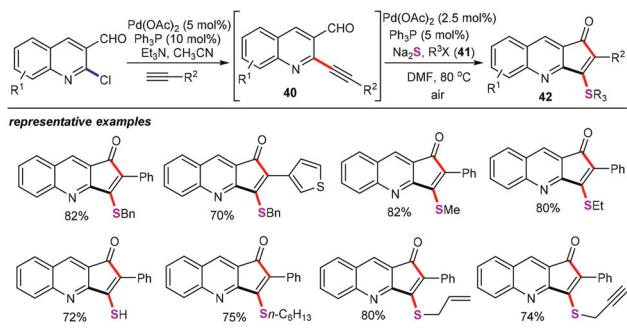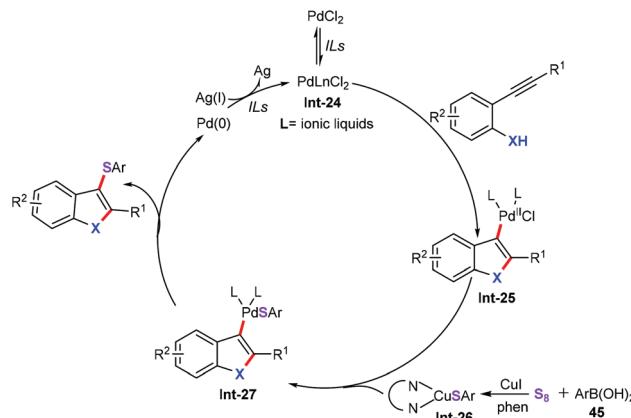
Scheme 17 Palladium-catalyzed sequential Sonogashira coupling and annulation reaction of ortho-alkynyl aldehydes.

**Scheme 19** Plausible mechanism for palladium-catalyzed cascade annulation/arylthiolation reaction.

In addition, Singh and co-workers developed a palladium-catalyzed sequential Sonogashira coupling and annulation reaction of *ortho*-alkynyl aldehyde (**40**) for the construction of various 3-alkylsulfanyl-cyclopenta[*b*]quinolin-1-ones (**42**) with sodium sulphide (Na$_2$S) as inorganic sulfur sources (Scheme 17).[39] The optimized system was successfully applied to a wide array of *ortho*-alkynyl aldehyde, including those bearing synthetically useful functional groups such as halogens and aromatic heterocycles. Moreover, the scope of this protocol was further expanded to a variety of alkyl and benzyl halides (**41**). The authors also showcased the utility of 3-sulfenylated cyclopenta[*b*]quinolinone by performing a number of elaboration reactions.

In 2016, our group disclosed an attractive and concise approach for the synthesis of 3-sulfenylbenzofurans (**46**) and 3-sulfenylindoles (**47**) *via* palladium and copper co-catalyzed cascade annulation/arylthiolation of 2-alkynylphenols (**43**) or 2-alkynylamines (**44**) with arylboronic acid (**45**) and S$_8$ in ionic liquids (Scheme 18).[40] This strategy tolerated a broad range of electron-neutral, electron-withdrawing, and electron-donating substrates, thereby furnishing the corresponding sulfenylated heterocycles scaffolds in moderate to excellent yields.

Additionally, a variety of conventional solvents (such as DMF, DMSO, CH$_3$CN, and toluene) and different types of ionic liquids were examined, and ionic liquids [Bmim]Cl were found to be the best solvent for this transformation. Other easily available sulfur sources such as Na$_2$S, S$_8$ and K$_2$S, were also screened, and S$_8$ was the most effective inorganic sulfur source. Considering the environmental impacts, ionic liquids as the solvent makes this transformation green and reusable.

Based on previous relevant reports,[41] and our experimental results, a tentative pathway is proposed in Scheme 19. In this transformation, a Pd complex (**Int-24**) is formed *in situ* in ionic liquids.[42] The nucleopalladation of 2-alkynylphenols or 2-alkynylamines gives vinyl palladium species **Int-25**. Then, the transmetalation of organocopper thiolate complex **Int-26** with intermediate **Int-25** forms aryl palladium complex **Int-27**. Reductive elimination leads to the formation of the target products. Finally, the resulting palladium(0) is additionally oxidized by silver salts to palladium(II) to complete the catalytic cycle.

Recently, our group has exploited another green and expeditious synthetic approaches for the assembly of various valuable 4-sulfenylisoxazole derivatives (**51**) by NHC-palladium-catalyzed three-component cascade *S*-transfer reaction in ionic liquids (Scheme 20).[43] Detailed investigations demonstrated that the best conditions for this chemical transformation are as follows: NHC-Pd(II) (**50**, 0.25 mol%), and ionic liquid (2 mL) under air at 80 °C for 12 h. Under optimized reaction conditions, both aromatic and aliphatic acetylinic oximes (**48**) proceeded smoothly in this reaction system, and different functional groups worked well and afforded the desired products **51** in satisfactory yield. However, when aliphatic halide (**49**) was explored as the substrate, there was no corresponding 4-sulfenylisoxazole product obtained. Moreover, excellent stereoselectivity was observed for one C–O and two C–S bond formation in the present protocol. Particularly, using ionic liquids as the green solvent and stabilizing agents, the palladium catalyst can be efficiently separated from the reaction mixture and recycled. Notably, Na$_2$S$_2$O$_3$ as an odorless sulfeny-

Scheme 18 Palladium-catalyzed cascade annulation/arylthiolation reaction.

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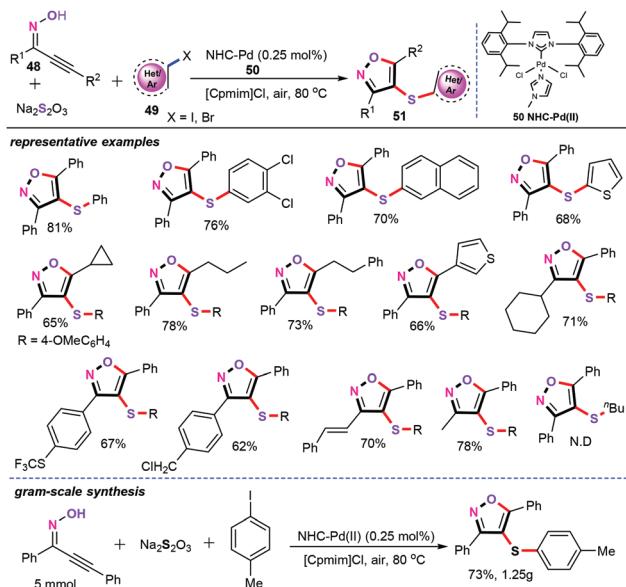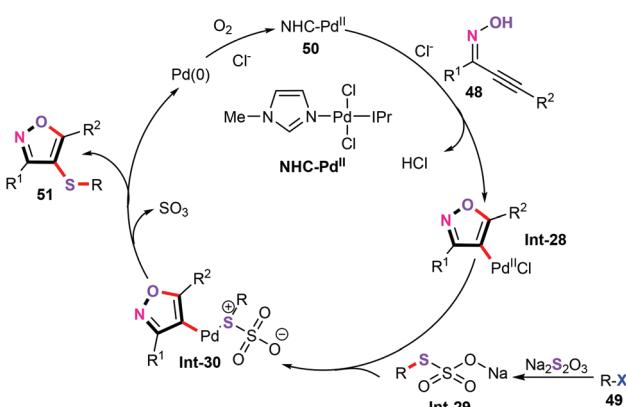
Scheme 20 Palladium-catalyzed three-component cascade *S*-transfer reaction in ionic liquids.
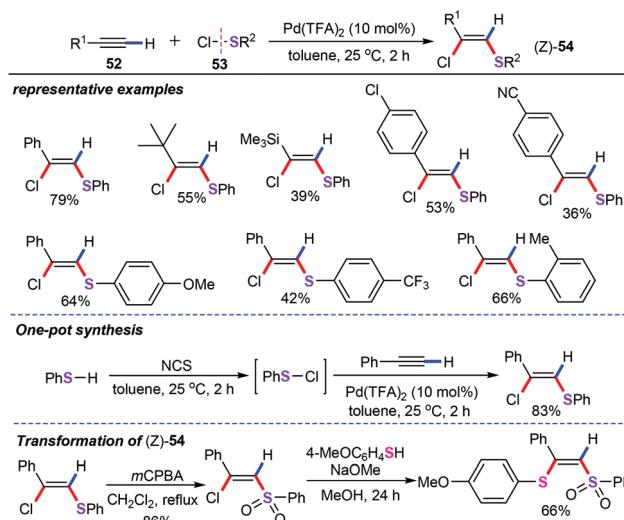
lation reagent under aerobic conditions in ionic liquids also makes this developed approach more eco-friendly.

The mechanism of palladium-catalyzed three-component cascade *S*-transfer reaction in ionic liquids for different 4-sulfenylisoxazoles was proposed (Scheme 21). Initially, *trans*-oxypalladation of oxime **48** gives σ-isooxazolylpalladium species **Int-28** along with losing a HCl molecule.[44] Meanwhile, aryl halides reacting with thiosulfate affords thiosulfate salt **Int-29**. Subsequently, successive ligand exchange/reductive elimination generates the target products **51**. Finally, Pd(0) is additionally oxidized by air to Pd(II) species, which completes the catalytic cycle.

In recent years, transition metal-catalyzed difunctionalization of alkynes have attracted considerable attention since they allow the rapid assembly of molecular complexity in an atom- and step-economical manners.[45] In this regard, a novel and

Scheme 21 Plausible mechanism for palladium-catalyzed 4-sulfenylisoxazoles synthesis.
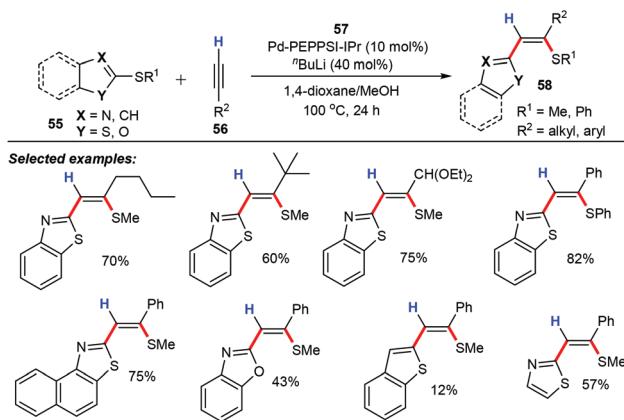

Scheme 22 Palladium-catalyzed selective chlorothiolation of alkynes.

atom-economical *syn*-chlorothiolation of terminal alkynes (**52**) with sulfenyl chlorides (**53**), furnishing (*Z*)-2-chloroalkenyl sulfides (**54**) with high regio- and stereoselective, has been recently developed by Nishihara and co-workers (Scheme 22).[46] In this report, functionalized sulfenyl chlorides were treated with various terminal alkynes with catalytic amounts of Pd(TFA)$_2$ (10 mol%) in toluene at 25 °C for 2 h. It is interesting to note that both aliphatic and aromatic alkynes were successfully introduced in this difunctionalization process. Compared with the previous anti-chlorothiolation of terminal alkynes, this discovered protocol offers a complementary synthetic route to chloroalkenyl sulfides. One-pot synthesis of (*Z*)-2-chloroalkenyl sulfides from benzenethiol with NCS (*N*-chlorosuccinimide) was also achieved.

After that, the same group described an atom-economical protocol for palladium-catalyzed carbothiolation of azolyl sulfides (**55**) with terminal alkynes (**56**) for constructing various 2-(azolyl)alkenyl sulfides (**58**) with good regio- and stereoselectivities (Scheme 23).[47] The optimization of reaction conditions showed that the conventional palladium/phosphine catalytic systems were found to be less active for this chemical transformation, and the palladium catalysts Pd-PEPPSI-IPr (**57**) and ([1,3-bis(2,6-diisopropylphenyl)imidazol-2ylidene](3-chloropyridine) palladium(II) dichloride) were superior to the others. Further screening of reaction conditions revealed that both *n*BuLi and MeOH were indispensable for this protocol. Remarkably, this approach could be used for the synthesis of various valuable polysubstituted olefin skeletons in a step- and atom-economical way, which are often found in natural products and materials science. Mechanistically, the selective alkynes insertion of a metal–sulfur bond was considered as the definitive step for the whole catalytic cycle.
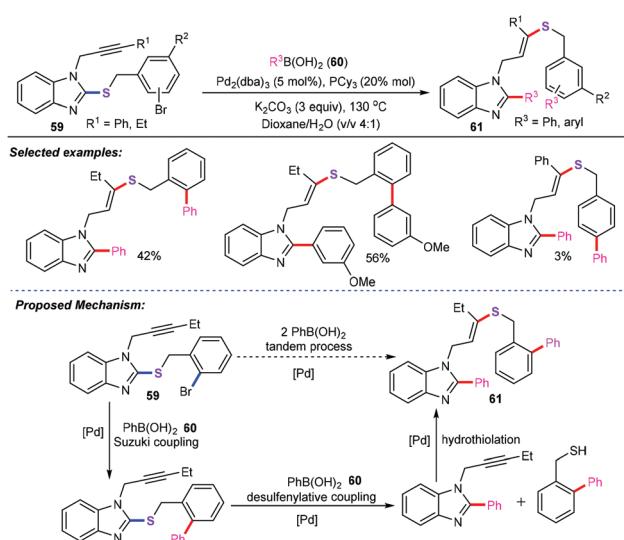
Recently, Gulea and co-workers have demonstrated a unique palladium-catalyzed cascade Suzuki-Miyaura coupling/desulfenylative coupling/hydrothiolation of 2-sulfenyl benzimidazoles (**59**) with boronic acids (**60**) for the preparation of

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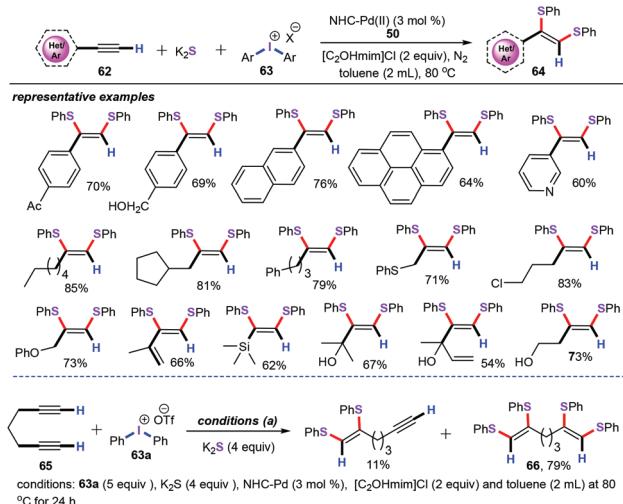
Scheme 23 Palladium-catalyzed carbothiolation of terminal alkynes with azolyl sulfides.

Scheme 25 Palladium-catalyzed three-component cascade bisthiolation.

various substituted benzimidazoles bearing a stereodefined alkenyl sulfide (**61**) (Scheme 24).[48] This cascade protocol was carried out with excess boronic acids (3 equiv.), Pd$_2$(dba)$_3$ (5 mol%), PCy$_3$ (20 mol%), and K$_2$CO$_3$ (3 equiv.) in dioxane/ H$_2$O (v:v 4/1) at 130 °C for 19 h. In most cases, the yields of the target products ranged between 42% and 82%. However, for alkyne moieties bearing a benzyl group, the reaction gave a lower yield (only 3%). The authors suggested a reaction mechanism that involves classical Suzuki debrominative cross-coupling, followed by desulfenylative coupling and intermolecular regioselective and stereoselective hydrothiolation.

In parallel to this line, our group accomplished a novel and practical palladium-catalyzed regioselective three-component cascade bisthiolation of terminal alkynes (Scheme 25).[49] This reaction was carried out under the following conditions: NHC-Pd (**50**) (3 mol%), 100 mg 4 Å MS, [C$_2$OHmim]Cl (2 equiv.), and toluene at 80 °C for 12 h. This methodology was

successfully used for the synthesis of a variety of functionalized (*Z*)-1,2-bis(arylthio)alkene derivatives (**64**) in moderate to good yields with K$_2$S as a stable and odourless sulfur reagent. Under optimized reaction conditions, both aliphatic terminal alkynes and aryl alkynes (**62**) bearing electron-withdrawing and electron-donating groups were smoothly transformed into the corresponding products with high regioselective. As for various diaryliodonium salts (**63**), the nature of the anion (such as OTs$^-$, BF$_4^-$, and Br$^-$) markedly affected the yields of the investigated substrates. Additionally, when hepta-1,6-diyne (**65**) was employed to react with diphenyliodonium triflate (**63a**, 5 equiv.), the desired bisthiolation product **66** was obtained in 79% yield.

Based on the above-mentioned results and previous reports, the reaction pathway is proposed in Scheme 26. This chemical transformation begins with *cis*-nucleopalladation of the terminal alkyne with an arylthiolate anion (**Int-31**) and gives vinylpalladium intermediate **Int-32**. Then, further oxidative coordi-

Scheme 24 Palladium-catalyzed cascade approach for the synthesis of substituted benzimidazoles.

Scheme 26 Plausible mechanism for palladium-catalyzed three-component cascade bisthiolation.

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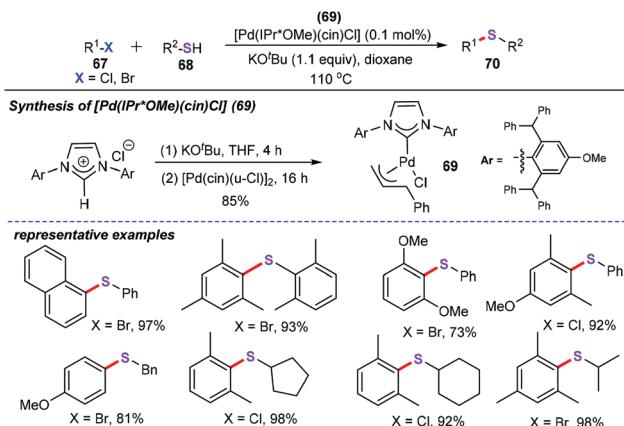
nation with an arylthiolate anion (**Int-31**) affords Pd[IV] intermediate **Int-33**.[50] Finally, reductive elimination produces the desired products **64**.

### 2.3. Sulfenylation of aryl halides

In the past two decades, transition metal-catalyzed straightforward sulfenylation of unactivated aryl/heteroaryl C–H bonds would be an economic and benign synthetic strategy, allowing direct and concise construction of diversiform sulfur-containing skeletons from the ready availability of starting materials. For instance, in 2013, Nolan and co-workers reported the well-defined palladium N-heterocyclic carbene (NHC) complex [Pd (IPr*OMe)(cin)Cl] (**69**)-catalyzed carbon–sulfur bond formation between nonactivated and deactivated aryl halides (**67**) with aliphatic or aromatic thiols (**68**) for the synthesis of aryl thioethers (**70**) (Scheme 27).[51] This newly active catalyst showed a remarkable catalytic performance in this sulfenylation reaction. With 0.1 mol% **69** as the catalyst, sterically hindered and deactivated compounds are well-tolerated without any additives or ligands.

Hierso and Roger also presented an efficient and flexible synthetic strategy access to a variety of heteroaryl thioethers through palladium-catalyzed cross-coupling reaction (Scheme 28).[52] With the [PdCl(allyl)]$_2$ (1 mol%) as the catalyst, and dppf as the ligand (1,1′-bis[(diphenyl)phosphanyl]-ferrocene), a broad range of electron-rich thiols (**71**) were allowed to react with 2-chloroheteroaromatics (**72**), which furnished diverse functionalized heteroaromatic thioethers (**73**) in good yields. However, electron-deficient groups of thiols such as trifluoromethyl, nitro, and ester groups did not participate in this chemical transformation. It is worth noting that the obtained thioethers could smoothly transform into sulfone derivatives by simple chemical transformation.

Jiang group developed a palladium-catalyzed double C–S bond construction with Na$_2$S$_2$O$_3$ as the sulfurating reagent. It was found that PdCl$_2$(dppf) can efficiently catalyze this approach in the presence of dppf (10 mol%) as the ligand and Cs$_2$CO$_3$ (3 equiv.) as the best base, thus offering diverse 1,4-

**Scheme 27** NHC-Pd-catalyzed sulfenylation of aryl/heteroaryl C–H bonds.
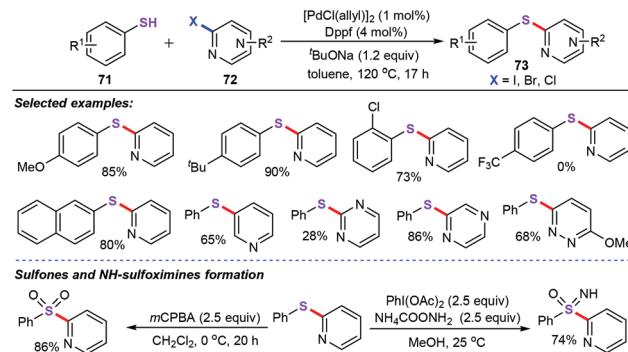
Scheme 28 Palladium-catalyzed thioetherification of thiols and 2-chloroheteroaromatics.
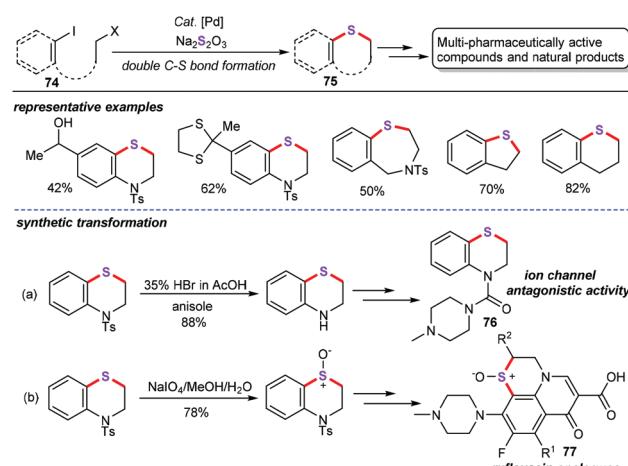
Scheme 29 Palladium-catalyzed double C–S bond formation coupling reaction.

benzothiazines (**75**) in moderate to good yields (Scheme 29).[53] Substrates (**74**) bearing Csp[3]-I, Br, Cl, OMs, and OTs on the saturated carbon could afford good to excellent yields. Additionally, neither S$_8$ nor Na$_2$S as the nontoxic and odourless sulfur source did favor this chemical transformation. In particular, gram-scale synthesis of this method was also achieved, showing potential capabilities to assemble specialized aromatic thioethers in synthetic and pharmaceutical chemistry. More importantly, *via* modification and synthetic transformation, the obtained 1,4-benzothiazines could be converted into the ion channel antagonistic activity molecule **76** and rufloxacin analogues **77**.

In a subsequent study, the double C–S bond formation strategy can be applied to more challenging reaction systems. For example, palladium-catalyzed double C–S bond formation with Na$_2$S$_2$O$_3$ as the sulfurating reagent resulted in a variety of unsymmetrically aromatic thioethers (**80**) with high regioselectivity, and this was accomplished by the same group (Scheme 30).[54] Under optimized conditions, a wide range of arylheterocycle substrates (**78**) bearing furan, pyridine, thiophene, and pyrazine frameworks were perfectly tolerated. It is

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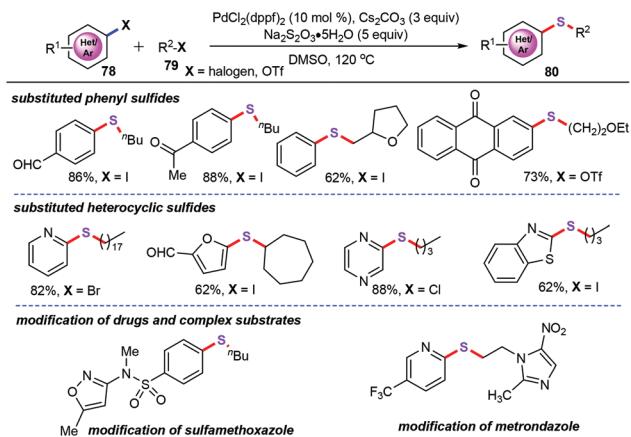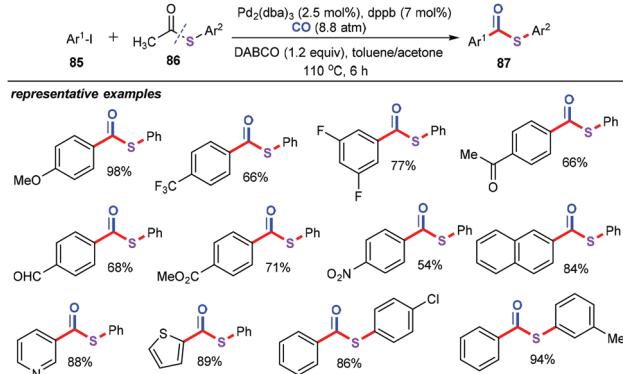
Scheme 30 Palladium-catalyzed cross-coupling access to diverse aromatic sulfides.

remarkable that a variety of halides (**79**) such as primary halides, secondary halides, even with sterically bulky halides were all amenable with this catalytic system, delivering the corresponding products in good to excellent yields. Furthermore, this protocol provides the potential synthetic application for accurately decorating some biologically active and pharmaceutical molecules.

Afterwards, the above synthetic methodologies were extended to the thiomethylation of aryl chlorides. Jiang group described palladium-catalyzed three-component cascade thiomethylation of aryl chlorides (**80**), masked inorganic sulfur (KSAc) and dimethyl carbonate (DMC, **81**), which afforded a variety of synthetically versatile aryl methyl sulfides (**82**) in good to excellent yields (Scheme 31).[55] In particular, this strategy offers a practical and green method for thiomethylation
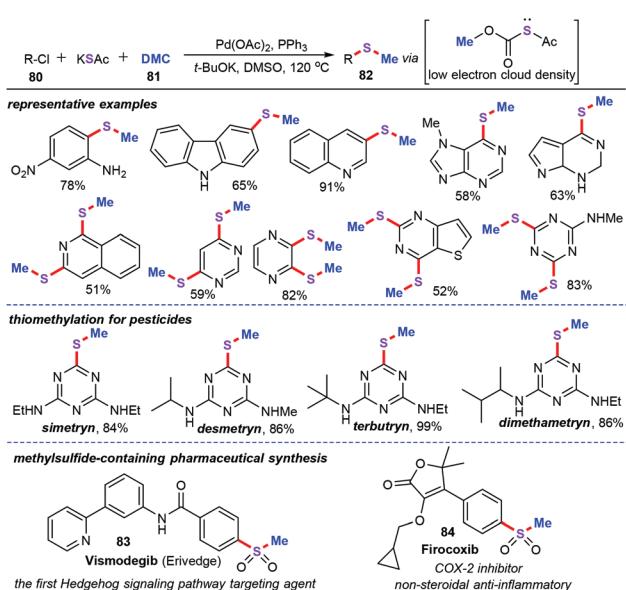
Scheme 31 Palladium-catalyzed three-component thiomethylation reaction.

Scheme 32 Palladium-catalyzed carbonylation for the synthesis of thioesters.

via the combination of commercially available inorganic sulfur source with an efficient methylation reagent. A gram-scale reaction for the preparation of diverse pesticides was performed under the standard conditions, showing potential capabilities in agriculture and industrial process. Importantly, this approach also provides a rapid and straightforward channel for the assembly of drug and biologically active molecules such as the marketed drug Vismodegib (**83**) and anti-inflammatory drug Firocoxib (**84**) through the developed thiomethylation reaction and further derivatizations.

Lee and Kim group reported elegant carbonylation of thioacetates and aryl iodides under a palladium/dppb catalytic system with 8.8 atm pressure of CO (Scheme 32).[56] In the presence of 2.5 mol% of $Pd_2(dba)_3$ as the catalyst, and 7 mol% of dppb as the ligand, treatment of a variety of aryl iodides with thioacetates at 110 °C for 6 h provided the corresponding *S*-aryl thioesters in good to excellent yields. Other ligands such as dppp and dppe also displayed the outstanding reactivity. With the Xantphos as the ligand, the sequential coupling of aryl iodides with KSAc followed by the carbonylation also offered the thioesters in good yields. Notably, several functional groups such as methoxyl, formyl, trifluoromethyl, acetyl, nitro, ester, and halogen groups were compatible with the current catalytic system. More importantly, this protocol represented the first deacetylative carbonylation for constructing versatile thioesters.

The reaction would be initiated by oxidative addition generated from Pd(0) with aryl iodides (Scheme 33). Then, migratory insertion of CO into the C–Pd bond of the vinylpalladium intermediate **Int-34** forms the acylarylpalladium **Int-35**. Concomitantly, with the aid of base, thioacetate gives the corresponding thiol.[57] Subsequently, ligand exchange between palladium species **Int-35** with thiol affords palladium complex **Int-36**. Finally, the catalytic cycle would be closed by the reductive elimination to generate the expected products **87**.

As a seminal work, Wu and co-workers developed a new palladium-catalyzed intermolecular transthioetherification reaction of aryl halides (**88**) with thioethers and thioesters (**89**) to afford a broad range of the corresponding thiomethylation and carbonylative thiomethylation products (>70 examples) in

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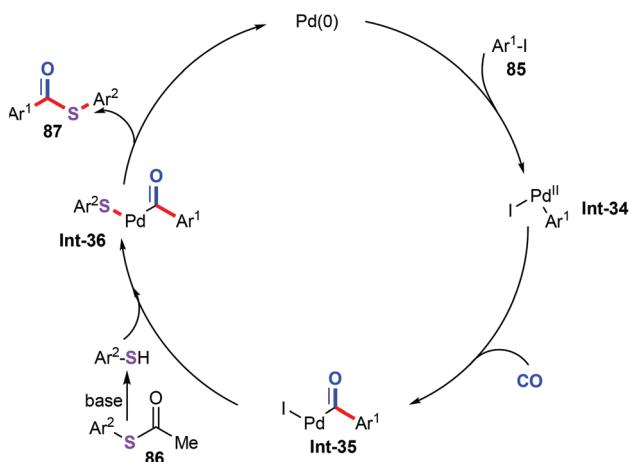
**Scheme 33** Plausible mechanism for carbonylation of thioacetates and aryl iodides.
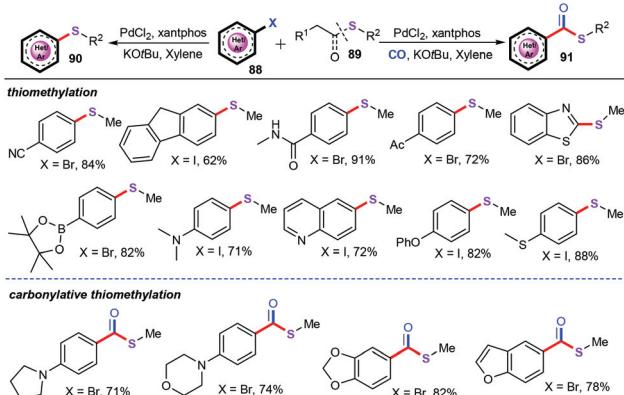
Scheme 34 Palladium-catalyzed transthioetherification reaction.

good to excellent yields with satisfying functional group compatibility (Scheme 34).[58] Moreover, this method provided the first example of carbonylative methylthioesterification of aryl halides under the similar reaction conditions. The scope of this system showed that both electron-poor and -rich substrates could be converted into the desired products with alkyl sulfides as the sulfur source. For further applications, some natural products of structural skeletons are also investigated for this transthioetherification reaction.

2.4 Other types of sulfenylation reaction

2.4.1 Decarboxylative cross-coupling reactions. Becht and co-workers disclosed the synthesis of diaryl sulfides (**94**) from the decarboxylative coupling reaction of electron-rich 2,6-dialkoxybenzoic acid derivatives (**92**) with diaryl disulfides (**93**) (Scheme 35).[59] As shown in Scheme 35, using 15 mol% Pd(CF$_3$CO$_2$)$_2$ as the catalyst, 2.2 equiv. Ag$_2$CO$_3$ as the base, and a mixture of 1,4-dioxane and tetramethylene sulfoxide (TMSO) (v : v, 65 : 1) as the solvent at 100 °C for 12 h, the corresponding sulfenylation products **94** were obtained in moderate yields. Additionally, this approach was adequate for the selenation
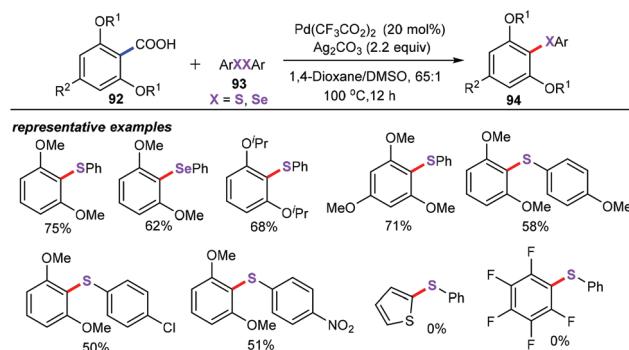

**Scheme 35** Palladium-catalyzed decarboxylative cross-coupling reactions.

process from arenecarboxylic acid for the first time. Disadvantageously, pentafluorobenzoic acid or 2-thiophenecarboxylic acid were not compatible with the developed conditions.

2.4.2 Desulfitative cross-coupling reactions. A later investigation by Jiang and co-workers discovered a palladium-catalyzed ligand-controlled divergent cross-coupling reaction involving an organosilicon reagent (Scheme 36).[60] With dppm (bis(diphenylphosphino)methane) as the ligand, the three-component cascade carbonylation of organic thiosulfate salts and organosilicon reagents (**96**) with carbon monoxide (CO) as a readily available C1 source successfully yielded structurally diverse thioesters (**98**) in moderate yields. In addition, in the absence of ligands, the Hiyama-type coupling of thiosulfate salts and organosilicon reagents could also react smoothly to deliver the corresponding thioesters (**97**) in moderate to good yields. Different types of silicon reagents including phenyltriethoxysilane (PhSi(OEt)$_3$), phenyltrimethoxysilane (PhSi(OMe)$_3$), diethoxydiphenylsilane (Ph$_2$Si(OEt)$_2$), and trimethyl(phenyl)silane (PhSiMe$_3$) were also screened, and the results indicated that PhSi(OEt)$_3$ was superior to others. In particular, thiosulfate is odorless, base-free, and compatible with the oxidizing system, showing unique advantages for this type of chemical transformation.

2.4.3 Oxidative dehydrazinative cross-coupling reaction. Zhao and co-workers also discovered a palladium-catalyzed oxi-
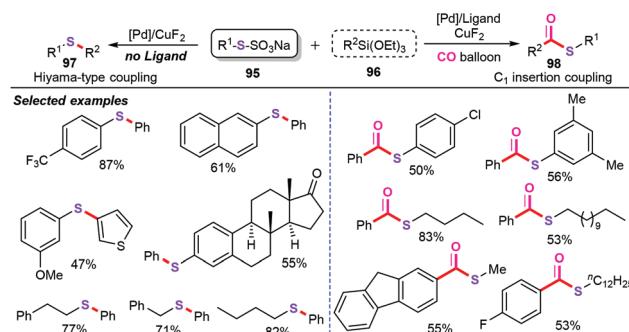
Scheme 36 Palladium-catalyzed ligand-controlled cross-coupling involving an organosilicon reagent.

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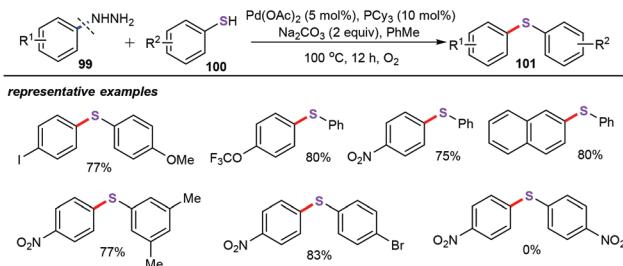
Scheme 37 Palladium-catalyzed oxidative cross-coupling of arylhydrazines with arenethiols.
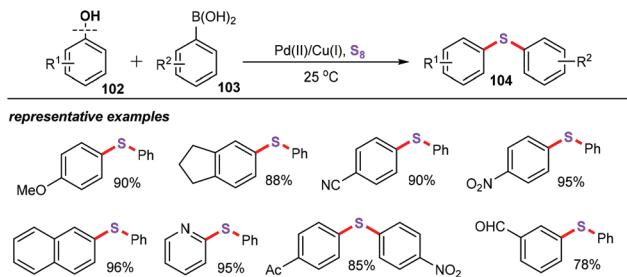
Scheme 38 Pd/Cu-co-catalyzed synthesis of unsymmetrical aryl sulfides.

dative arylthiolation of arylhydrazines (**99**) with arenethiols (**100**) using molecular oxygen as the sole oxidant.[61] As shown in Scheme 37, in the presence of 5 mol% of Pd(OAc)$_2$, PCy$_3$ (10 mol%), and Na$_2$CO$_3$ (1 equiv.), in toluene under an O$_2$ balloon at 100 °C for 12 h, a range of unsymmetrical diaryl sulfides (**101**) were obtained in good to high yields. More importantly, the substrates with different substituents on the phenyl ring such as halogen, trifluoromethoxy, and nitro group were well tolerated under the optimized reaction conditions. However, 4-nitrobenzenethiol was not compatible with this arylthiolation, and no corresponding product was detected.

2.4.4 Dehydroxylation cross-coupling reaction. Khakyzadeh and Rostami group designed and synthetized a novel Pd-nanoparticle ([SiO$_2$@organic-linker(OL)@Pd]) catalyst. With the new Pd-nanoparticle and CuI as the co-catalysts, the cross-coupling reaction of unreactive free-phenols (**102**) with arylboronic acids (**103**) performed well under optimized conditions (Scheme 38).[62] The developed catalyst [SiO$_2$@OL@Pd] showed ultra-high catalytic activity with TONs up to 19 000. Recycling experiments indicated that the palladium nanoparticle catalyst could be recycled up to five times without any decrease in the activity and regioselectivities. Notably, S$_8$ as an odorless sulfur source makes this protocol green and practical.

3 Sulfonylation reaction

In recent years, cascade sulfonylation reaction has been identified as the most powerful and practical synthetic methodology

for generating new C–S bonds from the corresponding sulfur source.[63] In this regard, a number of elegant developments have been typically discovered by transition metal-catalyzed cross-coupling approach. Moreover, many reviews on this topic have already extensively summarized.[64] For instance, Willis and co-workers reviewed the development and application of sulfur dioxide surrogates in synthetic organic chemistry in 2015.[65] Recently, Luo has also summarized the recent achievements in the synthesis of vinyl sulfones.[66] As a result, the cited papers were extensively selected from the latest published works that were not covered in the above reviews. Thus, we confine ourselves to recent improvements and new discoveries in the literature that have not been discussed before.

## 3.1 Potassium/sodium metabisulfites as SO$_2$ surrogates

In 2015, Shavnya and co-workers developed a novel palladium-catalyzed three-component cascade sulfonylation reaction for the preparation of functionalized aryl alkyl sulfones (**107**) from unactivated alkyl halides (**105**), aryl boronic acids (**106**), and potassium metabisulfite (K$_2$S$_2$O$_5$) (Scheme 39).[67] It was found that Pd(MeCN)$_2$Cl$_2$ (10 mol%) could efficiently promote this protocol in the presence of tBuXPhos (10 mol%) as the ligand and TBAB (1.1 equiv.) as the additive in DMF at 85 °C for 22 h, giving the corresponding sulfone derivatives in moderate to good yields. Under the optimized reaction conditions, various activated and unactivated alkyl electrophiles containing primary alkyl bromides, iodides, tosylates, even more hindered electrophiles were nicely tolerated, offering a breadth of aryl alkyl sulfones in good to excellent yields with high step-economy.

The authors also proposed the mechanism for this sulfonylation reaction as follows (Scheme 40): (i) transmetalation of arylboronic acid with palladium catalyst forms a vinylpalladium intermediate **Int-37**; (ii) SO$_2$ (generated from K$_2$S$_2$O$_5$)[68] insertion into the C–Pd bond produces the palladium sulfinate complex **Int-38**;[69] (iii) alkylation of alkyl halides gives the target alkyl sulfone products **107**.
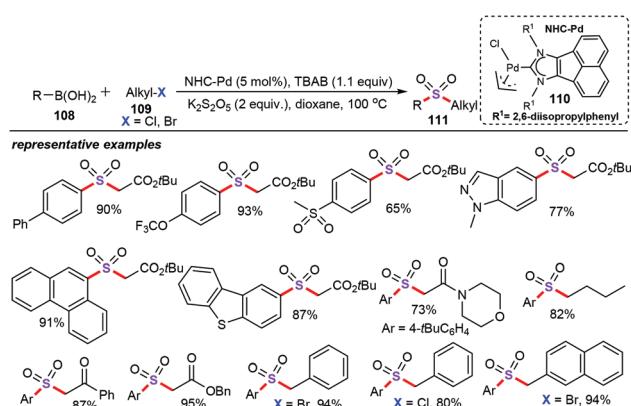
Similarly, Tu and co-workers reported an NHC-Pd-catalyzed alkylsulfonylation of boronic acids (**108**), (hetero)alkyl halides
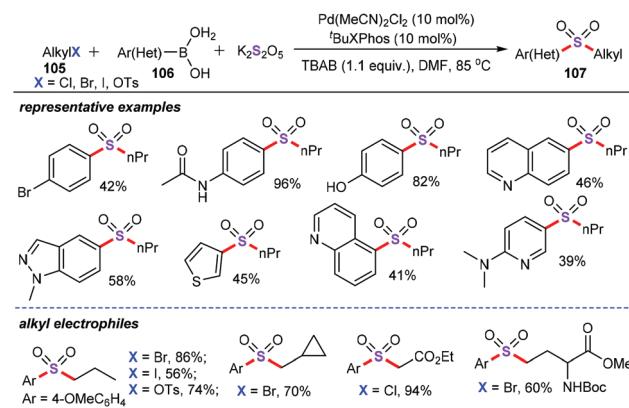

Scheme 39 Palladium-catalyzed three-component cascade sulfonylation reaction.

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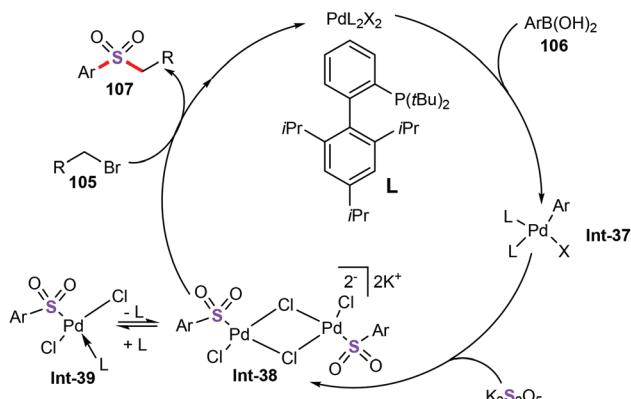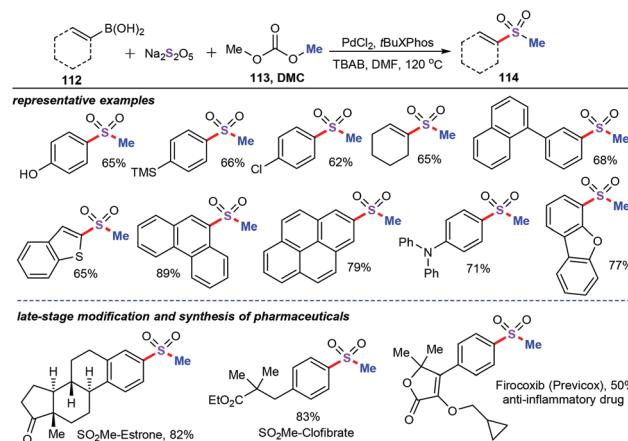
Scheme 40 Plausible mechanism for the three-component cascade sulfonylation reaction.

Scheme 41 Palladium-catalyzed alkylsulfonylation of boronic acids with alkyl halides.

Scheme 42 Palladium-catalyzed three-component cascade sulfonylation reaction.

(**109**), and potassium metabisulfites for the construction of diverse structurally distinct sulfones (**111**) (Scheme 41).[70] The well-defined NHC-Pd catalyst (**110**) exhibited the highest activity for this kind of redox-neutral reaction. Remarkably, it was found that the NHC ligand is crucial for this alkylsulfonylation approach. Various substituents on the phenyl ring of arylboronic acids, such as alkyl, trifluoromethoxy, halo, and sulfonyl groups, were well tolerated. The scope of diverse alkyl halides electrophiles such as α-bromoacetates, benzyl bromide and benzyl chloride as substrates was then thoroughly investigated. A detailed mechanistic study revealed that the dimeric palladium complex may be the true active species in this alkylsulfonylation protocol.[71]

Recently, Jiang and co-workers have described a novel palladium-catalyzed three-component cascade sulfonylation reaction for the synthesis of synthetically versatile aryl methyl sulfones (**114**) from boronic acid (**112**), sodium metabisulfite (Na$_2$S$_2$O$_5$), and dimethyl carbonate (DMC, **113**) (Scheme 42).[72] As one important sulfur dioxide surrogate, sodium metabisulfite was usually applied as an effective and eco-friendly sulfur dioxide source for this type of cascade sulfonylation reaction.[73]

In addition, the experimental results indicated that dimethyl carbonate acts as both the methylating reagent and the essential base for this protocol.[74] The optimized reaction conditions showed that PdCl$_2$ (10 mol%) can accurately catalyze the three-component cascade sulfonylation reaction in the presence of tBuXPhos (20 mol%) as the ligand, and TBAB (3 equiv.) as the additive in DMF in a N$_2$ atmosphere, affording a broad range of the desired aryl methyl sulfone products in moderate to good yields. Specifically, various fused aromatic rings, such as diphenyl, phenanthryl, naphthyl, and pyrenyl, were successfully accommodated under optimized conditions.

A plausible reaction mechanism was subsequently postulated in Scheme 43. Initially, PdCl$_2$ could coordinate with the ligand forms of palladium species, followed by the transmetalation of aryl boronic acid in the presence of alkoxide anion, producing aryl palladium intermediates **Int-40**.[75] Then, ligand exchange between aryl palladium complex **Int-40** with sodium metabisulfite (Na$_2$S$_2$O$_5$) generates intermediate **Int-41**. Afterwards, with the assistance of the electron-rich ligand, SO$_2$
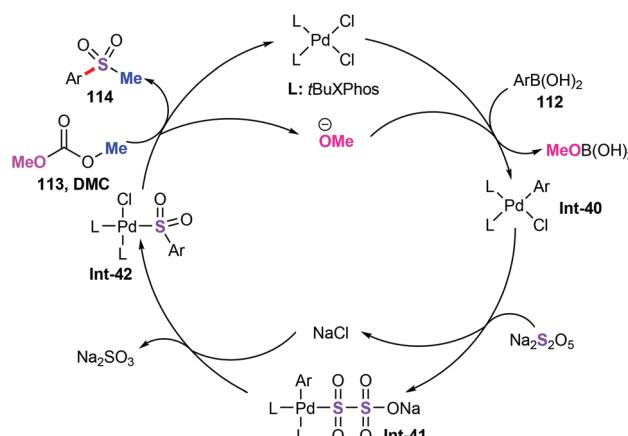
Scheme 43 Plausible mechanism for the three-component sulfonylation reaction.
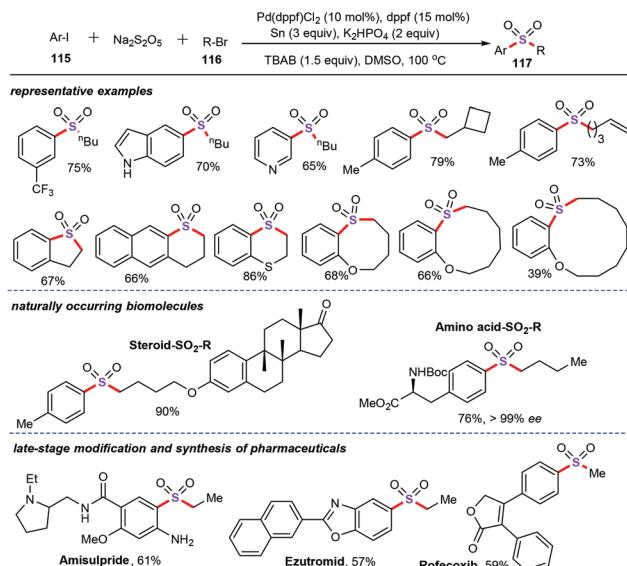
Scheme 44 Palladium-catalyzed multicomponent reductive cross-coupling reaction.

Scheme 45 Palladium-catalyzed synthesis of sulfinates from boronic acids and DABSO.

insertion into the Pd–C bond produces intermediate **Int-42**. Finally, alkylation process stimulating DMC gives the desired sulfone products **114**.

A year later, Jiang group described elegant palladium-catalyzed multicomponent reductive cross-coupling of aryl halides, alkyl halides, and sodium metabisulfite for the straightforward assembly of diversely functionalized sulfone derivatives (Scheme 44).[76] In the presence of 10 mol% PdCl$_2$(dppf), 20 mol% dppf, 3 equiv. zinc, 2 equiv. K$_2$HPO$_4$, and 1.5 equiv. TBAB in DMSO conditions, both the intermolecular and intramolecular reductive cross-coupling reactions were successfully explored, and generated a series of sulfones from the corresponding alkyl and aryl halides in good to excellent yields. Moreover, naturally occurring aliphatic compounds, such as steroids, saccharides, and amino acids, were well compatible with this SO$_2$-insertion reductive coupling approach. More importantly, four clinically applied drug molecules were also successfully prepared *via* alate-stage SO$_2$ insertion process. Mechanistically, control experiment demonstrated that alkyl radicals and sulfonyl radicals were both involved as the important intermediates in this transformation.

3.2 DABSO as the SO$_2$ surrogate

In 1957, Meerwein and co-workers reported that the first example of SO$_2$ gas was applied as the SO$_2$ surrogate for the preparation of aromatic sulfonyl chlorides *via* a new modification of the Sandmeyer reaction.[77] Furthermore, DABSO (DABCO·SO$_2$, the combination of DABCO with sulfur dioxide) as an air-stable and easy handling reagent was first reported in 1988 by Santos and co-workers.[78] After that, DABSO as the ideal SO$_2$ surrogate was pioneered by Willis[79] and Wu[80] in sulfonylation reaction in 2010 and 2012, respectively.
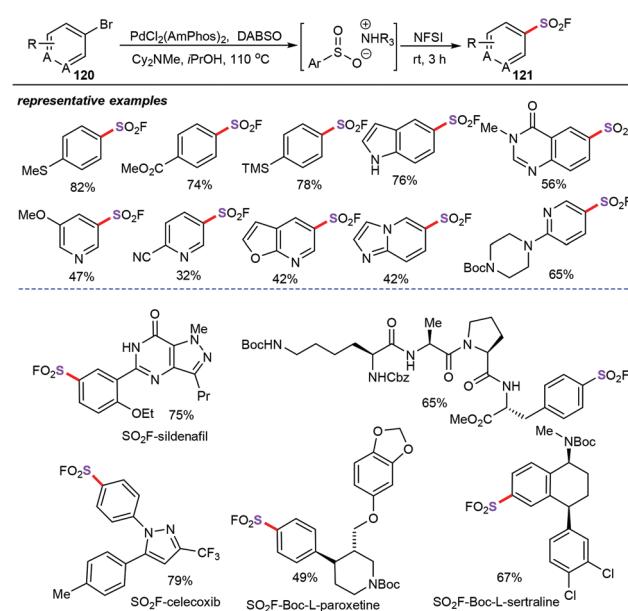
In 2016, Willis and co-workers described a palladium-catalyzed one-pot, two-step, redox-neutral and ligand-free synthetic
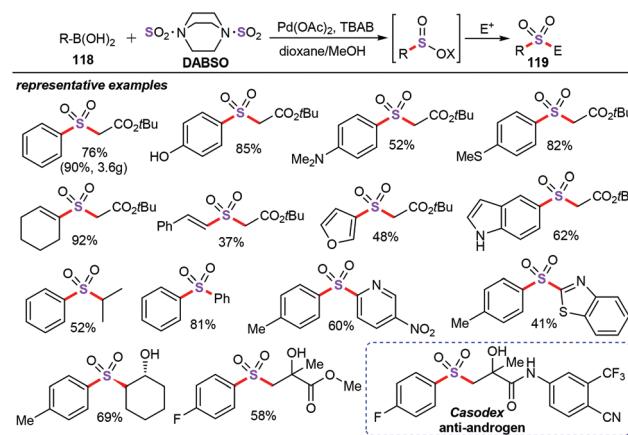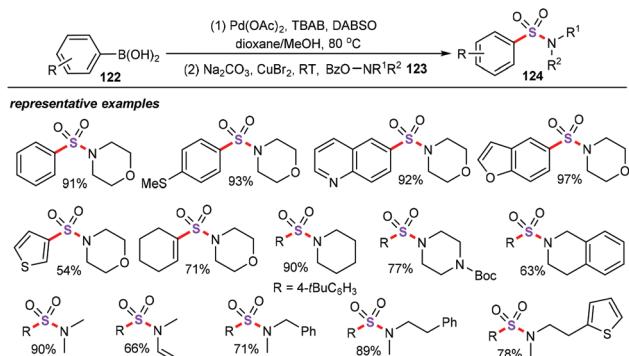
method for the generation of sulfinate derivatives by employing DABSO as the sulfur dioxide surrogate (Scheme 45).[81] Treatment of arylboronic acids (**118**) with various N-/ C-electrophiles in the presence of Pd(OAc)$_2$ (5 mol%) and TBAB (2 equiv.) in 1,4-dioxane/MeOH afforded the corresponding sulfinates (**119**) in moderate yields. Additionally, this one-pot approach can be applied for the gram scale synthesis. In particular, this sulfonylation reaction is exemplified in the derivatization and elaboration of the sulfinic acid derivatives into the *anti*-androgen pharmaceutical Casodex.[82]
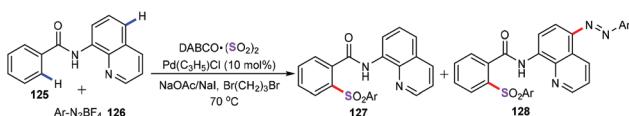
After that, the Willis group accomplished a novel and mild palladium-catalyzed sulfonylation reaction for the construction of sulfonyl fluorides (**121**) from aryl and heteroaryl bromides (**120**) with DABSO as the green SO$_2$ source (Scheme 46).[83] This

Scheme 46 Palladium-catalyzed sulfonylation reaction for the construction of sulfonyl fluorides.

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Scheme 47 Pd/Cu co-catalyzed three-component cascade sulfonylation reaction.

Scheme 48 Palladium-catalyzed direct sulfonylation reaction of C–H bonds.

protocol provides an efficient and straightforward synthetic strategy for the assembly of structurally diverse heterocyclic or aryl sulfonyl fluorides in moderate yields with high atom- and step-economy and exceptional functional group tolerance. Notably, this transformation allowed rapid construction of sulfonyl fluoride containing pharmaceutical and biologically important molecules.

In further investigation of this type of sulfonylation process, Tu group also reported an elegant one-pot bimetallic Pd/Cu-catalyzed three-component cascade sulfonylation reaction (Scheme 47).[84] With DABSO as the ideal sulfur source, various substituted arylboronic acids (122) were treated with cyclic and acyclic O-benzoylhydroxylamines (123) using Pd/Cu as the co-catalysts, and a series of structurally diverse sulfonamides (124) were obtained in good to excellent yields without additional ligands. Mechanistically, the authors also performed some control experiments to gain further insights into this synthetic strategy. Moreover, sodium sulfinate has been identified as the crucial intermediate for this transformation.

Especially, Xia and Wu and co-workers also demonstrated a facile and novel palladium-catalyzed direct sulfonylation strategy for the construction of diverse structurally distinct sulfonylative products (127) by C–H bond functionalization (Scheme 48).[85] In some cases, dual C–H functionalization products (128) were also detected with a lower yield. Notably, this observation may indicate that this approach presents the good combination of radical chemistry and palladium-catalyzed C–H bond activation.

3.3 Arylsulfonyl chlorides as the SO₂ surrogate

Zhang and Su and co-workers designed a strategy of highly efficient palladium-catalyzed C–H bond activation/functionali-
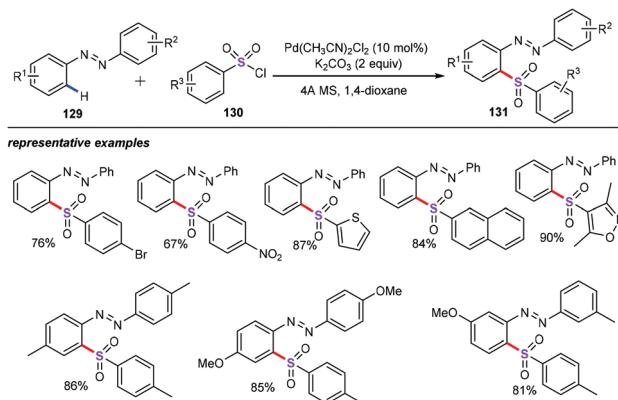

Scheme 49 Palladium-catalyzed C–H bond activation/sulfonylation reaction.

zation to produce ortho-sulfonylated azobenzenes (131) (Scheme 49).[86] Using PdCl₂(CH₃CN)₂ (10 mol%) as the catalyst, and K₂CO₃ (2 equiv.) as the base, azobenzene substrates (129) were successfully coupled with a whole variety of arylsulfonyl chlorides (130) to furnish a diverse range of unsymmetrical diarylsulfones in good to excellent yields with highly regioselectivities. Because of the mild reaction conditions, some sensitive functional groups such as nitro, halogen, methoxyl, and ester groups were compatible. On the basis of their mechanistic studies, the authors argued that this approach may occur through a cyclopalladated intermediate transition states by the ortho-C–H bond insertion.[87]

3.4 Sodium dithionite as the SO₂ surrogate

In comparison to the usually used SO₂ surrogate such as potassium/sodium metabisulfite, DABSO, and arylsulfonyl chlorides, sodium dithionite as the alternative SO₂ surrogate has rarely reported in recent years. In 2019, Jiang and co-workers discovered a nice and fascinating protocol for the synthesis of alkyl–alkyl and aryl–alkyl sulfones derivatives with a facile combination of halides (132), SO₂ surrogates, and phosphate esters (133) (Scheme 50).[88] Amazingly, under transition metal-free conditions, alkyl–alkyl sulfones (136) were obtained in moderate to good yields with the thiourea dioxide (135) as a reductive SO₂ surrogate. Additionally, aryl–alkyl sulfones (137) were achieved by an extremely low Pd catalyst loading using sodium dithionite (134) as the SO₂ surrogate. Specifically, the phosphate esters were employed as the stable and readily available alkyl source in this chemical transformation. Notably, this protocol has been applied to the late-stage modification of natural products and bioactive molecules.

In the beginning of 2020, Jiang and colleagues also successfully accomplished elegant multicomponent decarboxylative cross coupling of esters (138), sodium dithionite (134), and electrophiles for the preparation of sterically bulky sulfone derivatives (138) (Scheme 51).[89] Notably, the inorganic salt sodium dithionite not only served as the SO₂ source, but also acted as an efficient radical initiator for the decarboxylation process. Under the optimized conditions, various naturally
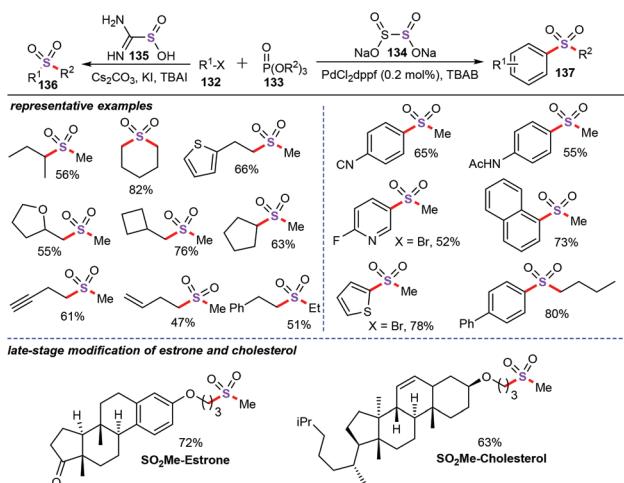
Scheme 50 General sulfone construction *via* SO₂ surrogate control.
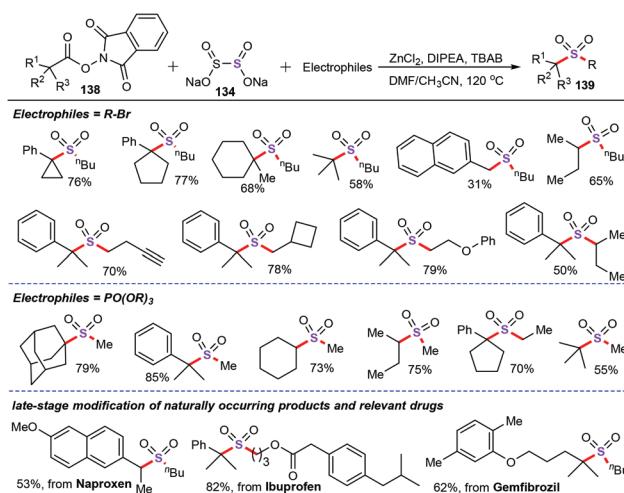
Scheme 51 Sodium dithionite-mediated decarboxylative sulfonylation.

abundant carboxylic acids and synthetically prepared carboxyl-containing drugs underwent efficient decarboxylative sulfonylation for the construction of diversely functionalized tertiary sulfones. Mechanistic studies suggested that decarboxylation was the rate-determining step and occurred *via* a single-electron transfer (SET) process with the assistance of sodium dithionite.

4 Summary

In this review, a good many of palladium-catalyzed sulfenylation and sulfonylation reactions have been summarized from 2010 to the beginning of 2020. Although many achievements have been made in C–H, C–C, as well as C–N bond functionalization, the widely existing C–S bond formation reactions were less reported and still highly desirable. In general, there are two main reasons: (i) many sulfur-containing reagents are

toxic and unstable, with repulsive odor and (ii) catalyst poisoning owing to the strong coordination of sulfur atom with transition metals catalytic species. Despite all these, numerous chemists have addressed themselves to the development of novel and useful synthetic strategies for constructing new and valuable C–S bonds. Moreover, a series of unique synthetic methodologies have been well developed for the assembly of diverse structurally sulfur-containing skeletons with excellent regio- and stereo-selectivities. As a result, various organic sulfur sources including thiols, disulfides, arylsulfonyl chlorides, sulfonyl hydrazides, and *N*-thioarylphthalimides have been typically investigated. In addition, several green and readily available inorganic sulfur reagents such as elemental sulfur (S_8), sodium sulfide (Na_2S), potassium sulfide (K_2S), sodium sulfinates ($NaSO_2R$), potassium thioacetate (KSAc), sodium metabisulfite ($Na_2S_2O_5$), potassium metabisulfite ($K_2S_2O_5$), and sodium thiosulfate ($Na_2S_2O_3$) have also been applied in the recent years. Most notably, some of the described methods in this review manifested that the above-mentioned palladium-catalyzed sulfenylation and sulfonylation reactions could provide efficient and rapid approaches for the assembly of complex pharmaceutical and biologically active molecules through further synthetic transformation and structural modification. In brief, this study on the palladium-catalyzed C–S bond formation reaction is now established as a captivating branch for transition metal-catalyzed C–S bond transformation.

Despite the tremendous achievements that have been made in this line, more challenges need to be overcome in this area. For instance, new-type, safe, inexpensive, nontoxic, and readily available sulfur reagents still need to be exploited. Additionally, the "inexpensive" and recyclable metal catalysts such as Fe, Zn, and Al were also explored. In particular, more eco-friendly conditions such as electrochemistry, photochemistry, and free radical chemistry protocols need to be explored in future research. As the old saying goes, "*nothing is impossible to a willing heart*", we profoundly believe that palladium-catalyzed C–S bond formation is continuously expanding. We hope this review will give the researchers a new perspective in this area.

Conflicts of interest

The authors declare no competing financial interest.

Acknowledgements

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