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Transition-metal mediated carbon–sulfur bond activation and transformations: an update

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Carbon–sulfur bond cross-coupling has become more and more attractive as an alternative protocol to establish carbon–carbon and carbon–heteroatom bonds. Diverse transformations through transition-metal-catalyzed C–S bond activation and cleavage have recently been developed. This review summarizes the advances in transition-metal-catalyzed cross-coupling *via* carbon–sulfur bond activation and cleavage since late 2012 as an update of the critical review on the same topic published in early 2013 (*Chem. Soc. Rev.*, 2013, **42**, 599–621), which is presented by the categories of organosulfur compounds, that is, thioesters, thioethers including heteroaryl, aryl, vinyl, alkyl, and alkynyl sulfides, ketene dithioacetals, sulfoxides including DMSO, sulfones, sulfonyl chlorides, sulfinates, thiocyanates, sulfonium salts, sulfonyl hydrazides, sulfonates, thiophene-based compounds, and C=S functionality-bearing compounds such as thioureas, thioamides, and carbon disulfide, as well as the mechanistic insights. An overview of C–S bond cleavage reactions with stoichiometric transition-metal reagents is briefly given. Theoretical studies on the reactivity of carbon–sulfur bonds by DFT calculations are also discussed.

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1. Introduction

In order to get cleaner fuels, continuous efforts have been devoted to sulfur removal from petroleum fractions through C–S bond activation/cleavage-involved hydrodesulfurization (HDS)[1] of organosulfur compounds including thiophenes, benzothiophenes, and dibenzothiophenes,[2–4] with biodesulfurization as a complementary alternative for the same purpose.[5] Although C–S bond cleavage by stoichiometric transition-metals has been extensively investigated for chemists to understand the C–S bond activation mechanisms of organosulfur

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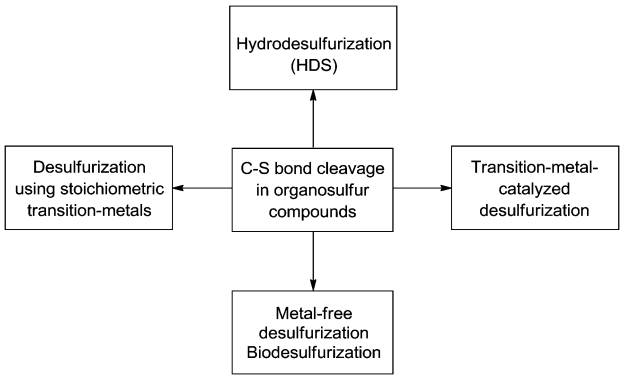
compounds,[6–9] transition-metal-catalyzed C–S cross-coupling has recently attracted more and more attention. As one of the fundamental chemical bonds C–S bond is also used for the construction of proteins and enzymes. In order to develop efficient catalyst systems for C–S bond cleavage in organosulfur compounds, considerable efforts have recently been made to probe into the C–S bond activation modes and C–S bond cleavage mechanisms.[10–28] Inspired by the successful application of the well-known Liebeskind–Srogl cross-coupling[10,12] in desulfitative carbon–carbon bond formation, diverse C–S transformations have been developed (Scheme 1). To help investigation of the C–S bond activation mechanisms in organosulfur compounds, homogeneous catalytic C–S transformation reactions are usually performed in the presence of a transition-metal catalyst, offering quite a number of useful or promising cross-coupling synthetic methods for the construction of C–C and C–heteroatom bonds. In early 2013, we published a critical review on transition-metal mediated C–S bond activation and transformations in *Chemical Society Reviews*.[17] Since then, important progress has been achieved in both the cross-coupling of C–S bonds and the mechanistic exploration of C–S bond activation and cleavage. Herein, we contribute a follow-up update to summarize the recent advances in this



Scheme 1 C–S bond cleavage strategies.

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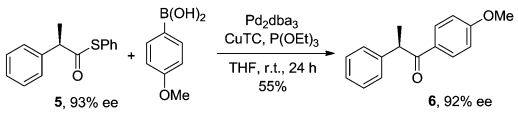
rapid-growing area. The present update review focuses on transition-metal-catalyzed C–S bond cleavage reactions by the categories of organosulfur compounds as well as the mechanistic insights. An overview of C–S bond cleavage reactions with stoichiometric transition-metal reagents and theoretical studies on C–S bond activation/cleavage is also briefly given. It should be noted that C–S bond cleavage under transition-metal-free conditions is not summarized in this review.

2. C–S bond cleavage in thioesters

2.1 Cross-coupling with organoboron reagents: Liebeskind–Srogl cross-coupling

The cross-coupling reaction of a nucleophilic organometallic compound with an electrophilic organohalide or pseudohalide catalyzed by a transition-metal catalyst can be applied to construct a C–C bond.[29] Thanks to Liebeskind's pioneering work[30] organosulfur compounds have recently been paid more and more attention as electrophilic coupling partners for the cross-coupling reactions. To accomplish a catalytic process for cleaving a C–S bond, oxidative addition of the C–S bond to a low-valent transition-metal is required. In this regard, a lot of examples have been documented.[5–8,31,32] However, it is usually difficult to establish a catalytic cycle for such a C–S bond cleavage process due to the low catalytic turnover of the potential transition-metal catalyst to convert organosulfur substrates. The key to enhance the catalyst efficiency is activation of the very stable bond formed between the catalytically active metal center and the soft sulfur atom. Thus, a compatible nucleophilic organometallic reagent should be used to facilitate the transmetalation step and establish a catalytic cycle. In 1997, Liebeskind *et al.* reported palladium- and nickel-catalyzed cross-coupling reactions of readily available tetramethylenesulfonium salts with organoboron, -tin, and -zinc reagents to construct C–C bonds for the first time.[30] In these cases, tetrahydrothiophene (THT) acted as an effective leaving group.

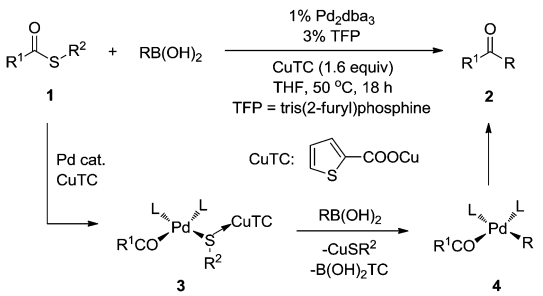
Under relatively mild and base-free conditions, Liebeskind and Srogl reported the first example of palladium-catalyzed, copper-mediated thioester–boronic acid cross-coupling for the synthesis of ketones in 2000 (Scheme 2),[33] the so-called (the first-generation) "Liebeskind–Srogl cross-coupling".[12] In the reaction no base is required, and a stoichiometric amount of copper(I) thiophene-2-carboxylate (CuTC)[34] should be used as a sacrificial reagent to remove the thiolate moiety in the thioester substrates. Copper(I) salt CuTC acts as a thiophilic metallic reagent due to the low thiophilicity of the boron atom and the relatively low nucleophilic reactivity of the organoboron compounds. Such a new thioorganic cross-coupling is understood to depend on the capability of the copper(I) carboxylate to activate the catalytic intermediate, $R^1COPdL_2SR^2$ (**3**), toward transmetalation by boronic acid, *etc.* Copper(I) thiolate $CuSR^2$ and $B(OH)_2TC$ are formed as the side products. Unlike the traditional Suzuki–Miyaura cross-coupling of organic halides with boronic acids, where the presence of a base is essential, a base is deleterious in the current chemistry. This "baseless" method opens new possibilities for the synthesis of highly functionalized and base-sensitive compounds. In comparison to the protocol involving a base and *in situ* generated alkylsulfonium salts[35] or sacrificial Zn(II) reagents,[36] Liebeskind–Srogl cross-coupling features a wider scope of readily available electrophilic substrates, easy manipulations, and higher efficiency.[37]



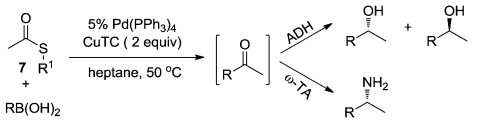
(1)

Under the typical Liebeskind–Srogl cross-coupling conditions, chiral thioester **5** was employed to synthesize the corresponding chiral ketone **6** (eqn (1)).[38] Biocompatible metal-assisted C–C cross-coupling with biocatalytic chiral reductions was developed in a tandem cascade (Scheme 3).[39] Thus, a concurrent chemo/biocatalytic one-pot reaction cascade was used for the production of chiral alcohols and amines by combining palladium-catalyzed, copper-mediated cross-coupling of thioesters **7** and arylboronic acids with an enantioselective enzymatic reduction. The second-step transformation was realized with enantiocomplementary alcohol dehydrogenases (ADHs) and ω-transaminases (ω-TAs), respectively. The chiral alcohols were obtained in 81% overall yield with 99% ee, and chiral 1-phenylethanamine was accessed in 51% yield with 99% ee over two steps. It is noteworthy that thioesters can also be applied for biosynthesis under mild conditions.[40,41]

In 2007, Liebeskind *et al.* realized Cu(I)-catalyzed cross-coupling of *S*-pendant-bearing thioesters with boronic acids (the second-generation Liebeskind–Srogl cross-coupling).[42] In this case, a Cu(I) compound such as Cu(I)-3-methylsalicylate (CuMeSal, **8**) was usually used as the catalyst, and a second equivalent of boronic acid was applied as the sacrificial reagent under aerobic conditions. Copper(I) was also rendered catalytically viable in the presence of a thiolate which was designed to



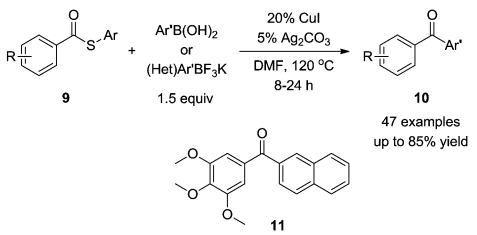
Scheme 2 Liebeskind–Srogl cross-coupling.



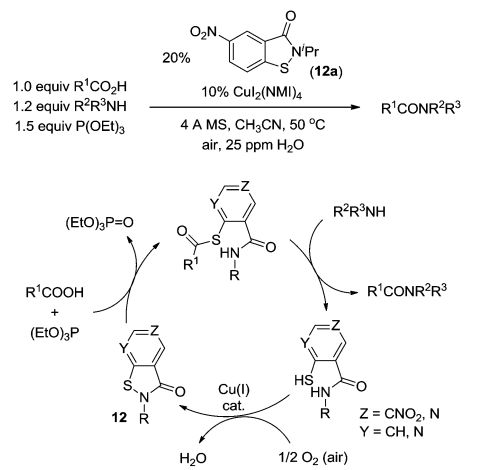
Scheme 3 A concurrent chemo/biocatalytic one-pot reaction cascade.

functionalize as an analog of the metallothionein system.[43] Both the copper reagent and the internal *O*-methyl oxime moiety in the substrates are important for the catalytic turnover. The intramolecular sulfur trap by the oxime nitrogen *via* the *in situ* generated Cu(I) thiolate formed a heterocyclic compound and Cu–OMe species which was thus rendered catalytically active for the C–S bond cleavage. Under the reaction conditions a large excessive amount of the organometallic reagent, Cu(I) catalyst, and a palladium catalyst are not necessary. Such a process is considered as the third-generation Liebeskind–Srogl cross-coupling. Due to the simple preparation of the *O*-methyl oxime-functionalized thioesters, this method can expand the applicability of the traditional Liebeskind–Srogl cross-coupling.

A Cu(I)/Ag(I) catalytic system was developed for the synthesis of biaryl ketones *via* the C–S bond cleavage of thioesters with either arylboronic acids or potassium aryltrifluoroborates.[44] This process requires neither a palladium catalyst nor CuTC mediator, and is efficient, versatile, operationally simple, and accommodates functionally diverse thioesters **9**, arylboronic acids, and potassium aryl and heteroaryltrifluoroborates (Scheme 4). Using this method biologically active naphthyl phenstatin (**11**) was synthesized. A very relevant process has recently been reported by Liebeskind *et al.*, in which the *in situ* generated thioester intermediates were transformed into the corresponding amides and peptides from carboxylic acids and amines or amino acids using $P(OEt)_3$ as the reductant and O_2 in air as the terminal oxidant under benzoisothiazolone (BIT) (**12a**) organo/copper(I) cocatalysis (Scheme 5).[45] By means of a



Scheme 4 Cu(I)/Ag(I)-catalyzed C–S bond cleavage of thioesters.

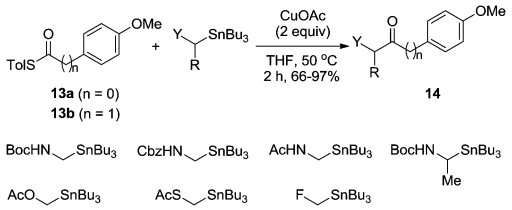


Scheme 5 Aerobic benzoisothiazolone (BIT)/Cu(I)-catalyzed amidation.

catalytic redox system consisting of 20% organocatalyst **12a** and 10% $CuI_2(NMI)_4$ (NMI = *N*-methylimidazole)[46] in MeCN under dry air at 50 °C, a variety of amides were obtained from 1.0 equiv. of carboxylic acid, 1.2 equiv. of amine, and 1.5 equiv. of triethyl phosphate. The method is compatible with oxidation-prone substrates such as alkenes, boron derivatives, furans, and indoles, as well as with electron-deficient heterocycles and benzene derivatives. The control experiments confirmed the intermediacy of an *S*-acylthiosalicyl-amide.[42,47] Because Cu(I) was oxidized under the aerobic reaction conditions used, $CuI_2(NMI)_4$ was applied as the aerobic reoxidation catalyst. The simple-to-run catalytic reactions provide practical and economical procedures for the acylative construction of a C–N bond from carboxylic acids and amines.

2.2 Cross-coupling with organotin and -zinc reagents

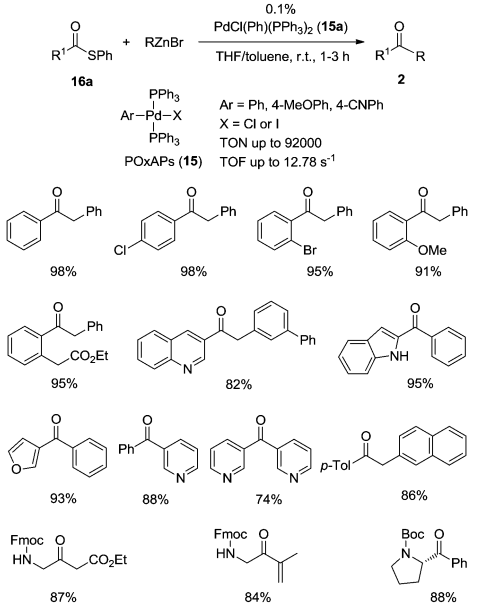
Other organometallic reagents can also be applied in Liebeskind–Srogl cross-coupling.[10–12] With $Pd(MeCN)_2Cl_2$ as the catalyst aryl thioesters were reacted with aryl, and primary or secondary alkylorganoindium compounds to yield the corresponding ketones.[48] In comparison to the cross-coupling of thioesters with boronic acids two advantages have been demonstrated: (a) no sacrificial copper(I) reagent was required to mediate the reaction; (b) in the case of alkyl transfer, no base was necessary to activate the organoindium reagents for the cross-coupling as is required for the coupling of thioesters with alkyl boron reagents.[49] In this regard, organotin and -zinc reagents exhibited much better applicability. With 20% Cu(I) catalyst CuMeSal (**8**) in DMF at 150 °C under microwave irradiation, the *O*-methyl oxime-functionalized thioesters efficiently reacted with 4-$MeOC_6H_4Sn^nBu_3$ to afford the corresponding diaryl ketone products in high yields.[43] In the presence of a stoichiometric amount of Cu(I) reagent **8** both the organotin reagent and boronic acid reacted well with thioesters. These results have suggested that the desulfitative cross-coupling reaction of thioesters with organotin reagents can catalytically take place under very harsh conditions, or occur under mild conditions in the presence of a stoichiometric amount of Cu(I) reagent. Thus, facile synthesis of α-heterosubstituted ketones was achieved under relatively mild conditions by copper-mediated cross-coupling of thioesters with functionalized organostannanes.[50] By means of 2 equiv. of CuOAc as the mediator in THF at 50 °C for 2 h both 4-methoxybenzothioate (**13a**) and 4-methoxyphenyl-acetothioate (**13b**) underwent efficient cross-coupling with Boc-, Cbz-, and acetyl-protected aminoethylstannanes to give the target ketone products **14** in good to excellent yields (66–97%) (Scheme 6). In the case of using *N*-Boc-α-aminoethylstannane the target ketones were obtained in 95–97% yield after heating at 80 °C for 24 h, and acetoxymethylstannane underwent the coupling reaction to afford the desired α-acetoxymethyl ketones (78–81%) in DMF at 80 °C for 24 h, while no reaction occurred with *tert*-butyldimethylsiloxymethylstannane even at elevated temperatures in DMF. Copper(I) diphenylphosphate (CuDPP) could act as a more effective copper mediator for the cross-coupling with acetylthiomethylstannane as compared to CuOAc, forming the



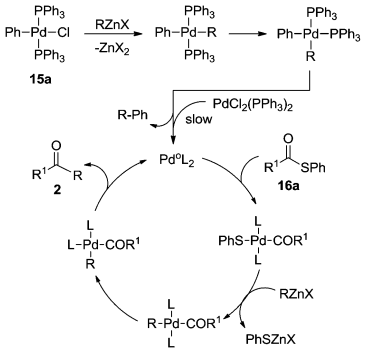
Scheme 6 C–S bond cleavage with organotin reagents.

products in 71–81% yields. Neither chloromethylstannane nor iodomethylstannane reacted with **13**, but fluoromethylstannane reacted well to produce the target products (72–78%). This methodology has been successfully applied for the conversion of carboxylic acids to 2-aminoimidazoles *via* thioesters. In a similar fashion, 2-aminothiazoles and -oxazoles were also prepared.

Organozinc reagents were used for C–C bond formation *via* palladium-catalyzed coupling with thioesters by Fukuyama *et al.* for the first time.[51] With 5–10% $PdCl_2(PPh_3)_2$ as the catalyst ethyl thioesters reacted with ethylzinc iodide as well as i-butyl-, benzyl-, phenyl-, β-phenethyl-, and vinylzinc iodides or benzyl-zinc bromide to give the corresponding ketone products (50–91%) in toluene or THF at room temperature. To execute the Fukuyama cross-coupling reactions of thioesters with relatively less reactive organozinc bromides, highly active palladium catalysts were applied. Thus, in the presence of a palladium complex catalyst, that is, POxAP (*i.e.*, post-oxidative-addition precatalyst) (**15**), aryl thioesters **16a** directly reacted with organozinc reagents RZnBr at room temperature, efficiently giving the ketone products (Scheme 7).[52] In this case, utilization of the precatalyst **15a** is crucial to render the catalytic reaction efficiently proceed even at 0.001% Pd loading, reaching a TON (turnover number) of up to 92 000 and a TOF



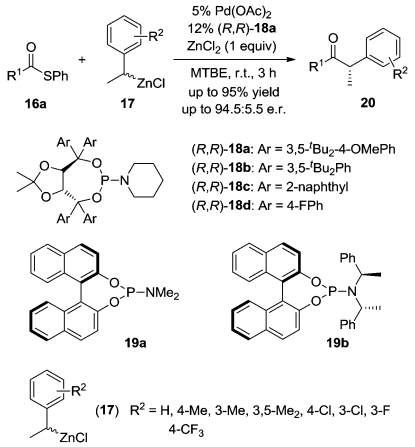
Scheme 7 C–S bond cleavage with organozinc reagents.



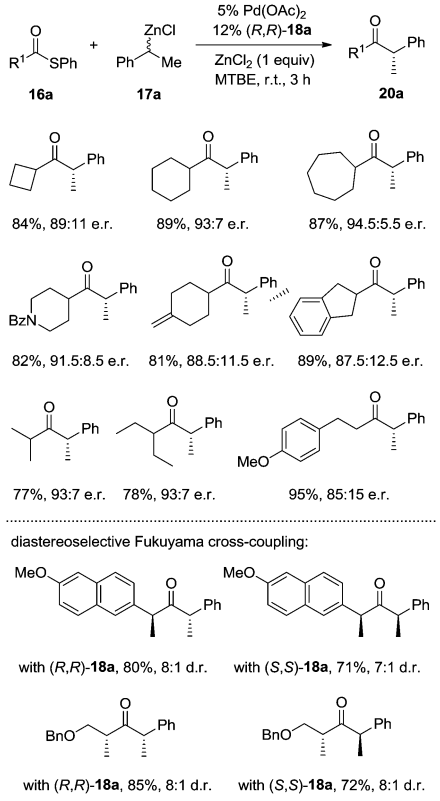
Scheme 8 The reaction mechanism with POxAP $PdCl(Ph)(PPh_3)_2$.

(turnover frequency) of up to 12.78 s^{-1}. The $PdX(Ar)(PPh_3)_2$ precatalysts respect the criteria of Pd-based OACs (oxidative addition complexes).[53] The well-known complex $PdCl(Ph)(PPh_3)_2$ has usually been cited in the mechanistic studies involving the first oxidative addition of Pd(0) and PhCl, but it has been seldom used as a catalyst. As shown in Scheme 8, in the presence of an organozinc reagent this complex follows a Negishi-like initiation step to be reduced to form Ph–R and Pd(0) species which subsequently initiate the Fukuyama cross-coupling. $PdCl_2(PPh_3)_2$ only exhibited poor catalytic activity under the same conditions due to its slow reduction to the catalytically active Pd(0) species. However, using equimolar amounts of $PdCl_2(PPh_3)_2$ and PhOH in the presence of organozinc reagents, $PdCl(Ph)(PPh_3)_2$ was generated *in situ* to promote the formation of the target products. Such a method was successfully applied in the synthesis of the key intermediate for the preparation of isoprekinamycin (IPK), remarkably enhancing the efficiency for the synthesis of such an intermediate from 16 steps (overall yield 3%) to 9 steps (overall yield 29%).

For the cross-coupling of unsymmetrical secondary alkyl fragments, the possibility of achieving control of the absolute stereochemistry greatly increases the utility and applicability of the synthetic methods. Although stereoconvergent, asymmetric cross-coupling of secondary sp^3-hybridized electrophiles has been well documented,[54] much less work has been contributed to the asymmetric coupling of sp^3-hybridized nuceophiles.[55] The enantioconvergent cross-coupling of racemic organometallic reagents still remains a challenge. Recently, enantioconvergent Fukuyama cross-coupling of racemic benzylic organozinc reagents (**17**) with thioesters **16a** has been realized by using TADDOL phosphoramidites (**18**) as the chiral ligands, among which ligand **18a** exhibited the highest enantioselectivity, but ligands of type **19** showed poor enantioselectivities (50 : 50 e.r. – 70 : 30 e.r.) (Scheme 9).[56] The Fukuyama cross-coupling proceeded through a RZnX species, but it is not effective for R_2Zn reagents. It has been known that alkylzinc halides engage in a Schlenk equilibrium with their dialkylzinc counterparts (R_2Zn). In the present case, addition of $ZnCl_2$ significantly improved both the yields and enantioselectivities of the target products, while use of LiCl, a common additive in Negishi cross-coupling, did not result in any change. MTBE and $Pd(OAc)_2$ were screened as the best solvent and catalyst, respectively. Under the optimal



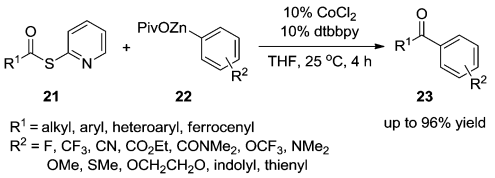
Scheme 9 Enantioconvergent Fukuyama cross-coupling.



Scheme 10 Synthesis of chiral acyclic α-disubstituted ketones.

conditions, up to 95% yields and 94.5 : 5.5 e.r. were achieved (Scheme 10). Variation of the ring sizes led to good yields and enantioselectivities. Benzoyl-protected piperidinyl and terminal alkenyl were tolerated. Acyclic thioester substrates also gave good conversions and enantiomeric ratios of up to 93 : 7. A drug development-relevant α-chiral thioester which was derived from the COX-inhibitor Naproxen was applied as the substrate to couple with the racemic organozinc reagent **17a** (R^2 = H), which gave the *anti* stereoisomer selectively (80% yield, 8 : 1 d.r.), while a 1 : 1 *anti*/*syn* mixture was obtained by using PCy_3 as the ligand. With the antipode of (*R*,*R*)-**18a**, the *syn* counterpart was cleanly accessed (71% yield, 7 : 1 d.r.). In a similar fashion, the configuration stability of two potentially labile benzylic stereogenic centers α to the carbonyl group was also established. This protocol provides a method for the construction of enantioenriched acyclic α-disubstituted carbonyl compounds.

A major drawback of the coupling reactions with organometallic reagents is the moderate chemoselectivity or the use of expensive catalysts. Recently, a simple base-metal-catalyzed cross-coupling reaction of 2-pyridyl thioesters (**21**) with organozinc pivalates (**22**) has been achieved to afford aryl ketones **23** (eqn (2)).[57] Cheap cobalt-catalyzed reactions have proven to be advantageous in many recent cases, and organozinc pivalates (RZnOPiv) were demonstrated as an attractive class of zinc organometallics due to their enhanced air- and moisture-stability and excellent compatibility with various transition-metal-catalyzed transformations. In the presence of 10% $CoCl_2$ as the precatalyst and 10% 4,4′-di-*tert*-butyl-2,2′-dipyridyl (dtbbpy) as the ligand, the reaction of 2-pyridyl thioesters and organozinc pivalates was conducted in THF at room temperature, giving the aryl ketone products in up to 96% yields. The protocol features wide substrate scopes with tolerance of functional groups such as electron-withdrawing F, CF_3, CN, CO_2Et, $CONMe_2$, OCF_3, and electron-donating NMe_2, OMe, SMe, and OCH_2CH_2O, *etc.* Heteroarylzinc pivalates could also be applied in the reaction. It is noteworthy that the present synthetic method was successfully employed for the preparation of α-chiral aryl ketones in 69–89% yields with >99% ee from the corresponding chiral thiopyridyl esters.



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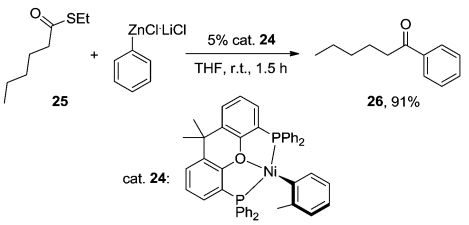
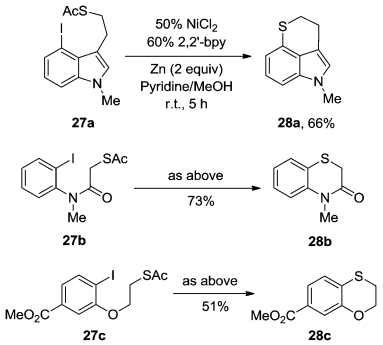


(3)

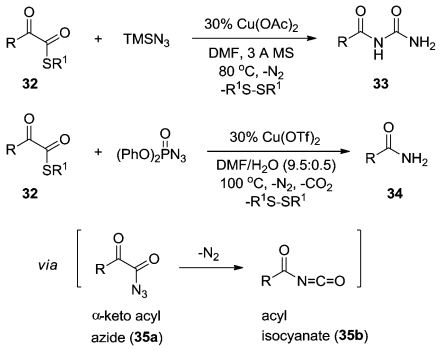
In the presence of a Ni(II)–Xantphos complex catalyst (**24**) a Fukuyama reaction occurred between thioester **25** and ArZnCl·LiCl in THF at room temperature (eqn (3)).[58] Thus, arylketone **26** was obtained in 91% yield *via* acyl radical intermediates, which were previously accessible from thioesters only by neutral photo- and thermolysis as well as reductive electrolysis and in a catalytic manner by photoredox catalysis.

2.3 Cross-coupling with other reagents

Thioesters can not only undergo Liebeskind–Srogl cross-coupling reactions with organoboron, -indium, -tin, and -zinc reagents, but they can also be applied in diverse cross-coupling transformations with other reagents through catalytic C–S bond



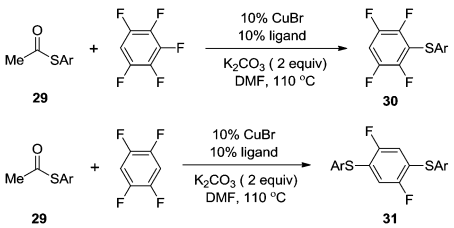
Scheme 11 C–S cross-coupling with thioacetates.



Scheme 13 Cross-coupling of α-keto thioesters with azides.

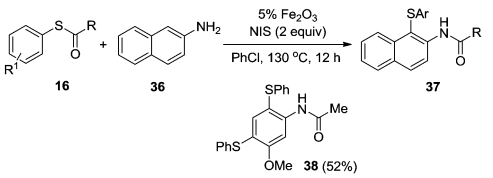
cleavage under transition-metal catalysis. In this regard, intramolecular C–S cross-coupling was achieved with iodothioacetates by means of a $NiCl_2$/2,2′-bipyridine catalytic system, giving S-heterocyclic compounds **28** (Scheme 11).[59] The use of thioacetates (**27**) as the sulfur source to access thioethers through transition-metal-catalyzed C–S cleavage overcomes the drawbacks of thiols such as a foul smell and sensitivity of oxidation to disulfides. In the presence of a copper catalyst double *S*-arylation of potassium thioacetate (KSAc) was realized with dibenziodolium triflates to form unsymmetrical dibenzothiophenes.[60] Diaryl sulfides were synthesized by copper-catalyzed cross-coupling of aryl bromides or iodides with thioacetic acid (MeCOSH) in water.[61] A Cu(I)-catalyzed C–S and C–F bond cleavage procedure was developed to prepare biaryl sulfides **30** in up to 95% yields from aryl and benzyl thioacetates **29** (Scheme 12).[62] The regioselective C–S bond cleavage was accomplished by copper-catalyzed regioselective C–F substitution of the electron-deficient perfluoroarenes. Double arylthiolation also occurred to form compounds **31** by means of 1,2,4,5-tetrafluorobenzene. Due to its high efficiency, good chemo- and regioselectivity, and excellent functional group tolerance, this protocol offers a useful and operationally simple access to polyfluoroaryl thioethers.

With a Cu(II) catalyst α-keto thioesters **32** were reacted with azides to form *N*-acylureas **33** and amides **34** *via* C–C and C–S bond cleavages, respectively, upon variation of the reaction conditions (Scheme 13).[63] In the presence of 30% $Cu(OAc)_2$ catalyst the α-keto thioesters reacted with trimethylsilyl azide ($TMSN_3$) to afford **33** with retention of the thioester keto group. With $Cu(OTf)_2$ as the catalyst and in the presence of water, compounds **32** reacted with diphenyl phosphoryl azide to give primary amides **34** *via* removal of the thioester group.



Scheme 12 Cross-coupling with perfluoroarenes.

These reactions are proposed to proceed through Curtius rearrangement of the initially formed unstable α-keto acyl azide **35a** by C–N cross-coupling to generate an acyl isocyanate intermediate **35b**, which further reacts with an additional amount of azide or water, and then rearranges to give the corresponding products. Although these reactions do not belong to the Liebeskind–Srogl cross-coupling category, the copper catalysts facilitated the C–S bond cleavage to form the reactive intermediate **35** for further rearrangement/addition reactions.

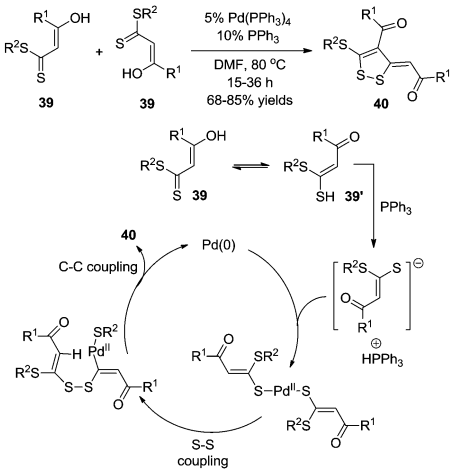


(4)

Under iron catalysis thioesters could act as the bifunctional reagents for 2-naphthylamine sulfuracylation (eqn (4)).[64] With Fe_2O_3 as the catalyst in the presence of *N*-iodosuccimide (NIS), 2-naphthylamines (**36**) reacted with thioesters **16** to form the target products **37** in moderate to good yields. Methoxy-substituted anilines were also applied in this reaction, and in the case of using 3-methoxyaniline the corresponding disulfuracylation product **38** was obtained in 52% yield.

Through double C–S activation α-enolic dithioesters (**39**) underwent self-coupling in the presence of a $Pd(PPh_3)_4$ catalyst and PPh_3 ligand to form 3,4,5-trisubstituted 1,2-dithioles **40** (Scheme 14).[65] Palladium(0) facilitated activation of both the *in situ* generated S–H and C–S bonds to achieve the cascade coupling, forming new S–S and C–C bonds through sequential S–S and C–C couplings. This protocol has demonstrated an efficient homo-coupling of α-enolic dithioesters for the synthesis of 3,4,5-trisubstituted 1,2-dithioles through tandem palladium-catalyzed consecutive S–S and C–C couplings in a single synthetic operation for the first time, providing a new strategy for the synthesis of densely functionalized drug-development-relevant 1,2-dithiole derivatives.

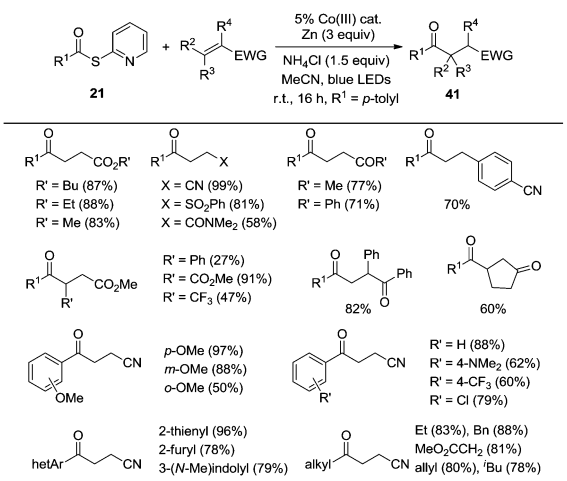
Although the addition reactions of thioesters to alkynes have been well documented, similar reactions of thioesters to alkenes have seldom been reported. Recently, light-driven, vitamin B_{12}-catalyzed addition of 2-*S*-pyridyl thioesters **21** to activated alkenes



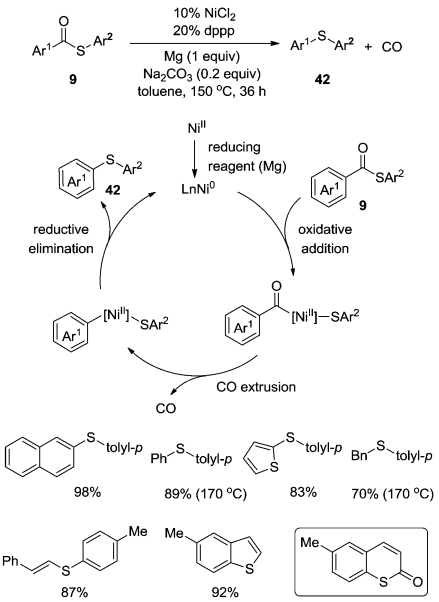
Scheme 14 Double C–S bond activation of dithioesters.

has been successfully achieved.[66] Vitamin B_{12}, that is, a natural Co complex, can serve as an environmentally benign and efficient catalyst for many reactions. In its Co(I) form it reacts with various electrophiles. It is expected that nucleophilic Co(I) complexes can react with acyl derivatives through the addition–elimination mechanism to give acyl-cobalt derivatives, providing a straightforward route to acyl radicals *via* subsequent photolytic cleavage of the Co–C bond. In such a manner, the replacement of commonly used acyl chlorides with their reduction-stable surrogates such as thioesters can be reached. Thus, in the presence of a catalytic amount of heptamethyl cobyrinate, a vitamin B_{12} derivative (porphyrinoid-type Co(III) complex) and 2-*S*-pyridyl thioesters (**21**) were added to activated (electron-deficient) alkenes *via* a radical mechanism (Table 1). Such a porphyrinoid-type Co(III) complex exhibited excellent catalytic efficiency presumably due to its capability to stabilize the acyl radicals *via* a persistent radical effect. It is noteworthy that zinc metal is required to reduce the Co(III) precursor complex to the catalytically active Co(I) species during the reaction. The remarkable electronic and steric effects were observed from the (hetero)aryl moieties in the aryl and heteroaryl thioester substrates, whereas the alkyl thioesters efficiently reacted to give the target products in good to excellent yields. The present method features broad substrate scopes, good functional group tolerance, and mild reaction conditions.

Table 1 Photocatalytic addition of thioesters to alkenes



Pt(0)-Catalyzed decarbonylative carbothiolation of thioesters with alkynes was documented through the decarbonylative C–S addition to an alkynyl functionality,[67,68] but decarbonylative self-coupling of thioesters has not yet been paid much attention. Very recently, it was found that thioesters could undergo decarbonylative thioetherification in the absence of a coupling partner under nickel catalysis (Scheme 15).[69] A reducing reagent such as Mg metal was required to promote the *in situ* generation of the catalytically active nickel(0) species, which rendered the C–S bond cleavage and decarbonylation cascade proceed smoothly. In this manner, diaryl, heteroaryl aryl, vinyl aryl, and alkyl aryl thioethers were synthesized in good to excellent yields (70–98%). It is noteworthy that 5-methylbenzothiophene was also efficiently accessed from the corresponding cyclic thioester. This synthetic method features an intramolecular reaction pathway involving double C–S bond cleavages, and avoids use of toxic and stinking thiophenols or thiols. The protocol may find applications in organic synthesis, retrosynthesis, and late-stage modifications. The decarbonylative thioetherification could also be applied in the cross-coupling reactions of esters and amides with thiophenols or aliphatic mercaptans under the same conditions, forming biaryl or aryl alkyl thioethers. A similar catalytic system using a Ni(dppp)Cl_2 complex (dppp = 1,3-bis-(diphenylphosphino)-propane) as the catalyst was developed for the same purpose with a much broader substrate scope.[70] With palladium and Ni(0) complexes bearing bulky monophosphine ligands such as P(*o*-tolyl)$_3$, BrettPhos, and PAd_2Bn (Ad = adamantyl) as the catalysts, decarbonylative thioetherification of thioesters was also achieved in toluene or *p*-xylene at 130–150 °C, affording diverse thioethers in moderate to excellent yields.[71]

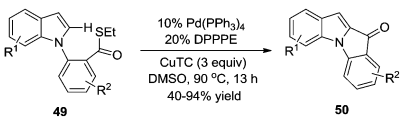


Scheme 15 Nickel-catalyzed decarbonylative self-coupling.

The combination of $Pd[P(o\text{-tolyl})_3]_2$ and PAd_2Bn, or $Ni(cod)_2$ and PCy_3 acted as the most efficient catalyst under the stated conditions. This method was successfully employed for the functionalization of the carboxylic acid-containing drug probenecid.

Using $Ni(cod)_2/PPh_3$ as the catalyst in toluene at 150 °C *S*-aryl 2-oxo-2-arylethanethioates, that is, α-ketothioesters **43**, underwent mono-decarbonylation to form the corresponding thioesters of type **9**, and diaryl thioethers **42** were generated from the double decarbonylation of the same substrates or from the monothioester intermediates **9** (Table 2).[72] By switching the ligands the reaction pathways were altered. Ligand screening revealed that PPh_3 and IPr^{Me}·HCl (IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene) worked as the most effective ligands for the mono- and double decarbonylation of the α-ketothioesters, respectively. A range of functional groups were tolerated, including methyl, methoxy, *tert*-butyl, isopropyl, fluoro, chloro, bromo, and ester groups. Under the optimal conditions, the target products thioesters **9** and diaryl thioethers **42** were obtained in 63–87% and 57–77% yields, respectively. In comparison to the known methods for C–S bond formation the present protocol has demonstrated the advantages of high atom efficiency, synthetic flexibility, and use of inexpensive nickel catalysts, providing an alternative route to thioesters and thioethers. It is noteworthy that ruthenium(II)-catalyzed intramolecular decarboxylative C–S cross-coupling of carbonothioates was also achieved for the synthesis of aryl allyl thioethers.[73]

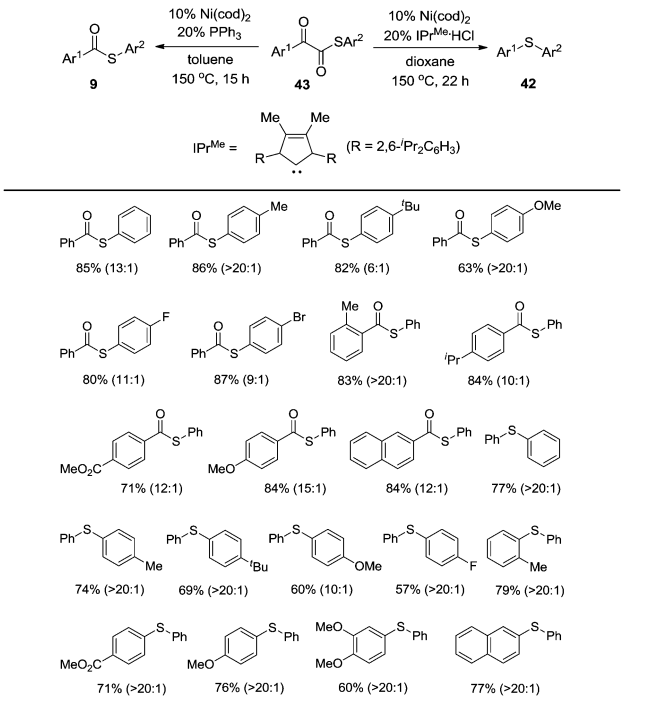
C–H functionalization has recently become a promising method for direct construction of C–C and C–heteroatom bonds.[74,75] In this area, intramolecular C–S/C–H cross-coupling was reported to construct S-heterocycles and carbocycles by means of thioesters through transition-metal-catalyzed C–S bond cleavage. A combination of $Pd(OAc)_2$ and P^tBu_3·HBF_4 was applied for the intramolecular C–S/C–H cross-coupling of aryl-functionalized thioacetates **44** in the presence of Ag_2CO_3, affording S-heterocyclic compounds **45** and **46**, respectively (Scheme 16).[76] For the synthesis of the five-membered S-heterocycles water was found to promote formation of the target products. The electron-withdrawing substituents such as CF_3, F, and NO_2, a bulky group such as phenyl on the aryl backbone of **44**, or a spiro alkyl group obviously diminished the reaction efficiency (32–61% yields), while dibenzothiophene derivatives were formed in good to excellent yields (79–90%). The six-membered S-heterocycles were efficiently obtained in up to 90% yields, and the electron-withdrawing substituents or sterically hindered 2-methoxy on the aryl backbone of **44** deteriorated the reaction. A palladium-catalyzed, thioester sulfur-assisted arene sp^2 C–H activation/C–S cleavage mechanism was proposed to depict the reaction pathway, in which water is involved in the reductive elimination step, and Ag_2CO_3 acts as an oxidant to regenerate the catalytically active Pd(II) species *in situ* from Pd(0).

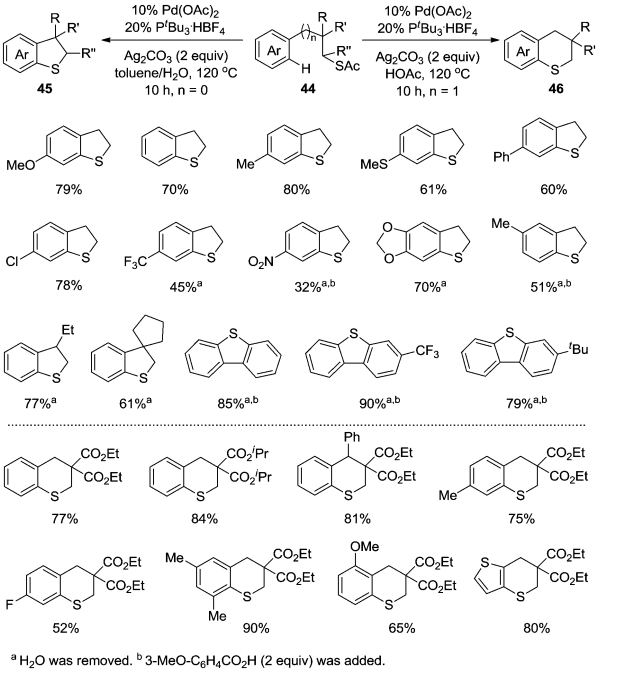


(5)

Intramolecular olefin hydroacylation of unsaturated aldehydes has been well studied, but access of cycloalkanones through the analogous coupling reaction of carboxylic acid derivatives and alkenes has been paid less attention.[77] Under palladium catalysis, δ,ε-unsaturated-α-phenyl acid chloride did not undergo intramolecular cyclization to give the desired cyclic ketone product. However, the corresponding δ,ε-unsaturated thioester reacted to

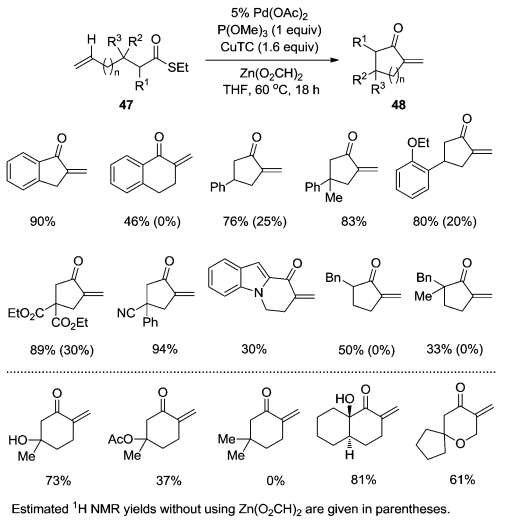
Table 2 Ligand-enabled decarbonylations of α-ketothioesters





[a] H_2O was removed. [b] 3-MeO-$C_6H_4CO_2H$ (2 equiv) was added.

Scheme 16 Palladium-catalyzed C–S/C–H cross-coupling.



Scheme 17 Palladium-catalyzed desulfitative C–H cross-coupling.

afford the target product through desulfitative C–H/C–S cross-coupling (Scheme 17).[78] A combination of $Pd(OAc)_2$/CuTC, $P(OMe)_3$ ligand, and $Zn(O_2CH)_2$ rendered the intramolecular desulfitative cross-coupling proceed smoothly. A variety of thioesters **47** were applied to illustrate the substrate scope and the method generality, affording five- and six-membered carbocycles **48** in moderate to excellent yields. The critical role of zinc formate in this transformation is evident, and the reaction could not occur or formed the product only in a poor yield in the absence of $Zn(O_2CH)_2$. Functional groups such as ether, ester, and cyano are tolerated. Competitive decarbonylation and β-hydride elimination occurred to diminish the catalyst turnover. Internal alkenylthioesters did not undergo the same type of reaction. It is proposed that the acyl-Pd intermediates should be rapidly intercepted by the pendant nucleophiles in the thioester substrates. Under the optimal conditions, the target six-membered cyclohexanone products were obtained (37–81%). The *gem*-dimethyl thioester gave no detectable amount of the desired product. A fused bicyclic structure was also constructed (61%). These results are consistent with a role for internal coordination of the acyl-Pd intermediates and provide a practical solution to expand the substrate scope of this method. It is noteworthy that intramolecular desulfitative heteroaryl C–H/C–S cross-coupling could also occur in an indolyl-based aryl thioester (**49**) under palladium catalysis (eqn (5)).[79] The combination of the Pd(0) catalyst and 1,5-bis(diphenylphosphino)pentane (DPPPE) as the ligand worked most efficiently, affording the target products **50** in moderate to high yields.

3. C–S bond cleavage in thioethers

During a complicated HDS process organosulfur compounds, such as thiophene derivatives, are usually reduced to thioethers, and then from thioethers to mercaptans, and from mercaptans to arenes and/or alkanes under the harsh reductive conditions.[1] To improve the efficiency of a HDS process and understand the desulfurization mechanism, it is necessary to probe into the activation/cleavage modes of C–S bonds in these organosulfur compounds.

For the relevant C–S bond cleavage in thiols, relatively harsh reductive conditions or activated cross-coupling reagents should be employed by means of Pt(II), Pt(III), and Pd(II) catalysts/H_2 (60 atm) or Co(0) catalyst/CO (60 atm).[80,81] Thiols can also be used as a sulfur source in transition-metal-catalyzed desulfitative cross-couplings. By means of $CuSO_4{\cdot}5H_2O$ as the catalyst in the presence of an excessive amount of KOH base, aryl halides were reacted with aliphatic dithiols to efficiently form aryl thiols in up to 97% yields.[82] The reaction of *p*-tolyl iodide with 1,2-ethanedithiol or 1,4-butanedithiol gave *p*-tolyl thiol (**51a**) as the only product, while its reaction with 1,3-propanedithiol, 1,5-pentanedithiol, 1,6-hexanedithiol, and 2-mercaptoethanol formed aryl alkyl thioethers of type **52** as the major products. Under the optimal conditions a variety of aryl thiols **51** were prepared in good to high yields (Table 3). The aryl iodides, bromides, and chlorides could be used as the substrates with a good tolerance of functional groups such as alkyl, aryl, amino, hydroxy, methoxy, acetyl, formyl, ester, amido, cyano, carboxylic acid, bromo, chloro, trifluoromethyl, and nitro. The heteroaryl thiols were aslo obtained in 84–94% yields.

The desulfitative cross-coupling of heteroaryl thiols was developed by means of a Pd/Cu catalyst system. In the presence of 5% $Pd(PPh_3)_2Cl_2$, CuTC (1 equiv.), CuI (0.5 equiv.), 20% dppp,

Table 3 Thiolation of aryl halides with 1,2-ethanedithiol

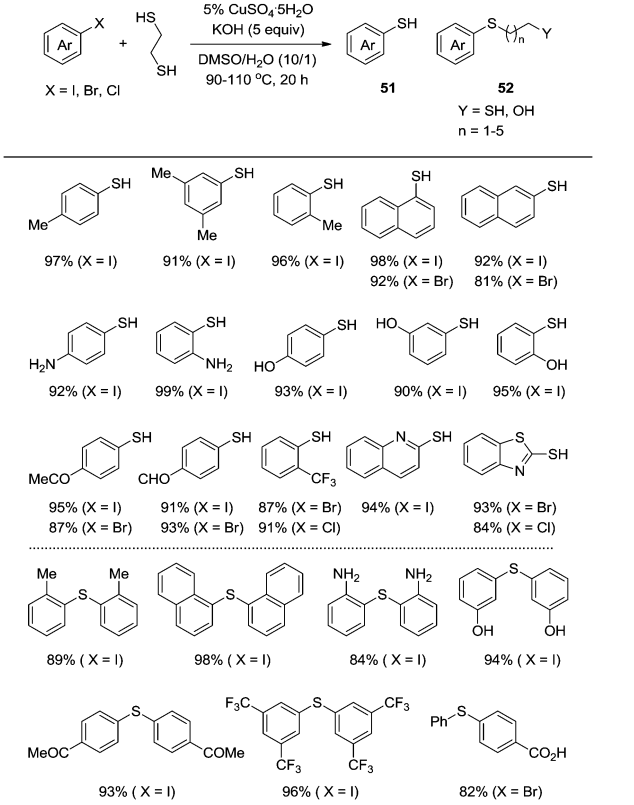
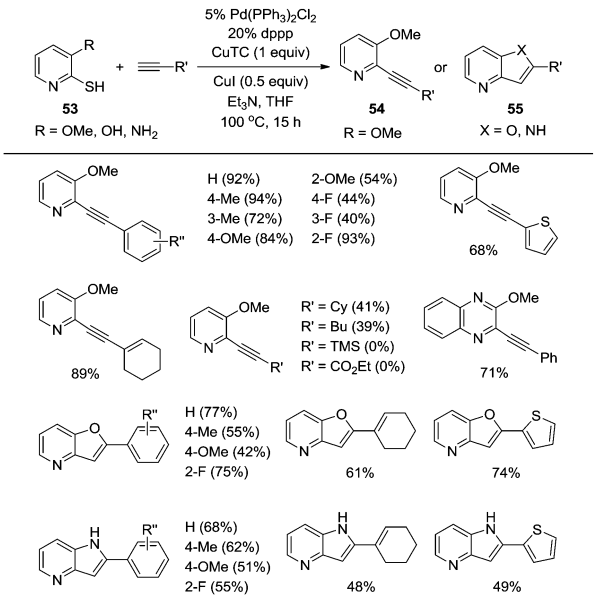


Table 4 Desulfitative C–H/C–S cross-coupling



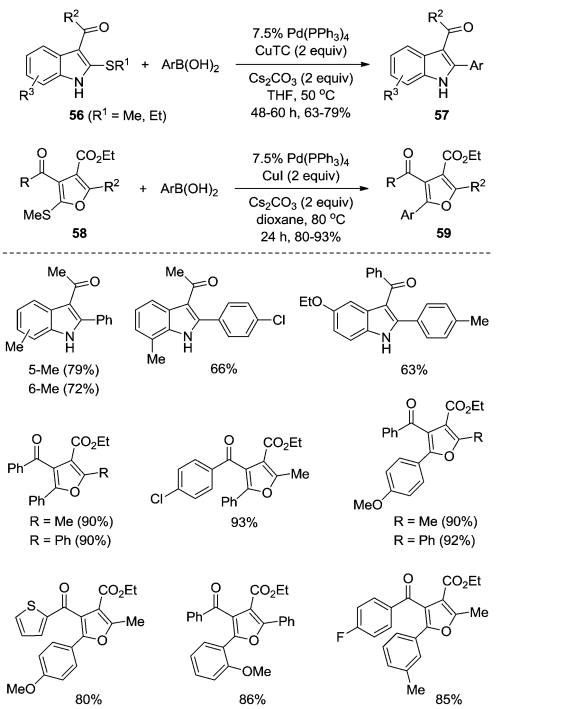
and an excessive amount of Et_3N, 3-methoxypyridin-2-thiones (**53**) reacted with terminal alkynes in THF at 100 °C to give the 2-alkynylated products **54** in 39–94% yields (Table 4).[83] It is noteworthy that the presence of the weakly coordinating 3-methoxy group is crucial for the cross-coupling, and the reaction could not occur in the cases of using 2-(1*H*)-mercaptopyridine, 3-Ph, 3-F, 3-NO_2, 3-CO_2Me, or 4-MeO-bearing 2-mercaptopyridines, revealing a remarkable *ortho*-group assistance effect. Trialkylsilyl or ester-functionalized alkynes did not react with **53** under the same conditions. When the substrates bear a free OH or NH_2 group, heteroannulation reactions occurred to form the corresponding heteroarenes **55** in moderate to good yields (42–77%). The present method offers a route to 2-alkynylated pyridines, furo[3,2-*b*]pyridine and 1*H*-pyrrolo[3,2-*b*]pyridine derivatives. With 2% [Ni(xantphos)(*o*-tolyl)Cl] (**24**) as the catalyst, desulfitative Kumada cross-coupling of thiophenols with Grignard reagents ArMgBr·LiCl proceeded smoothly in THF at 60 °C to produce the corresponding biaryls in moderate to excellent yields (39–98%).[84] It is noteworthy that in the presence of the same Ni(II) complex catalyst (**24**) a Fukuyama–Migita reaction could occur between thioester **25** and ArZnCl·LiCl in THF at room temperature, giving a keto-thioether product in 56% yield from the atom-economical tandem Fukuyama–Migita reaction, which formally corresponds to the insertion of a 1,4-phenylene spacer into the thioester C–S bond.

As a matter of fact, the desulfitative cross-couplings of thiols are usually encountered with limited substrate scopes, complicated additives as well as the stinking smell, which limit their applications as coupling partners. Fortunately, thioethers have recently been demonstrated to have versatile applications as coupling partners *via* C–S bond cleavage in transition-metal-catalyzed cross-coupling reactions for C–C and C–heteroatom bond formation.[20]

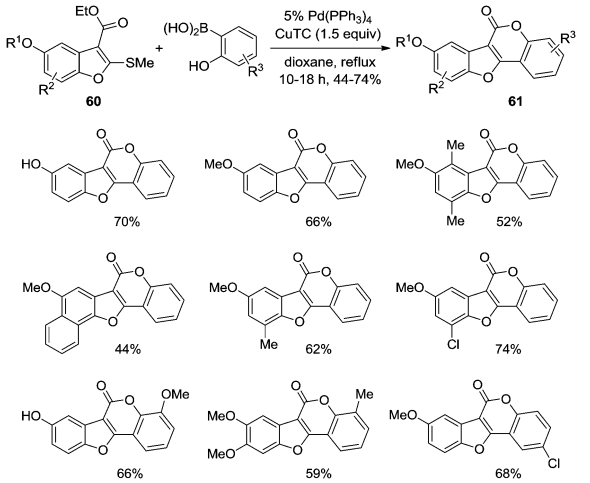
3.1 Heteroarene C(sp^2)–S bond cleavage

The cross-coupling of heteroaromatics, although a process of great synthetic potential, has not been well applied in organic synthesis due to the limited availability of the corresponding heteroaromatic halides. In this regard, transition-metal-catalyzed C–S cross-coupling seems to fill this void. Recently, heteroaryl and aryl-based C–S bond cleavage was achieved for carbon–carbon bond formation. The typical Liebeskind–Srogl cross-coupling conditions using [Pd]/Cu(I) were well applied for the desulfitative arylation of heteroaryl thioethers with aryl boronic acids.[85–87] Such a method was also applied as an efficient protocol for the functionalization of indole and furan derivatives.

With the $Pd(PPh_3)_4$/CuTC/Cs_2CO_3 catalytic system, the reaction of 2-alkylthio-3-acylindoles (**56**) and arylboronic acids proceeded smoothly in THF at 50 °C to afford 2-arylated indoles **57**.[88] Using CuI instead of CuTC the cross-coupling of 2-methylthio-substituted furans (**58**) with arylboronic acids efficiently formed the corresponding arylated furans **59**[89] (Scheme 18). In the case of using hydroxy-functionalized aryl boronic acids, a palladium-catalyzed, copper(I)-mediated heteroaryl thioether–aryl boronic acid cross-coupling/transesterification cascade proceeded to give tetracyclic coumestan derivatives **61**.[90] A variety of 2-methylthio-3-ester-benzofurans (**60**) were reacted with *o*-hydroxyaryl boronic acids in the presence of 5% $Pd(PPh_3)_4$ and CuTC (1.5 equiv.) in refluxing dioxane, giving the target products **61** in moderate to good yields (44–74%) (Scheme 19). Functional groups such as hydroxy, methoxy, bromo, and chloro were tolerated. The reaction is proposed to occur through

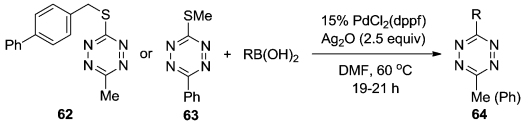


Scheme 18 Functionalization of indoles and furans *via* C–S bond cleavage.



Scheme 19 Desulfitative cross-coupling/transesterification cascade.

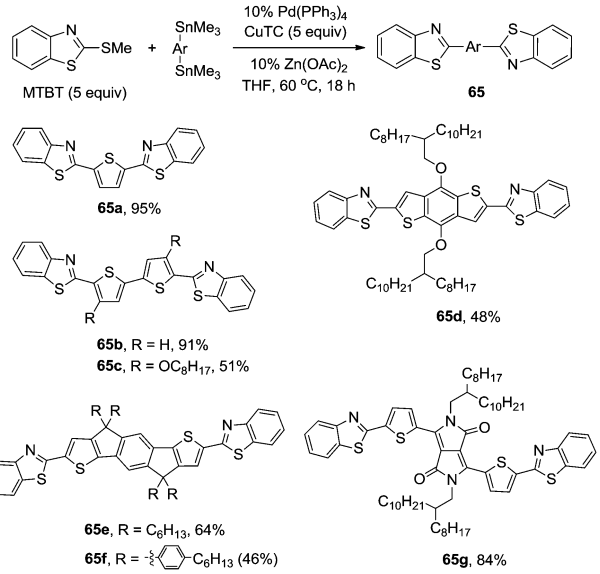
Pd-catalyzed C–S bond activation under Liebeskind cross-coupling conditions and sequential intramolecular transesterification cascade. This research provides a useful protocol for the construction of coumestan skeleton from readily available starting materials.



(6)

Installation of minimal tetrazines was realized through copper-catalyzed, silver-mediated Liebeskind–Srogl cross-coupling with arylboronic acids (eqn (6)).[91] With 15% $PdCl_2$(dppf) as the catalyst, Ag_2O instead of CuTC as the mediator, 3-((*p*-biphenyl-4-ylmethyl)thio)-6-methyltetrazine (**62**) was coupled with arylboronic acids, efficiently introducing minimal, linker-free tetrazine functionality under mild conditions. The analog of **62**, that is, 3-methylthio-6-phenyltetrazine (**63**) could also be used as the effective coupling partner. Use of the Ag_2O mediator resulted in a wide range of aryl and heteroaryl boronic acids as well as styryl boronic acid, affording the target products **64** in moderate to high yields, and provides an improved access to a fluorogenic tetrazine BODIPY conjugate.

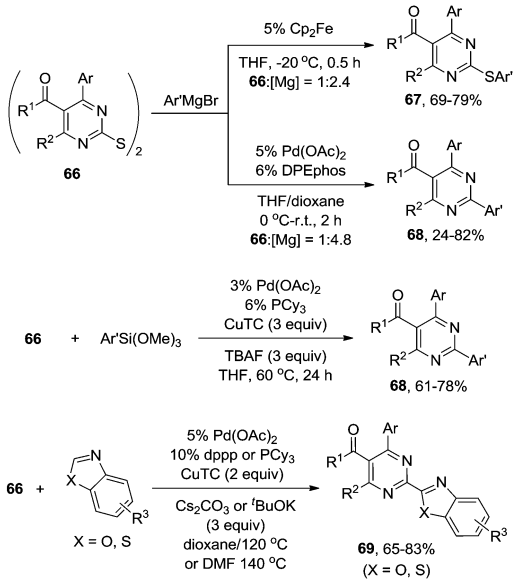
Heteroaromatic thioethers can also undergo desulfitative cross-coupling with organotin reagents under palladium catalysis in the presence of a Cu(I) reagent. Benzothiazole derivatives are important organic waste and originate from the benzothiazoles used in large volumes as vulcanization accelerators,[92] among which 2-(methylthio)benzo[*b*]thiazole (MTBT) exhibits acute and chronic toxicity. Different oxidation methods have been applied to remove this organic waste. Considering MTBT as a heteroaryl thioether the known desulfitative cross-coupling strategy was employed to convert this waste molecule to useful materials such as organic semiconductor compounds. Thus, in the presence of 10% $Pd(PPh_3)_4$ catalyst, CuTC mediator (5 equiv.), and 10% $Zn(OAc)_2$ as the additive, 2,5-bis(trimethylstannyl)-thiophene was reacted with an excessive amount of MTBT (5 equiv.) in THF at 60 °C for 18 h to give the target product, that is, 2,5-di-heteroarylated



Scheme 20 Desulfitative conversion of MTBT to organic semiconductor compounds.

thiophene **65a**, in 95% yield.[93] Under the optimal conditions, different aromatic moieties were employed to react with MTBT, affording the organic semiconductor compounds **65b–65g** in 46–91% yields (Scheme 20). The bithiophene-based substrate gave the product (**65b**) in 91% yield, whereas the analogous alkoxy-functionalized substrate exhibited a much lower reactivity to form **65c** (51%). In a similar fashion, other organotin substrates could also react with MTBT to yield products **65d–65g** (46–84%). The side chains in the substrates obviously diminished the reaction efficiency due to the resultant steric hindrance as well as the possible electronic effect. It is noteworthy that the diketopyrrolopyrrole moiety afforded the product (**65g**) in 84% yield, while the reaction of the corresponding Bpin-ester of the diketopyrrolopyrrole with MTBT produced **65g** only in 40% yield. The applications of these organic semiconductor compounds for organic field effect transistors (OFETs) and cell imaging have demonstrated the potential to convert an organic waste into useful materials, and extended the new utilization of the widely available heteroaromatic thioethers.

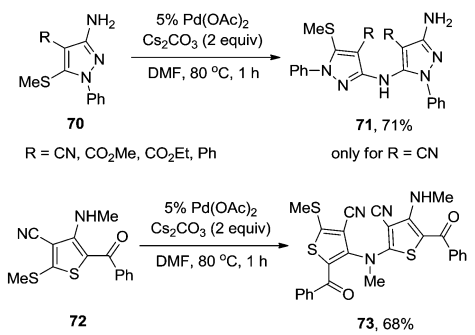
Chemo-controlled cross-coupling of di(heteroaryl) disulfides **66** with Grignard reagents was developed for the construction of new C–S and C–C bonds by means of ferrocene and palladium acetate as the catalysts, respectively[94] (Scheme 21). Ferrocene favored formation of the C–S coupled products **67** at low temperature (−20 °C), while the C–C bond coupling to produce **68** was favored in the presence of a $Pd(OAc)_2$/DPEphos catalyst and a large excess of the Grignard reagents (4.8 equiv.). It is noteworthy that the protocol is suitable for the construction of a variety of molecules with pyrimidine and pyridine scaffolds. A Pd catalyst/Cu(I) mediator combination was applied to functionalize the same di(heteroaryl)disulfides with aryl tri(methoxy)silanes through Hiyama-type cross-coupling[95] or by means of the C–S/C–H cross-coupling strategy[96] (Scheme 21). In the former case, CuTC was found to be the efficient mediator, and PCy_3 acted as the optimal ligand. TBAF was crucial for the



Scheme 21 Chemo-controlled C–S bond cleavage with Grignard reagents.

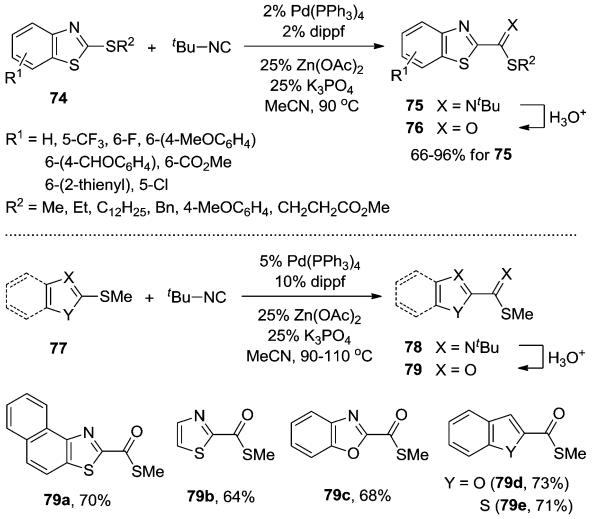
desulfitative cross-coupling reaction to proceed smoothly under relatively mild conditions, and the target products could be formed only in $<5\%$ yield in the absence of TBAF. Vinyl and alkyltri(methoxy)silanes could not react under the same conditions. In the latter case, prefunctionalization of oxazoles and thiazoles was not necessary and they were directly used in the reaction. Cs_2CO_3 base was crucial for the transformations using oxazoles, while strong KO^{t}Bu base and harsh conditions were required in the case of using the thiazole substrates. It should be noted that activated heteroaryl thioethers can also undergo desulfitative reactions with Grignard reagents in the absence of a transition-metal catalyst.[97]

Other reagents were also used as the coupling partners to react with heteroaryl thioethers under transition-metal catalysis. Under palladium catalysis in the presence of the Cs_2CO_3 base, 3-amino-functionalized 5-methylthiopyrazole (**70**) and 5-methylthiothiophene (**72**) underwent desulfitative homo-coupling in DMF at 80 °C, yielding the corresponding bis(heteroaryl)amines **71** and **73** (68–71%), respectively.[98] The homo-coupling only occurred for the heteroaryl thioethers bearing a directing group such as CN and/or carbonyl *ortho* to the amino group on the heteroaryl ring (Scheme 22).

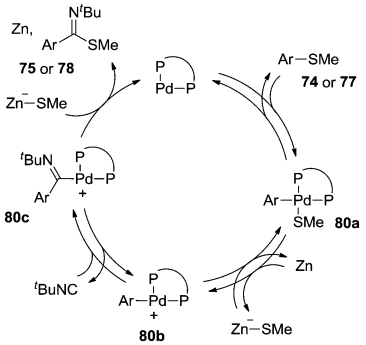


Scheme 22 Desulfitative amination *via* homo-coupling.

Insertion of a specific functional group into a C–S bond can be used to cleave less reactive or unactivated C–S bonds. Using $Pd(PPh_3)_4$ as the catalyst in the presence of ligand 1,1′-bis-(diisopropylphosphino)ferrocene (dippf), additive $Zn(OAc)_2$, and K_3PO_4 base, insertion of isocyanide into the C–S bond of heteroaryl sulfides **74** was achieved to give the thioimidate products **75** which were easily hydrolyzed to the corresponding thioesters **76** (66–96%) after acidic work-up (Scheme 23).[99] The reaction tolerated functional groups such as fluoro, chloro, methoxy, formyl, CF_3, ester, and thienyl. In a similar fashion by increasing the catalyst loading to 5% $Pd(PPh_3)_4$ and elevating the reaction temperature to 90–110 °C, the less reactive heteroaryl thioether substrates **77** were also efficiently transformed into thioesters **79** *via* initial formation of the thioimidate products **78** followed by acidic hydrolysis. The reaction mechanism is proposed as shown in Scheme 24. Initially, oxidative addition of heteroaryl sulfide **74** or **77** to dippf-ligated Pd(0) species generates arylpalladium thiolate intermediate **80a** which interacts with Lewis acid zinc salt $Zn(OAc)_2$ to form cationic complex species **80b**. Complex **80b** may be coordinated by *tert*-butyl isocyanide. Subsequent migratory insertion occurs to yield imidoyl palladium species **80c** which further reacts with the zinc thiolate species to give the target product **75** or **78** through reductive elimination,



Scheme 23 Isocyanide insertion with heteroaryl sulfides.

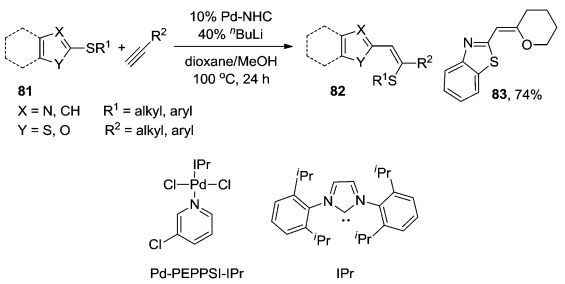


Scheme 24 Isocyanide insertion into a heteroaryl C–S bond.

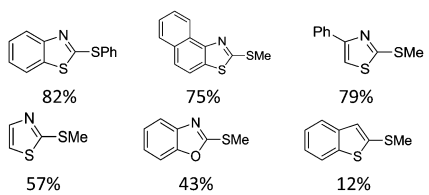
and regenerates the catalytically active Pd(0) species, finishing a catalytic cycle. This insertion reaction strategy is useful because the starting heteroaryl thioethers are readily available or prepared by the conventional methods. Pd(II)-Catalyzed, cyano-directed insertion of isocyanide to the heteroarene C(sp^2)–SMe bond of thiophene derivatives was found to effectively recycle the SMe activating group into the thioimidate products.[100]

Transition-metal-catalyzed alkyne insertion into a heteroaryl C–S bond was also achieved. In this regard, a Pd–NHC complex catalyst, that is, Pd–PEPPSI–IPr ([1,3-bis(2,6-diisopropylphenyl)-imidazol-2-ylidene](3-chloropyridine)-pallaium(II) dichloride),[101] was used to catalyze the carbothiolation of terminal alkynes with azoyl sulfides (**81**) in dioxane/methanol at 100 °C for 24 h, forming the corresponding vinyl thioether products **82** (Table 5).[102] The conventional palladium/phosphine catalyst systems ($Pd(PPh_3)_4$, $Pd(OAc)_2/PPh_3$, and $Pd(dba)_2/PCy_3$) were much less efficient than the present Pd–NHC catalyst. A small amount of water was found to promote the reaction, which is presumably attributed to the formation of LiOH from ^{n}BuLi and water *in situ*. LiOH thus acted as an efficient reductant of a Pd(II) precursor. This assumption was strongly supported by the reaction with $LiOH{\cdot}H_2O$. Methanol was screened as the most effective additive. The reaction could also be complete within 40 minutes under microwave irradiation at 160 °C. Phenylacetylene and its arylacetylene analogs bearing an electron-donating group reacted well with MTBT to form the target products in 81–93% yields, while the electron-deficient CF_3-fucntionalized and bulky arylacetylenes reacted less efficiently. Alkylacetylenes were applicable to the reaction, producing the products in 67–70% yields. The steric hindrance of *tert*-butyl slightly affected the reaction efficiency. 3,3-Diethoxy-1-propyne reacted well with MTBT to afford the product in 75% yield. When diynes were used as the substrates, the carbothiolation selectively occurred at one of the two alkyne functionalities to give the 1 : 1 adducts. Unexpectedly, the reaction of 5-hexyn-1-ol reacted with MTBT gave the carboetherification product **83** (74%), suggesting that the resultant carbothiolation product of type **82** could further undergo palladium-catalyzed carboetherification. Exploration of the heteroaryl thioether scope revealed that MTBT and 2-benzothiazolyl phenyl sulfide are the most suitable herteroaryl thioethers for the alkyne insertion reaction. Internal akynes diphenylacetylene and dimethyl acetylenedicarboxylate did not undergo the desired reaction. A reaction mechanism involving oxidative addition of a C–S bond to the Pd(0) species followed by regio- and stereoselective alkyne insertion into the C(heteroaryl)–Pd bond, and subsequent reductive elimination is proposed to generate the target product. The C(heteroaryl)–S bond cleavage occurs in preference to those of the C(methyl)–S and C(phenyl)–S bonds, resulting from a favorable coordination of the heteroatom(s) in the heteroaryl thioether substrate to the palladium center prior to oxidative addition.

Table 5 Alkyne insertion into a heteroaryl C–S bond



Entry	R^2 (R^1 = Me using MTBT)	Yield (%)
1	Ph	93
2	*p*-$MeOC_6H_4$	81
3	*p*-MeC_6H_4	91
4	*p*-$CF_3C_6H_4$	44
5	1-Naphthyl	34
6	*n*-Hexyl	67
7	^{n}Bu	70
8	^{t}Bu	60
9	$CH(OEt)_2$	75[a]
10	*p*-$(HC{\equiv}C)C_6H_4$	52
11	$HC{\equiv}C(CH_2)_3$	30
12	$HO(CH_2)_4$	74[b]

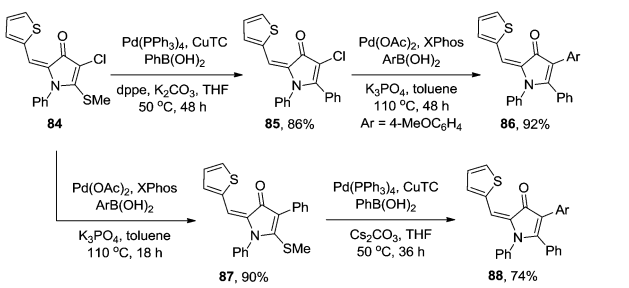


[a] Microwave irradiation at 160 °C for 40 min. [b] The reaction with 5-hexyn-1-ol formed **83**.

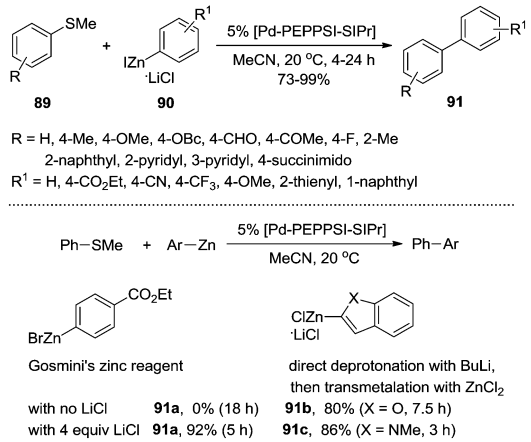
A tunable Suzuki/Liebeskind–Srogl cross-coupling method was recently documented.[103] By varying the palladium catalyst, ligand, base, solvent, and CuTC reagent, 5-methylthio-4-chloro-3-pyrrolone (**84**) was reacted with phenylboronic acid to form 5-phenyl-4-chloro-3-pyrrolone (**85**) in 86% yield by palladium-catalyzed C–S bond cleavage, and the subsequent Suzuki cross-coupling of the remaining C–Cl bond gave 4,5-diaryl-3-pyrrolones **86** (92%). Switching the reaction sequence altered the cleavage order of the C–S and C–Cl bonds in **84** (Scheme 25).

3.2 Arene C(sp^2)–S bond cleavage

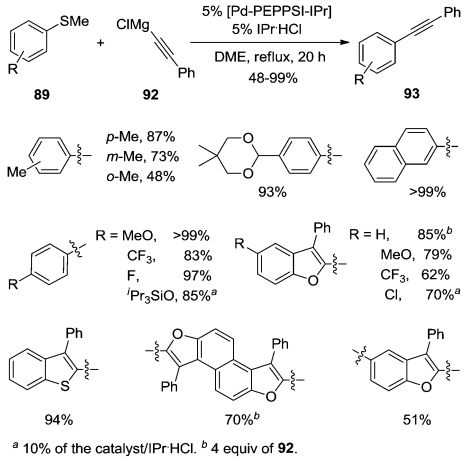
The C(sp^2)–S bonds in aryl thioethers (aryl sulfides) are less reactive than those in the corresponding heteroaryl thioethers. Organometallic reagents are usually employed to react with such unactivated organosulfur compounds. With arylzinc reagents as the coupling partners unactivated aryl thioethers **89** were transformed into biaryls **91** in the presence of a palladium–NHC catalyst under mild conditions (Scheme 26).[104] The cross-coupling of aryl alkyl thioethers **89** with ArZnI·LiCl (**90**)



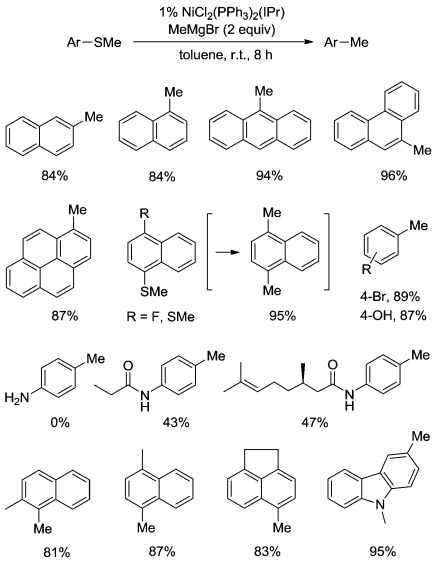
Scheme 25 Switchable C–S/C–Cl bond cleavages.



Scheme 26 Cross-coupling of aryl thioethers with organozinc reagents.



Scheme 27 Alkynylation of aryl thioethers.

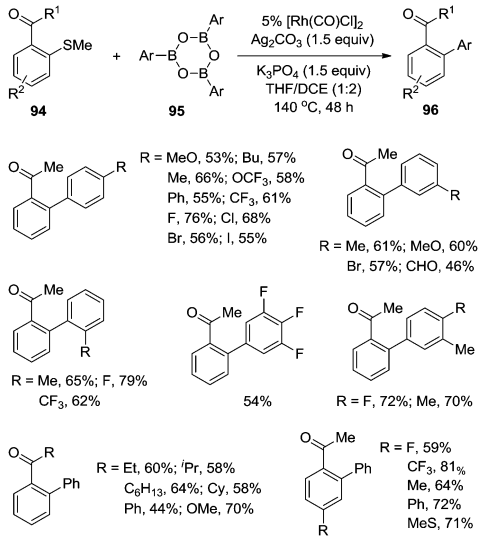


Scheme 28 Methylation of aryl thioethers.

proceeded smoothly, even at room temperature or below, with 5% [Pd–PEPPSI–SIPr] as the catalyst. The leaving sulfanyl moiety is not limited to a methylthio group. Odorless dodecylsulfanyl and phenylthio are good leaving groups (99% yield of **91a** in both cases). The presence of lithium chloride is crucial for the success of the arylation.[105] Without addition of LiCl or with the mere arylzinc reagent the cross-coupling reaction hardly occurred. Gosmini's arylzinc reagent prepared from ethyl 4-bromobenzoate and zinc powder in the presence of $CoBr_2$ did not undergo the coupling with thioanisole (**89a**) at all in the absence of lithium chloride. However, addition of LiCl accelerated the arylation with Gosmini's arylzinc reagent to form **91a** in 92% yield (Scheme 26). Deprotonation of benzofuran and *N*-methylindole by butyllithium followed by transmetalation with $ZnCl_2$ provided the corresponding heteroarylzinc chloride·lithium chloride, which efficiently underwent the cross-coupling with **89a** to give the target products **91b** (80%) and **91c** (86%), respectively. It has been demonstrated that the ArZnX compounds require either a high dielectric solvent or a low polarity solvent loaded with enough salt such as LiCl to increase the medium's ion-solubilizing ability to break down residual ArZnX aggregates.[105]

By means of the Pd–NHC precatalyst (Pd–PEPPSI–IPr)/IPr·HCl, thioethers **89** were alkynylated with phenylethynyl magnesium chloride (**92**) to afford the alkynylation products **93** in 48–99% yields (Scheme 27).[106] An excess of the Grignard reagent was required for the reaction and generation of the NHC ligand *in situ*. This protocol was successfully applied for the synthesis of benzofuran-based fluorescent molecules by taking advantage of characteristic organosulfur chemistry. In the presence of the simple Ni–NHC complex precatalyst $NiCl_2(PPh_3)_2$(IPr), methylation took place to give methyl-functionalized arene derivatives under mild conditions through C–S cleavage of diversely functionalized aryl thioethers by the methyl Grignard reagent (Scheme 28).[107] With MeMgBr as the coupling partner thioethers **89** reacted to give the target products in moderate to excellent yields (43–96%). Besides naphthalene groups, a methylthio substituent on a variety of aromatic rings including anthracene, phenanthrene, and pyrene could be applied in the reaction. Bromo, hydroxy, amide, and alkenyl were tolerated as the functional groups, while the amino group was not compatible with the reaction. As for the fluoro-substituted aryl thioether both defluorination and desulfurization occurred. The late-stage modification of a bioactive citronella derivative was realized by the desulfitative methylation of the C–S bond. It is noteworthy that other alkylzinc reagents could also be applied in the reaction, but in the cases of using EtMgBr, ^{i}PrMgBr, and $^{n}C_6H_{13}MgBr$, 2-naphthyl methylthioether was reduced to naphthalene or the reaction did not occur under the stated conditions. In order to make their reaction occur, the more catalytically active $Ni(cod)_2$/dcype (dcype = 1,2-bis(dicyclohexylphosphino)ethane) precatalyst was employed in toluene at 90 °C to give the target alkylated products in 61–92% yields. The present method provides a protocol for modification of diverse sulfur-containing molecules under mild conditions.

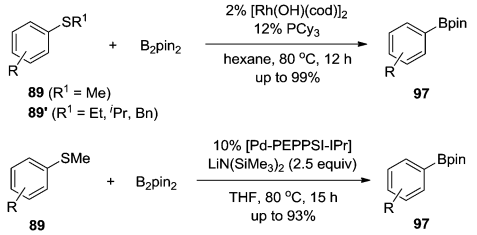
It has been well known that cross-couplings can be used to construct C–C bonds through the cleavage of unreactive bonds



Scheme 29 Rh(I)-Catalyzed cleavage of relatively unreactive C–S bonds.

with the directing group strategy in the presence of a transition-metal catalyst. Thus, by means of the relatively unreactive aryl methyl thioethers (**94**) as the electrophiles Rh(I)-catalyzed desulfitative cross-coupling with aryl boroxines (**95**) was achieved to give the corresponding functionalized biaryls **96** (Scheme 29).[108] The reaction was not sensitive to the electronic effects of the aryl boroxines. Sterically hindered boroxines did not diminish the reaction efficiency, resulting in the target products in 79% and 87% yields from the reactions of **94a** (R^1 = Me, R^2 = H) with 2-methylphenyl boroxine and 2-naphthylphenyl boroxine, respectively. Heteroaryl (2-benzofuryl, 2-thienyl, and 2-furyl) boroxines also effectively reacted with **94a** to form the desulfitative cross-coupling products (54–69%). A variety of aryl methyl thioethers bearing an *ortho*-COR^1 moiety as the directing group were applied in the reaction to produce the products (44–70%). The benzoyl group reduced the yield to 44%, while the methyl ester group also acted as an effective directing group to facilitate formation of the target product (70%). These results have demonstrated the construction of biaryls *via* rhodium-catalyzed C–C bond formation through unreactive aryl C–S bond cleavage by coupling with aryl boroxines. A combination of rhodium(I) precatalyst $[Rh(OH)(cod)]_2$ with K_3PO_4 was employed to catalyze the desulfitative cross-coupling of 3-thienyl thiosulfonate and 3-thienylboronic acid, affording di(3-thienyl)sulfide, which has been reported as the precursor of DTT (DTT = DL-dithiothreitol).[109]

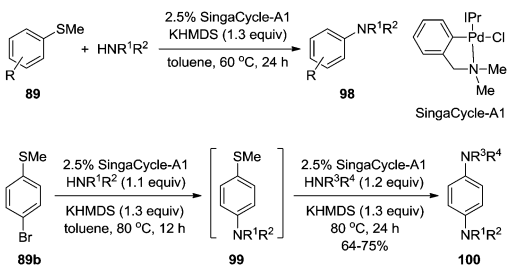
Transition-metal-catalyzed C–S cross-coupling can be applied for the construction of carbon–heteroatom bonds. In the presence of Rh(I) complex $[Rh(OH)(cod)]_2$ as the precatalyst the cross-coupling of thioethers **89** and their analogs **89′** with bis(pinacolato)diboron (B_2pin_2) proceeded smoothly to produce arylboronic acid pinacol esters **97** *via* arene C(sp^2)–S bond cleavage[110] (Scheme 30). In this case, a mixture of the precatalyst, ligand, and B_2pin_2 was stirred in hexane at 80 °C for 1 h, and then the thioether was added to initiate the cross-coupling reaction. Use of the PCy_3 ligand and nonpolar solvent is crucial



Scheme 30 Borylation *via* C–S bond cleavage.

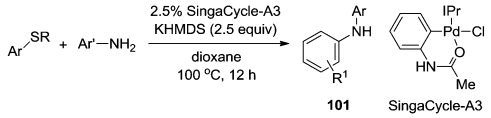
for the success of such a transformation. The Pd–PEPPSI–IPr catalyst was successfully employed for the same transformation in THF in the presence of $LiN(SiMe_3)_2$[111] (Scheme 30). Both the Rh and Pd catalytic systems exhibited good tolerance of functional groups such as halogens, ester, alkoxy, Bpin, hydroxy, CF_3, and heteroaryl, *etc.* The Rh catalyst usually showed a higher catalytic activity than the Pd–NHC catalyst with a lower loading and shorter reaction time. A similar Pd–NHC, complex catalyst SingaCycle-A1 (chloro[[1,3-bis(2,6-diisopropyl-phenyl)imidazol-2-ylidene](*N*,*N*-dimethylbenzylamine)palladium(II)]),[112] was used to promote the desulfitative C–N bond formation *via* arene C(sp^2)–S bond cleavage, and KHMDS base was required for the amination of aryl or heteroaryl alkyl thioethers **89** with aliphatic amines, yielding the corresponding amines **98** (Scheme 31).[113] SingaCycle-A1 exhibited a catalytic activity higher than both Pd–PEPPSI–IPr and SingaCycle-A3 (chloro[[1,3-bis(2,6-diisopropyl-phenyl)-imidazol-2-ylidene]-(ace-tanilide)palladium(II)]).[101] A cascade process was thus established by a one-pot, two-step reaction of 4-bromothioanisole (**89b**). The reaction proceeded preferentially at the C–Br bond, while the C–S bond remained unchanged. Such a chemoselective protocol allowed the installation of two different amino groups on the aromatic ring in compounds **100** in one pot. Palladium complex catalyst SingaCycle-A3 could also exhibit a higher catalytic activity than Pd–PEPPSI–IPr to give the desulfitative amination product (88%) in the cross-coupling reaction of **89a** (R = H) with aniline, while the latter Pd–NHC catalyst only reached 76% yield under the same conditions. The combination of SingaCycle-A3 and potassium hexamethyldisilazide (KHMDS) enabled the desulfitative amination of thioethers **89** and analogs with anilines in dioxane at 100 °C, giving a wide range of diarylamines **101** (64–99%) (Table 6).[114]

Palladium-catalyzed C–S bond metathesis was recently achieved by Morandi and co-workers (Scheme 32).[115] With aryl



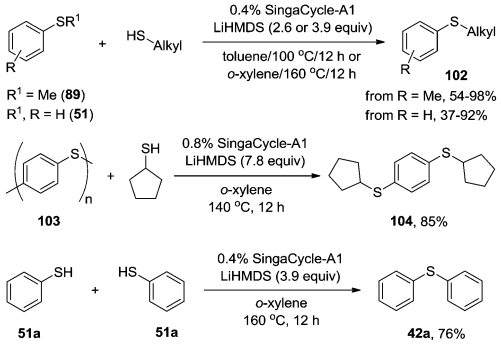
Scheme 31 Amination *via* C–S bond cleavage.

Table 6 Amination *via* C–S bond cleavage



Entry	Ar	R	R^1	Yield (%)
1	Ph	Me	4-Me	91
2	Ph	^{t}Bu	4-Me	65[a]
3	Ph	Ph	4-Me	99[a]
4	Ph	Me	3-Me	92[b]
5	Ph	Me	2-Me	75
6	Ph	Me	H	85
7	Ph	Me	4-MeO	90
8	Ph	Me	4-F	88
9	Ph	Me	3-CF_3	65[b]
10	4-MeC_6H_4	Me	4-Me	72[c]
11	3-MeC_6H_4	Me	4-Me	80[c]
12	2-MeC_6H_4	Me	4-Me	64
13	4-FC_6H_4	Me	4-Me	65[c]
14	4-$CF_3C_6H_4$	Me	4-Me	0
15	3-$CF_3C_6H_4$	Me	4-Me	83
16	4-$MeOC_6H_4$	Me	4-Me	73[d]
17		Me	4-Me	68[b]

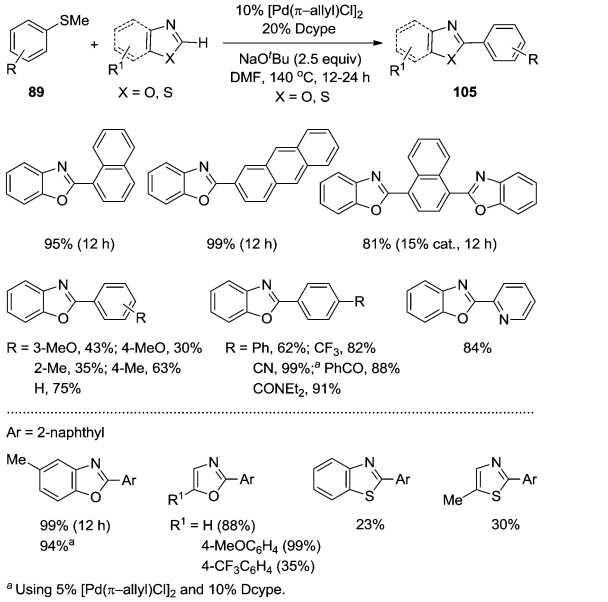
[a] Determined by ^{1}H NMR analysis. [b] 10% catalyst. [c] 5% catalyst. [d] 2.5 × 3% catalyst.



Scheme 32 Palladium-catalyzed C–S bond metathesis.

alkyl thioethers **89** as the substrates, Pd–NHC complex SingCycle-A1 as the catalyst, and LiHMDS as the base, the C–S bond metathesis reaction with alkyl thiols proceeded in toluene at 100 °C for 12 h to give new aryl alkyl thioethers **102** in 54–98% yields. Heteroaryl or vinyl alkyl thioethers could also be applied in the C–S bond metathesis reactions. Such C–S bond metathesis occurred between thiophenols **51** and alkyl thiols in *o*-xylene at 160 °C for 12 h, yielding the target products of type **102** (37–92%). Alkyl thiolate salt MeSLi or Li_2S was formed as the side product. It is noteworthy that the arene C(sp^2)–S bond was cleaved for the C–S/S–H cross-coupling transformation. Depolymerization[116] of thermoplastic polymer **103** was achieved by the C–S bond metathesis process to recycle it into the simple chemical building blocks. Under the modified reaction conditions polymer **103** (MW ~ 10^4) reacted with cyclopentyl thiol to give a single aromatic thioether **104** (85%). Homodimerization of thiophenol (**51a**), which usually plagues the efficiency of a chemoselective coupling process, did not interfere with the C–S bond metathesis reaction when a more nucleophilic alkyl thiol was used. However, if no cross-coupling partner was present in the reaction mixture, homodimerization of thiophenol resulted in diphenyl thioether (**42a**) in 76% yield. Nickel-catalyzed inter- and intramolecular arylthioether metathesis was also recently realized.[117] These results have demonstrated that the metathesis of C–X bonds has diverse potentials for the discovery and functionalization of many molecules and materials.

Intramolecular C–S/C–H cross-coupling was achieved in thioesters under palladium catalysis (Schemes 16 and 17).[76,78] In this regard, a few examples of C–S/C–H cross-coupling of aryl alkyl thioethers with electron-rich heteroarenes or activated arenes were also documented. In the presence of 10% [Pd(π-allyl)Cl]$_2$ as the catalyst, 20% bis(dicyclohexylphosphino)-ethane (Dcype) as the ligand, and 2.5 equiv. NaO^{t}Bu as the base, the reaction of thioethers **89** with benzoxazoles/azoles or benzothiazoles afforded the corresponding 2-aryl-substituted heteroarenes **105** (Scheme 33).[118] The Pd–PEPPSI–IPr precatalyst did not promote the reaction of 2-naphthyl methyl thioether and benzoxazole. A combination of [Pd(π-allyl)Cl]$_2$ with a ligand such as IPr·HCl, IMes·HCl, PCy_3, TFP, XPhos, Xantphos, dppe, or DPEphos did not initiate the reaction or only led to a low conversion of the thioether substrates. However, the combination of [Pd(π-allyl)Cl]$_2$ with Dcype worked well for the C–S/C–H cross-coupling reaction. Thus, a variety of 2-arylated heteroarenes were obtained in moderate to excellent yields. The reaction tolerated a wide range of functional groups, *i.e.*, MeO, CF_3, CN, PhCO, $CONEt_2$, and pyridyl. The electron-donating groups on the aryl ring of the aryl methyl thioethers diminished the reaction efficiency, while the electron-withdrawing groups facilitated the reaction, and the functional

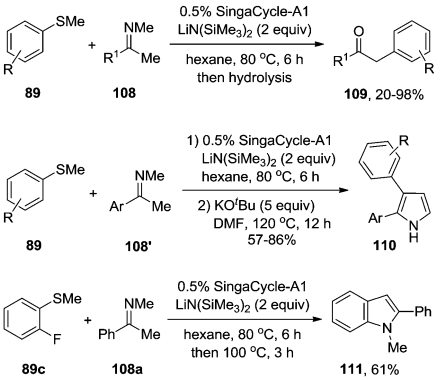


Scheme 33 Palladium-catalyzed arene C–S/C–H cross-coupling with heteroarenes.

groups on the azole ring exhibited an opposite substituent effect. It is noteworthy that benzoxazoles and azoles reacted much more efficiently than benzothiazoles (Scheme 33). Diaryl thioethers were also the suitable coupling partners for the reaction. This work has provided a useful complement to the direct C–H arylation of azoles and thiazoles.

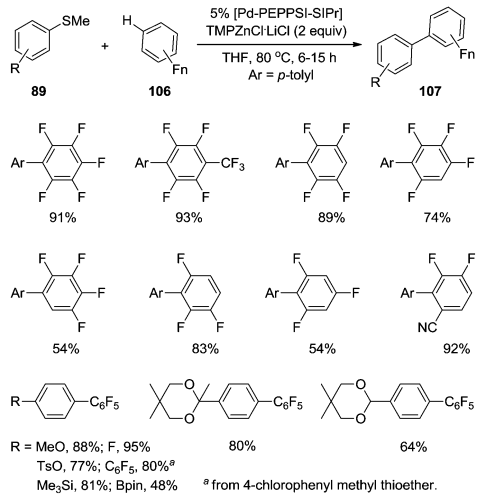
By means of the precatalyst Pd–PEPPSI–SIPr and a bulky zinc amide, that is, a 2,2,6,6-tetramethylpiperidylzinc chloride·lithium chloride complex (TMPZnCl·LiCl),[119] as the base, the cross-coupling of aryl methyl thioethers **89** with perfluorinated arenes or less fluorinated arenes **106** efficiently afforded the target fluorinated biaryl products **107**.[120] Functional groups such as F, TsO, Me_3Si, and Bpin were tolerated on the aryl ring of the thioethers, while the 4-chloro group in 4-chloroaryl thioethers was transformed into 4-Ar^F under the stated conditions (Scheme 34). The same catalytic system was employed for 2-arylation of azoles and thiazoles by using 4-tolyl methyl thioether as the electrophile.

Palladium-catalyzed α-arylation of ketimines with thioethers **89** was conducted *via* arene $C(sp^2)$–S/$C(sp^3)$–H cross-coupling assisted by the $LiN(SiMe_3)_2$ base.[121] Thus, the reaction of **89** with ketimines **108** formed aryl alkyl ketones **109** (20–98%) after hydrolysis of the initially generated α-arylated ketimine products (Scheme 35). Me, MeO, Me_2N, OH, F, Cl, MeCO, CO_2H, Me_3Si, and 2-naphthyl were tolerated as the substituents in the thioethers, and aryl, alkyl, and ferrocenyl ketimines were used in the reaction. The initially formed α-arylated ketimines are significantly important for the potential synthetic utility. After the initial reaction of **89** with aryl ketimine **108′** at 80 °C was complete, an excess of KO^{t}Bu base (5 equiv.) was added and the reaction was continued at a higher temperature (120 °C) to give 2,3-diarylated pyrroles **110** (57–86%). With 2-fluorophenyl methyl thioether (**89c**) as the substrate a cascade process was developed with aryl ketimine (**108a**) by elevating the reaction temperature from 80 °C to 100 °C, affording 2-phenylindole (**111**) in 61% yield. The resultant α-arylated ketimines showed diverse synthetic utilities. These results have demonstrated a new efficient palladium-catalyzed α-arylation protocol of ketimines with catalytically poisonous aryl thioethers.

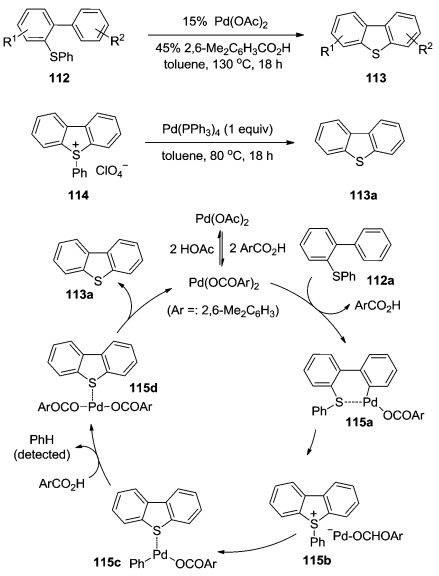


Scheme 35 α-Arylation of ketimines *via* C–S bond cleavage.

An intramolecular arene $C(sp^2)$–S/C–H cross-coupling was achieved under palladium catalysis to synthesize dibenzothiophene derivatives **113**.[122] In the presence of the $Pd(OAc)_2$ catalyst and a substituted benzoic acid ligand, biphenyl thioethers **112** underwent intramolecular desulfitative cyclization through C–S/C–H cross-coupling (Scheme 36). A sulfonium compound **114** was tested to react with an equimolar amount of $Pd(PPh_3)_4$ to give dibenzothiophene (**113a**) in 94% yield, suggesting that a sulfonium intermediate of type **114** might be involved in the reaction. For the mechanistic aspect, $Pd(OAc)_2$ initially undergoes ligand exchange with the benzoic acid ligand to generate $Pd(OCOAr)_2$, which reacts with diaryl thioether **112a** to form palladacycle species **115a** *via* a sulfur-directed cyclometalation process. Subsequent C–S bond forming reductive elimination leads to a sulfonium intermediate, that is, ion pair **115b**, an analog of compound **114**. Then, oxidative addition of the Ph–S bond in dibenzosulfonium to the Pd(0) metal center results in adduct complex **115c** through



Scheme 34 Palladium-catalyzed arene C–S/C–H cross-coupling.



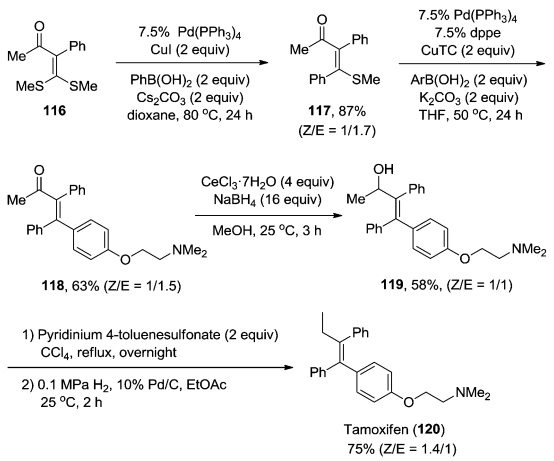
Scheme 36 Intramolecular cyclization *via* C–S bond cleavage.

C–S bond cleavage. The cleaved phenyl group is removed by formation of benzene upon interaction with the benzoic acid, regenerating $Pd(OCOAr)_2$ and affording the target dibenzothiophene product **113a** (Scheme 36). This work provides a new method for the synthesis of dibenzothiophene derivatives through intramolecular C–S/C–H cross-coupling. In contrast to the existing methods for dibenzothiophene synthesis, the present protocol avoids external oxidants or reactive functionalities such as C–X or S–H, allowing its application to access elaborate π-systems.

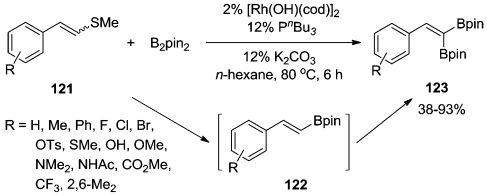
3.3 Alkene C(sp^2)–S bond cleavage

Due to the diversity and potential applications of heteroarene and arene C(sp^2)–S bond cleavages the cross-coupling using vinyl thioethers has recently been paid considerable attention. A programmable C–S arylation protocol was successfully applied for the synthesis of pharmaceutical tetrasubstituted alkene, Tamoxifen (**120**), which has been the most widely used anticancer drug for the clinical treatment of breast cancer.[123] Thus, α-oxo ketene dithioacetal **116** was subjected to double C–S arylation with aromatic boronic acids under Liebeskind–Srogl cross-coupling conditions to give the triarylated alkene **118** (63%) *via* intermediate **117** (87%). Subsequent reduction/dehydration/reduction from intermediate **118** afforded the target product **120** (Scheme 37).[124] Under similar conditions, CF_3-functionalized ketene monothioacetals were desulfitatively arylated by arylboronic acids to form tetrasubstituted alkenes.[125]

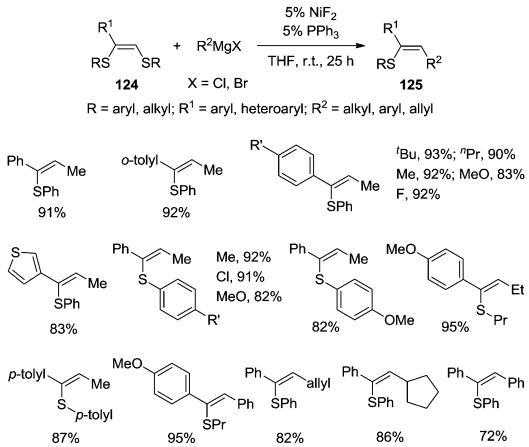
Under rhodium(I) catalysis desulfitative *gem*-diborylation of 2-arylvinyl thioethers (**121**) was realized by the coupling with B_2pin_2 in the presence of the P^nBu_3 ligand and a catalytic amount of K_2CO_3 base (Scheme 38).[126] Without K_2CO_3 base the reaction did not occur at 80 °C. In the presence of K_2CO_3 base the reaction formed a mixture of the monoborylated product **122** (minor) and the target product **123** (major) even at room temperature for 24 h, while the same reaction formed **123** as the only product in high yield at the elevated temperature (80 °C) within 6 h. The control experiments verified that the (*Z*)-isomer of **121** impeded the desired transformation. These results suggest that (*E*)-**122** is the reaction intermediate.



Scheme 37 Synthesis of Tamoxifen *via* double C–S bond cleavages.



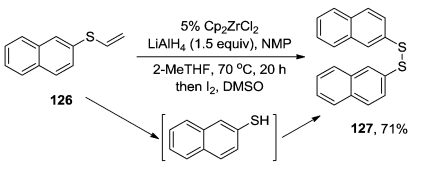
Scheme 38 *gem*-Diborylation of 2-arylvinyl thioethers *via* C–S bond cleavage.



Scheme 39 Synthesis of RS-functionalized alkenes.

The reaction tolerated electron-donating and electron-withdrawing substituents on the aryl ring. It is noteworthy that benzothiophene- and naphthalene-based vinyl thioethers reacted well with B_2pin_2 to give the target products in decent yields. Compounds of type **123** are potentially useful for the synthesis of trisubstituted alkenes.

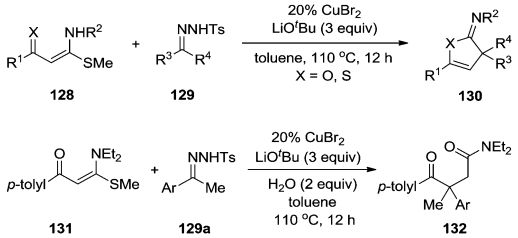
In a manner similar to the transition-metal-catalyzed cross-coupling of thioesters and (hetero)aryl thioethers with Grignard reagents, the nickel-catalyzed desulfitative cross-coupling strategy was applied to functionalize vinyl thioethers. With 5% NiF_2 as the catalyst in the presence of 5% PPh_3, (*Z*)-vinylic thioethers **125** were accessed through highly regio- and stereoselective coupling of (*Z*)-1,2-bis(aryl(alkyl)thio)alkenes (**124**) with Grignard reagents at room temperature, reaching 72–95% yields (Scheme 39).[127] Compounds **125** are potentially important building blocks for drugs and natural products, which has been demonstrated by the synthesis of (*Z*)-Tamoxifen through a four-step synthetic procedure. A similar $Ni(PPh_3)_2Cl_2$-catalyzed desulfitative cross-coupling of monoalkyl(aryl)thio-substituted alkenes was also developed to prepare trisubstituted alkenes in 61–86% yields.[128] It should be noted that the alkylthio moiety in a vinyl alkyl thioether usually acts as an activating, directing, and/or leaving group, and in the cross-coupling reaction the alkene C(sp^2)–S bond is preferentially cleaved.



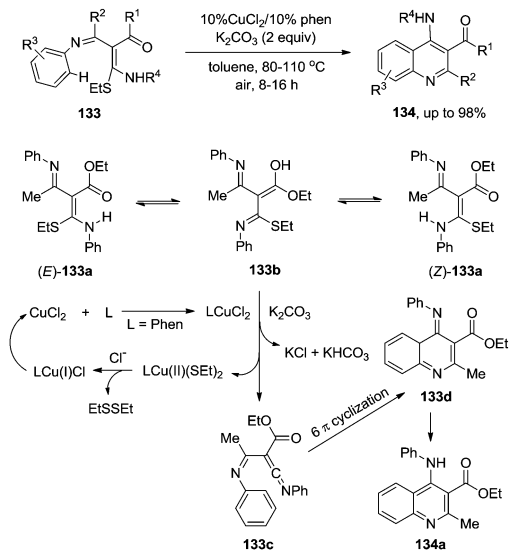
(7)

With a reducing agent such as $LiAlH_4$, vinyl thioether, that is, 2-naphthyl vinyl thioether (**126**) was reduced to the corresponding diaryl disulfide **127** (eqn (7)).[129] In this case, 5% Cp_2ZrCl_2 was used as the catalyst. An NMR analysis of the crude reaction mixture revealed very good conversion to 2-thionaphthol. Auto-oxidation of the thiol could not be completely suppressed, thus the crude mixture was treated with iodine to execute the complete formation of **127** which was isolated in 71% yield.

N,*S*-Acetals are known as diverse reagents in organic synthesis.[130,131] In this regard, ketene *N*,*S*-acetals have exhibited specific reactivities. With 20% $CuBr_2$ as the catalyst, efficient formal carbene migratory insertion into the vinylic C=C bond of ketene *N*,*S*-acetals **128** was achieved by means of ketone *N*-tosylhydrazones **129** as the carbene precursors (Scheme 40).[132] The resultant iminofurans **130** were further converted to the corresponding 2(3*H*)-furanones or γ-ketoesters by acidic hydrolysis. Using a secondary amine-derived ketene *N*,*S*-acetal, that is, compound **131**, led to γ-ketoamides **132** in moderate yields by the assistance of water under the same conditions. Copper(II)-catalyzed aerobic oxidative intramolecular cross-coupling of the readily available *N*-arylimino ketene *N*,*S*-acetals **133** was realized to give the desulfitative cyclization products 4-aminoquinolines **134** (Scheme 41).[133] The reaction efficiently proceeded under mild conditions without any exogenous thiolate scavenger, affording the target products in good to excellent yields (66–98%). The proposed reaction mechanism suggests that the initial tautomerization of **133a** results in species **133b** which interacts with K_2CO_3 base to generate carboimide **133c**. The *in situ* generated **133c** then undergoes 6π-cyclization to form imino-N-heterocycle **133d**. Subsequent aromatization leads to the target product **134a**. A single electron transfer (SET) process then occurs to establish the catalytic cycle for the intramolecular formal C–H/C–S cross-coupling in the presence of a Cu(II) catalyst under an air atmosphere. This work offers an alternative protocol to access 4-aminoquinoline derivatives from readily available starting materials.



Scheme 40 Carbene-involved C–S bond cleavage.



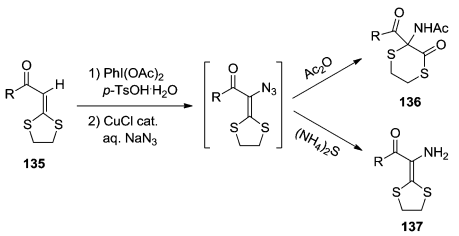
Scheme 41 Intramolecular C–S bond cleavage to form pyridines.

3.4 Alkene C(sp^2)–S bond cleavage in ketene dithioacetals

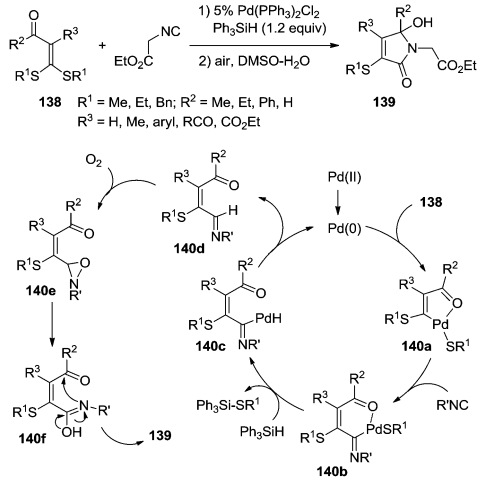
Dithioacetal functionalities are widely used in organic synthesis because they can be conveniently deprotected to their parent aldehydes or ketones under acidic or other conditions.[134] Auto-oxidation of the thiol could not be completely suppressed, thus the crude mixture was treated with iodine to the bidentate coordination capability of a dithioacetal moiety, it is usually difficult to recycle a transition-metal catalyst and make the C–S bond cleavage reaction of a dithioacetal motif proceed catalytically. Thus, the C–S bond cleavage reactions of ketene dithioacetals are usually performed under strong basic conditions or by means of Brønsted or Lewis acids.[18] Fortunately, progress has recently been achieved in the catalytic C–S bond cleavage of ketene dithioacetals.[17,19] Two C–S bonds exist at one terminus of the vinylic C=C bond of a ketene dithioacetal, and this kind of organosulfur compounds can also be classified as vinyl thioethers. In the presence of a transition-metal catalyst, the alkene C(sp^2)–S bond instead of the alkane C(sp^3)–S bond in such a vinyl alkyl thioether is usually cleaved to undergo cross-coupling transformations. Although base and acid-promoted transformations of ketene dithioacetals have been well documented,[18] the relevant summary is not given in this review. In this section, only transition-metal-catalyzed C–S bond cleavage of ketene dithioacetals is presented.

A one-pot, two-step protocol was developed to cleave the C–S bonds in cyclic α-oxo ketene dithioacetals under copper catalysis.[135] Under copper(I) catalysis, $PhI(OAc)_2$-mediated ring-expansion/thiolactonization of ketene dithioacetals **135** was efficiently conducted *via* azidation of the internal vinylic C–H bond with sodium azide. Sequential amination, ring-expansion rearrangement, and thiolactonization occurred to give the aminated thiolactones **136** in the presence of acetic anhydride, while unprotected enamines **137** were produced through C–H amination by means of ammonium sulfide as the reducing agent (Scheme 42). The *in situ* formed vinyl azides were identified as the reactive intermediates, which were captured by phenylacetylene to afford the corresponding triazoles. This work has established a concise route to highly functionalized thiolactone derivatives and unprotected enamines.

Palladium-catalyzed one-pot, two-step aerobic oxidative cyclization of tetrasubstituted α-oxo ketene dithioacetals **138** was achieved in the presence of isocyanides and Ph_3SiH, giving



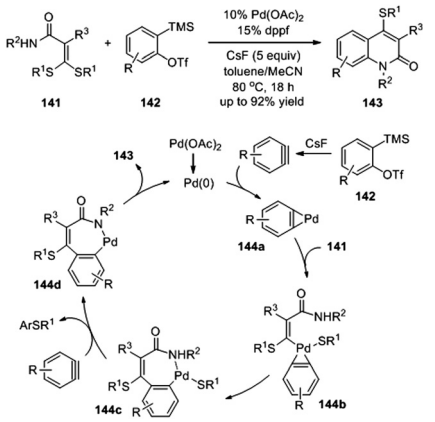
Scheme 42 C–S bond cleavage in cyclic α-oxo ketene dithioacetals.



Scheme 43 Reductive C–S bond cleavage in tetrasubstituted α-oxo ketene dithioacetals.

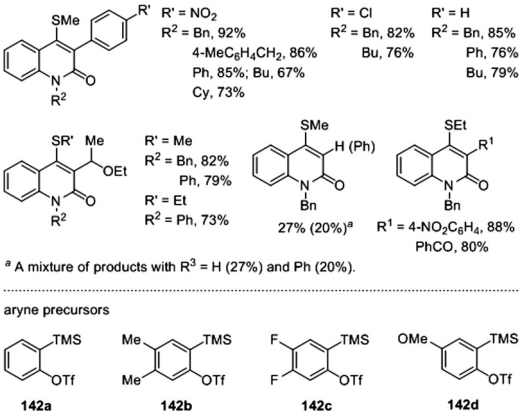
α,β-unsaturated lactam derivatives **139** in 58–92% yields (Scheme 43).[136] A variety of functional groups such as aryl, acyl, ester, halogens, and methoxy were tolerated. The resultant RS-functionalized products could be effectively coupled with aryl boronic acids to yield 4-aryl-α,β-unsaturated γ-lactams. In the reaction mixture, intermediates **140b** and **140d** were detected by HRMS analysis, which suggests that oxidative addition of one of the C–S bonds in **138** to the palladium metal center generates **140a** and is followed by isocyanide insertion and reductive elimination from **140c** during the reaction. It should be noted that water played a crucial role in the isocyanide insertion transformation. During the C–S bond activation in ketene dithioacetals vinyl-Pd–S species are usually generated so that a potential insertion reaction may occur with suitable reactants.

An efficient palladium-catalyzed method was developed for the synthesis of 2-quinolinones **143** from the reaction of 2-carbamoyl ketene dithioacetals **141** with arynes generated *in situ* from *o*-(trimethylsilyl)aryl triflates **142** in the presence of CsF base (Scheme 44).[137] Cyclopalladation of the *in situ* generated aryne forms palladacycle **144a** which subsequently inserts into the C–S bond of **141** to give intermediate **144c**, presumably *via* Pd(IV) species **144b**. Substitution of **144c** by another molecule of the aryne forms heteropalladacycle **144d** with release of aryl alkyl thioether $ArSR^1$. Subsequent reductive elimination affords the annulation product **143** and regenerates



Scheme 44 Aryne-involved C–S bond cleavage.

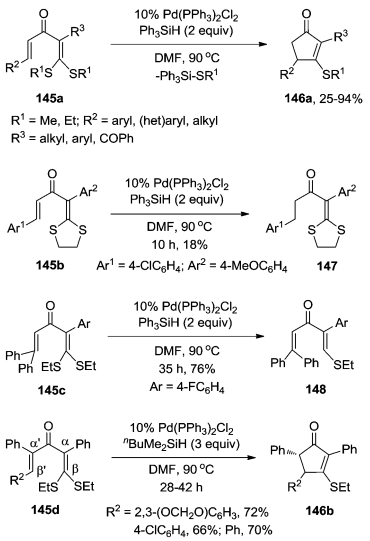
the catalyst for the next catalytic cycle. MeS and EtS-functionalized ketene dithioacetals were suitable for the reaction. Aryl, alkyl, and unprotected amido groups as well as other diverse functional groups at the α position of the starting ketene dithioacetals could be tolerated (Scheme 45). When *o*-(trimethylsilyl)aryl triflate **142a** was used as the aryne precursor, the fully substituted ketene dithioacetals reacted to give the target products in good to excellent yields (67–92%), and only in the case of using the unprotected amido group ($CONH_2$)-bearing substrate was the product obtained in <15% yield. With the trisubstituted ketene dithioacetal (R^3 = H) the product was obtained in 27% yield with formation of the α-phenylation product (20%). The first palladium-catalyzed C–H α-phenylation of the trisubstituted ketene dithioacetal occurred to give the corresponding tetrasubstituted ketene dithioacetal, and subsequent annulation with benzyne resulted in the α-phenylated 2-quinilinone product. Arynes bearing both electron-donating and electron-withdrawing groups were compatible with the standard conditions, forming the target products in moderate yields (41–51%), which were increased to 77–87% in the presence of 5 equiv. of an aryne. However, in the case of using the aryne derived from **142c** with two electron-withdrawing groups, an excessive amount of aryne did not improve the reaction efficiency. When the unsymmetrical aryne generated from **142d** was applied, a mixture of two product



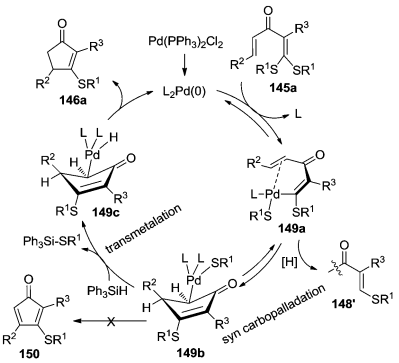
Scheme 45 Aryne-involved synthesis of 2-quinolinones.

isomers bearing 3-OMe or 4-OMe was obtained. These results have demonstrated the first example for the reaction of arynes with thioorganics based on palladium-catalyzed C–S bond activation/cleavage, providing a useful method to access diverse functionalized 2-quinolinone derivatives.

Although α-alkenoyl ketene dithioacetals can undergo diverse transformations under metal-free conditions,[18] less work has been devoted to transition-metal-catalyzed C–S bond cleavage reactions of these compounds. In this regard, palladium-catalyzed reductive Heck-type cyclization of α-acryloyl ketene dithioacetals (**145a**) was documented to prepare cyclopentenones (**146a**) in 25–94% yields by using silane as the reductant (Scheme 46).[138] Various functional groups such as alkoxy, halogens, benzoyl, and 2-furyl were tolerated. The reaction was sensitive to the ketene dithioacetal substrates without any substituent at the α position (R^3 = H), resulting in a complex mixture under the stated conditions. When cyclic ketene dithioacetal **145b** was used, product **147**, in which the C=C bond of the alkenoyl moiety was reduced by the silane, was formed in 18% yield within 10 h. Substrate **145c** bearing β′,β′-diphenyls was found not to be a proper reactant, and under the stated conditions it was reduced to the corresponding ketene monothioacetal **148** (76%). The stereoselectivity of the reaction was investigated by palladium-catalyzed cyclization of α′,β′-disubstituted substrates **145d** with ^{n}BuMe$_2$SiH (3 equiv.), and the cyclopentenone products (**146b**) were isolated as regio- and diastereoisomers with the R^2 group situated *trans* to α′-phenyl (Scheme 46). The proposed mechanism suggests that the C–S bond of **145** undergoes oxidative addition to the Pd(0) species to generate intermediate complex **149a** which may be additionally stabilized *via* coordination with the alkenoyl C=C bond (Scheme 47). *syn*-Carbopalladation then proceeds in a selective 4-*endo*-trig manner to form species **149b**. No β-hydrogen being *syn*-coplanar with the Pd metal center of the rigid cyclic intermediate blocks β-elimination to generate cyclopentadienone **150**. Transmetalation in the presence of a silane results in intermediate **149c** with release of (alkylthio)-trialkylsilane.



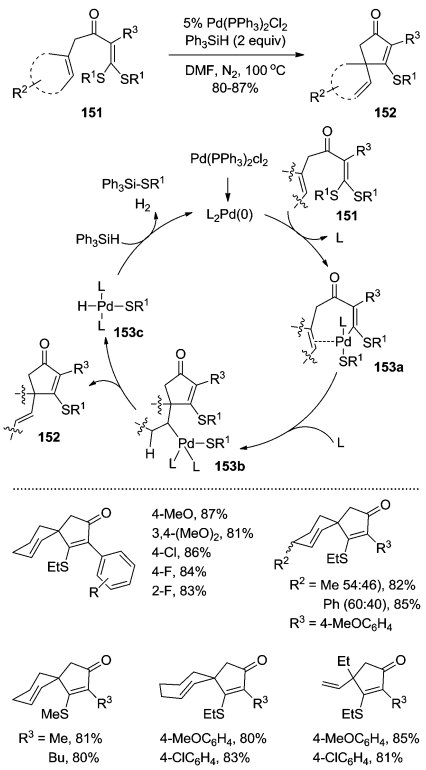
Scheme 46 C–S bond cleavage in α-alkenoyl ketene dithioacetals.



Scheme 47 Heck cyclization of α-alkenoyl ketene dithioacetals.

Subsequently, reductive elimination from **149c** gives the target product **146a** and regenerates the catalytically active Pd(0) species. If the carbopalladation of **149a** is inefficient, the transmetalation preferentially takes place to form the desulfurization product **148′**. This work has developed a hydrogenolysis-terminated Heck-type cyclization of the readily available β,β-di(alkylthio)dienones under palladium catalysis, offering an efficient access to 2-cyclopentenones with excellent regio- and diastereoselectivities.

However, Heck-type cyclization of α-(3-butenoyl)ketene dithioacetals (**151**) proceeded under similar conditions, giving the spiro 2-cyclopentenones (**152**) in 80–87% yields (Scheme 48).[139] α-(Cyclohexenyl)acetyl ketene dithioacetals bearing aromatic or aliphatic substituents on both the α position and cyclohexenyl ring reacted to give the target products in high yields (80–87%). The



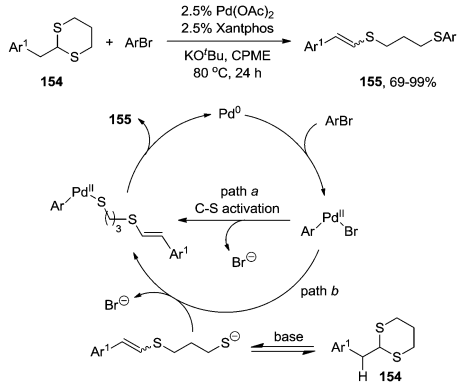
Scheme 48 Synthesis of spiro 2-cyclopentenones.

cycloheptenyl-based and acyclic substrates also efficiently yielded the target products (80–85%). The reaction may be initiated by the oxidative addition of the C–S bond of **151** to the Pd(0) metal center, forming intermediate **153a** with assistance through coordination by the alkenoyl C═C functionality. An intramolecular *syn*-carbopalladation gives species **153b** bearing a β-hydrogen *syn* to the Pd metal center. Subsequent β-elimination yields the Heck-type product **152** along with the production of PdH species **153c** which further interacts with the silane to regenerate the catalytically active Pd(0) species, forming dihydrogen and removing the alkylthio moiety as Ph_3SiSR^1 (Scheme 48). The present method provides a protocol for the regioselective synthesis of spiro 2-cyclopentenones.

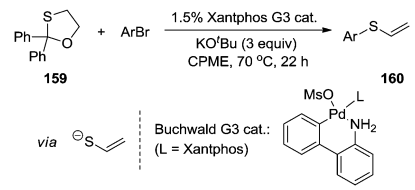
3.5 Alkane C(sp^3)–S bond cleavage

Alkyl C–S bonds can also undergo desulfitative cross-coupling, but their reactions are usually performed under relatively harsh conditions in comparison to those in thioesters, heteroaryl, aryl, and vinyl thioethers, and ketene dithioacetals. In addition, much less progress has been achieved in alkane C(sp^3)–S bond cleavage for transition-metal-catalyzed transformations. Disubstituted dithioethers **155** were accessed through potassium *tert*-butoxide-promoted elimination/ring-opening of 1,3-dithianes **154** followed by palladium-catalyzed C–S bond formation (Scheme 49).[140] Two pathways may be involved to cleave the C–S bond by either palladium-catalyzed C–S bond activation or base-assisted C–S bond dissociation, followed by reductive elimination to afford the target product. The combination of $Pd(OAc)_2$ catalyst and Xantphos ligand is crucial for the reaction, which is compatible with a wide range of functional groups and heteroaromatic coupling partners. The reaction proceeded in good to excellent yields (69–99%) with good stereoselectivity, forming the (*E*)-alkenes as the major diastereomers. This method offers an access to unsymmetrical propylene styryl/aryl dithioethers, a new class of thioether compounds.

Iron-catalyzed, dithiane radical-induced C–S cleavage strategy was also applied for the construction of functionalized dithioethers. With 10% $FeCl_3$ as the catalyst in the presence of *N*-chlorosuccinimide (NCS) 1,3-dithiane (**156**) was efficiently added to enones **157** at room temperature, affording dithioether products **158** (68–92%) bearing a terminal formyl group through

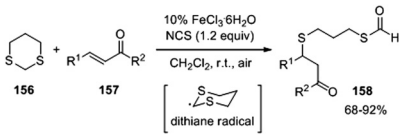


Scheme 49 C–S bond cleavage in 1,3-dithianes.



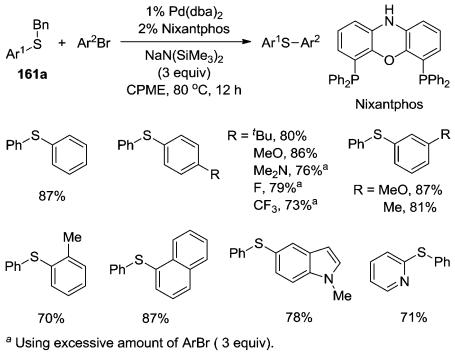
Scheme 50 C–S bond cleavage in 1,3-oxathiolane.

radical C–S bond cleavage (eqn (8)).[141] An analog of 1,3-dithiane, that is, 2,2-diphenyl-1,3-oxathiolane (**159**), was used as a vinyl thioether surrogate to react with aryl bromides under palladium catalysis, giving aryl vinyl thioethers **160** (Scheme 50).[142] During the reaction, compound **159** slowly liberated a short-lifetime vinyl sulfide anion under the basic conditions. Such a transient sulfide species was effectively trapped by the aryl bromide coupling partners. A Pd(0)/Pd(II) catalytic cycle was proposed to rationalize the transformation, and the palladium catalyst, that is, Buchwald G3 catalyst, with Xantphos as the ligand is essential for the decomposition/initial activation of the aryl vinyl thioethers. These cases have demonstrated a C(sp^3)–S bond cleavage with simultaneous C(sp^2)–S bond formation.



(8)

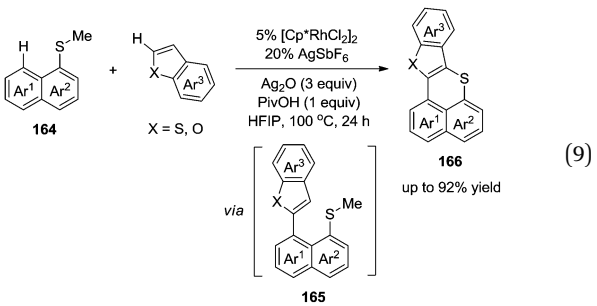
A similar case of C(sp^3)–S bond cleavage/formation was reported through palladium-catalyzed debenzylative cross-coupling of aryl benzyl thioethers with aryl bromides.[143] In the presence of $Pd(dba)_2$ as the precatalyst with Nixantphos (4,6-bis(diphenylphosphino)-10*H*-phenoxazine) as the ligand, aryl benzyl thioethers **161a** efficiently reacted with aryl bromides to give the diaryl thioether products in good to excellent yields (Scheme 51). A variety of functional groups such as methoxy, dimethylamino, fluoro, and trifluoromethyl were tolerated. The steric hindrance from *o*-methyl and the electronic effect from the electron-withdrawing groups had a negative impact on the reaction efficiency. The mechanistic studies have suggested that the $Pd(dba)_2$/Nixantphos catalyst promotes three distinct catalytic reactions involving



Scheme 51 Debenzylative C–S bond cleavage.

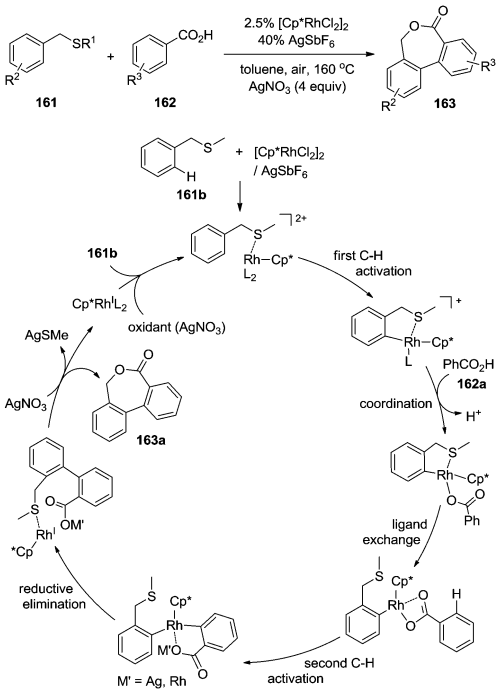
α-arylation of benzyl aryl thioether, benzylic C–S bond cleavage, and C–S bond formation. This work provides a route to functionalized biaryl thioethers from readily available benzyl aryl thioethers.

The C–S cleavage strategy was successfully combined with a double C–H activation process for the synthesis of polycyclic compounds. In the presence of a Rh(III) precatalyst, the cross-coupling of benzyl thioethers **161** and aryl carboxylic acids **162** proceeded under the direction of two different directing groups (SR and COOH), forming dibenzo[*c*,*e*]oxepin-5(7*H*)-ones **163** (Scheme 52).[144] The proposed mechanism indicates a Rh^{III}–Rh^{I}–Rh^{III} pathway. The directing groups were either incorporated into the product or removed *in situ* during the reaction. Halogens, methoxy, and alkyls were tolerated as the functional groups. The drawback of the present protocol is that the target products are usually obtained in moderate to good yields (29–72%), and the presence of a nitro substituent diminishes the product yield to 7%. The tricyclic motif is the privileged core in some important natural products and bioactive molecules. This work has exhibited the power of using two different directing groups to enhance the selectivity of a double C–H activation process, and may find applications for the synthesis important natural products.

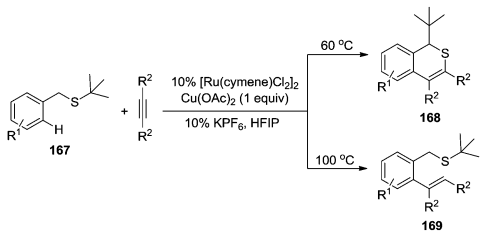


(9)

A rhodium(III)-catalyzed, Ag(I)-mediated *peri*-selective heteroarylation/single electron transfer annulation cascade of 1-(methylthio)naphthalenes (**164**) and analogs was developed through sequential oxidative C–H/C–H coupling and formal C–H/C–S coupling in hexafluoroisopropanol (HFIP) (eqn (9)).[145] Moderate to high yields were obtained for the target products. The first-step oxidative C–H/C–H cross-coupling gave heteroaryl-functionalized naphthyl methyl thioether **165** which was then annulated to the polycyclic heterocycle **166**. The EPR experiment revealed that the reaction occurred through a radical pathway. By means of $[Ru(cymene)Cl_2]_2$/10% KPF_6 as the catalyst system in the presence of $Cu(OAc)_2$ as the oxidant, the oxidative cross-coupling of benzyl *tert*-butyl thioethers **167** with internal alkyl alkynes proceeded smoothly in HFIP solvent to form new cyclic thioethers, that is, (1*H*)-isothiochromenes (**168**) (Scheme 53).[146] The target products **168** instead of the hydroarylation products **169** were obtained in moderate to high yields (37–96%). The reaction occurred *via* Ru(II)-catalyzed, sulfur-directed C–H activation at the *ortho* position of the aryl ring, migratory insertion of the alkyne, 1,2-thio-Wittig rearrangement of the *tert*-butyl group, and reductive elimination by the C–S coupling between the resultant anionic sulfide and the vinyl



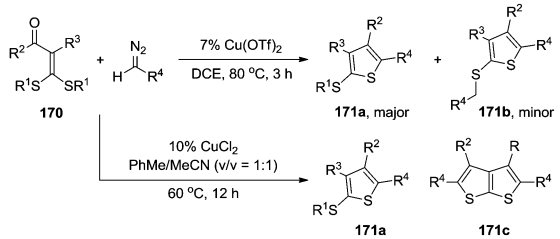
Scheme 52 Double C–H activation by two different directing groups.



Scheme 53 Reaction kinetics-controlled C–S coupling *vs.* hydroarylation.

carbon. Such a reaction kinetic nature can be employed to design new C–H activation and C–S cleavage cascades.

Under specific conditions, the alkyl C–S bonds in ketene dithioacetals can also be cleaved. By means of aldehyde diazo compounds $Cu(OTf)_2$-catalyzed annulation of α-EWG ketene dithioacetals **170** was recently realized in DCE at 80 °C, forming alkylthio-functionalized polysubstituted thiophenes **171a**/**171b** in moderate to good yields (Scheme 54).[147] When the R^3 groups in **170** were CO_2Me, CO_2Et, and 4-$MeOC_6H_4$, polysubstituted thiophenes **171a** (43–59%) and **171b** (24–32%) were



Scheme 54 sp^3 C–S bond cleavage in ketene dithioacetals.

simultaneously formed. In the cases of using cyano, amide, and benzoyl as the R^3 groups, the target products of type **171a** (72–76%) were exclusively produced. Change of the R^3 groups to propionyl and acetyl led to thienothiophenes **171c** (55–81%) as the major products and **171a** (6–36%) as the minor products. In a similar fashion using the same type of ketene dithioacetal, the same types of products **171a** and **171c** could be selectively accessed in high yields by means of 10% $CuCl_2$ as the catalyst, and toluene/MeCN (1 : 1, v/v) as the solvent at 60 °C.[148] In these cases the vinyl C–S bonds were not cleaved. This work offers a promising method to construct highly functionalized thiophene motifs. It should be noted that photocatalytic methods have also been documented to cleave the alkyl C–S bonds.[149]

3.6 Alkyne C(sp)–S bond cleavage

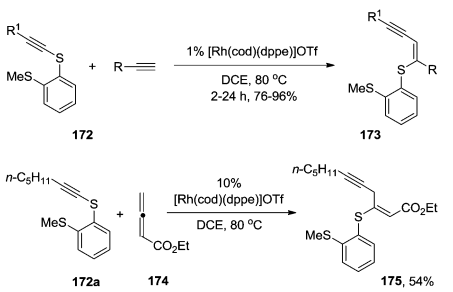
Alkyne C(sp)–S bond cleavage can be achieved under transition-metal catalysis, but only a limited number of examples have been documented to date. Palladium(0)-catalyzed alkynylthiolation of alkynes with triisopropylsilylethynyl sulfide was achieved to afford the corresponding phenylthio-functionalized enynes.[150] Such a reaction proceeded smoothly with perfect regio- and stereoselectivities *via* C–S bond activation. The proposed mechanism suggests that the reaction follows an oxidative addition/alkyne insertion/reductive elimination pathway. With cationic complex [Rh(cod)(dppe)]OTf (cod = 1,5-cyclooctadiene) as the precatalyst, sulfur-directed C(sp)–S bond cleavage of alkynyl sulfides **172** regioselectively occurred with terminal alkynes to afford (*Z*)-enynyl thioethers **173** in high yields (76–96%) (Scheme 55).[151] However, the terminal *o*-methylthio-substituted arylthioalkyne could only exhibit a very low reactivity to interact with *p*-ethynyltoluene, giving a 12% yield. Ethyl allenoate (**174**) was employed in the reaction with **172a** to form the target product **175** in 54% yield.

4. C–S bond cleavage in sulfoxides and sulfones

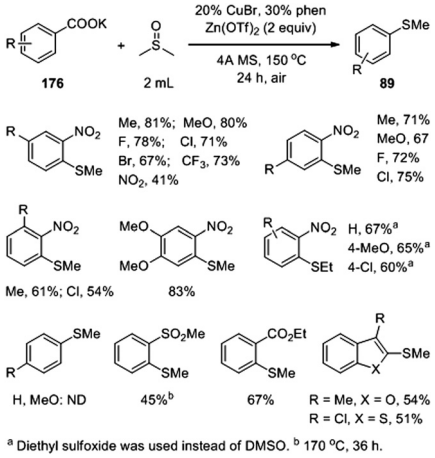
4.1 DMSO

Recently, dimethyl sulfoxide (DMSO) has been found to be a useful synthetic reagent, exhibiting a significant practical advantage. Under transition-metal catalysis or transition-metal-free conditions, DMSO can undergo diverse transformations.[152] Although transition-metal-catalyzed C–X/S^-–M^+ and C–H/S–H cross-couplings have been documented for the preparation of thioethers, simple, cheap, and easy-to-handle methylthiolation reagents have always been desired. In this regard, DMSO has shown practical potential. By means of 20% CuBr, 30% 1,10-phenanthroline (phen), 2 equiv. of $Zn(OTf)_2$, and 4A molecular sieves, decarboxylative methylthiolation of potassium aromatic carboxylates **176** occurred in DMSO at 150 °C, giving aryl methyl thioethers **89** as the products (Scheme 56).[153] An electron-withdrawing group such as nitro, sulfonyl, or ester is required on the aryl ring. Otherwise, the reaction could not occur. An additional nitro group diminished the yield to 41%, while an additional methoxy group facilitated the reaction to proceed more efficiently, enhancing the yield from 67% to 83%. The *meta* substituents exhibited an obvious steric effect. Diethyl sulfoxide also underwent the same type of decarboxylative reaction. This work provides a useful route to aryl methyl thioethers by using DMSO as the methylthiolation source. The proposed mechanism suggests that interaction of the Cu(I) catalyst with carboxylate salt **176** forms a Cu(I) benzoate species by anion exchange. Decarboxylation then occurs to give the aryl-Cu(I) species which is oxidatively added by the *in situ* generated dimethyl disulfide from DMSO in the presence of air as the oxidant. Subsequent reductive elimination from the Cu(III) intermediate proceeds to give product **89** and regenerate the catalyst (Scheme 57).

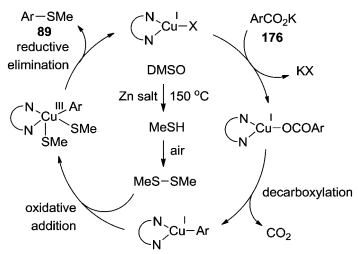
DMSO was documented as the building block for sulfones through cleaving one of its C–S bonds. By means of



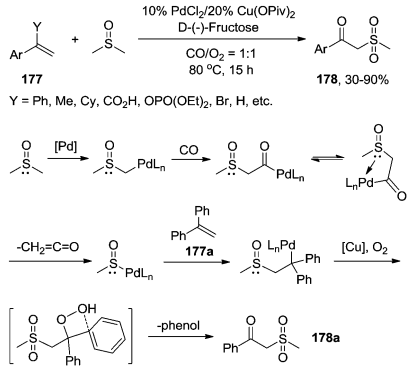
Scheme 55 Rh(I)-Catalyzed C–S bond cleavage of thioalkynes.



Scheme 56 Decarboxylative C–S bond cleavage in DMSO.



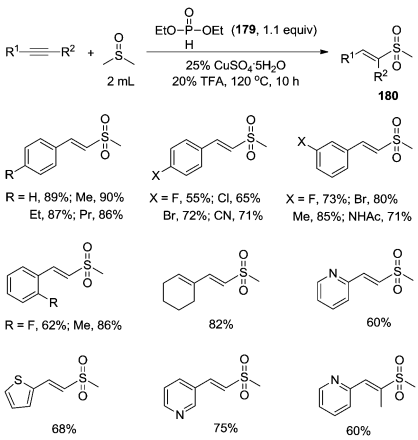
Scheme 57 Cu(I)-Catalyzed decarboxylative C–S bond cleavage in DMSO.



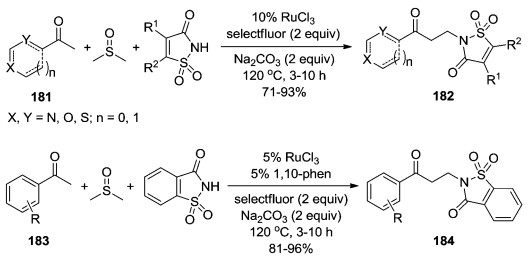
Scheme 58 CO-involved C–S bond cleavage of DMSO.

$PdCl_2/Cu(OPiv)_2$ as the catalyst, aerobic oxidative oxosulfonation of alkenes **177** with DMSO proceeded to produce β-oxo sulfones **178** (Scheme 58).[154] Under the stated conditions, C–C, C–S, C–O, and C–Br bond cleavages were efficiently achieved in a one-pot reaction system. The mechanistic investigations revealed that CO/O_2 assisted the bond cleavage, and the leaving groups from the starting materials were trapped by O_2. A combination of 25% $CuSO_4{\cdot}5H_2O$, 20% trifluoroacetic acid (TFA), and diethyl *H*-phosphonate (**179**, 1.1 equiv.) facilitated the reaction of alkynes with DMSO at 120 °C, giving (*E*)-vinyl alkylsulfones **180** in good to excellent yields (55–90%) (Scheme 59).[155] For the model reaction of phenylacetylene and DMSO, the target product was only obtained in 30% yield without the acid promoter, and in the absence of mediator **179** the reaction did not occur at all. In solvent DMF, toluene, dioxane, or acetic anhydride the reaction hardly occurred. The present protocol offers an alternative access to functionalized vinyl sulfones, featuring the use of cheap catalysts, readily available starting materials, operational simplicity, and high regio- and stereoselectivities.

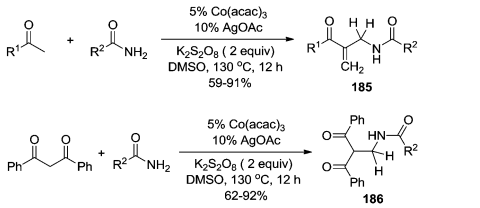
By using $RuCl_3$ as the catalyst, oxidative C–S bond cleavage of DMSO for dual C–C and C–N bond formation was realized, yielding the precursor compounds **182** to β-amino ketones from acetyl heteroarenes **181**.[156] Acetone could also be applied as an



Scheme 59 Sulfone synthesis *via* C–S bond cleavage of DMSO.



Scheme 60 DMSO as C1 synthon *via* C–S bond cleavage.

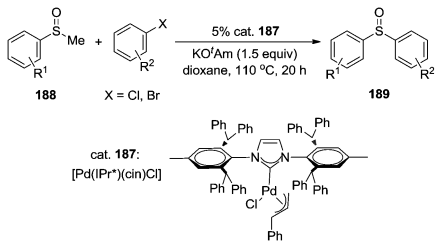


Scheme 61 DMSO as the methylene source *via* C–S bond cleavage.

effective substrate to give the target product in 97% yield. In particular, the indispensable formaldehyde analog in Mannich reactions can be replaced with environmentally benign DMSO as the one-carbon bridge in the procedure. With acetopheones **183** as the substrates the target products **184** were obtained in high yields (81–96%) under similar conditions[157] (Scheme 60). The mechanisitic studies have suggested that *N*-methylation between imine and DMSO is involved in the reaction. Very recent report has demonstrated that DMSO can be used as the methylene source in the synthesis of 3,3′-methylenebisthioflavone derivatives[158] and β-amino ketones (Scheme 61).[159] In the latter case, the Co(III)/Ag(I)-catalyzed reaction of acetophenones and benzamides in the presence of $K_2S_2O_8$ in DMSO formed β-amino ketones **185** in high yields with simultaneous incorporation of two methylenes into the products. With 1,3-diketone dibenzoylmethane as the substrate only one methylene could be introduced to the target products **186**. In all these cases, DMSO acted as both the reaction solvent and one carbon synthon.[160]

4.2 Sulfoxides

Sulfoxides have not been well reported as coupling partners, and in the limited reports they were usually used as the sulfenate sources for C–S cross-coupling. Direct palladium-catalyzed *S*-arylation of unactivated arylsulfoxides was achieved by using the well-defined Pd–NHC complex catalyst Pd(IPr*)(cin)Cl (**187**: IPr* = 1,3-bis[2,6-bis(diphenylmethyl)-4-methylphenyl]-imidazol-2-ylidene; cin = cinnamyl),[161,162] and methyl arylsulfoxides **188** were thus coupled to various aryl halides, giving diaryl sulfoxides **189** in moderate to good yields (Scheme 62).[163] The substrate scopes are relatively limited because the electronic and steric effects exhibited an obvious impact on the reaction efficiency. Aryl bromides usually demonstrated a higher reactivity than the corresponding chlorides, while the aryl iodides did not react under the same conditions. The sterically hindered 2-methyl

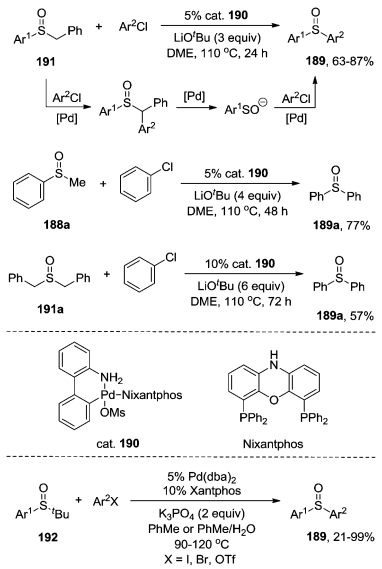


Scheme 62 Palladium-catalyzed *S*-arylation of unactivated arylsulfoxides.

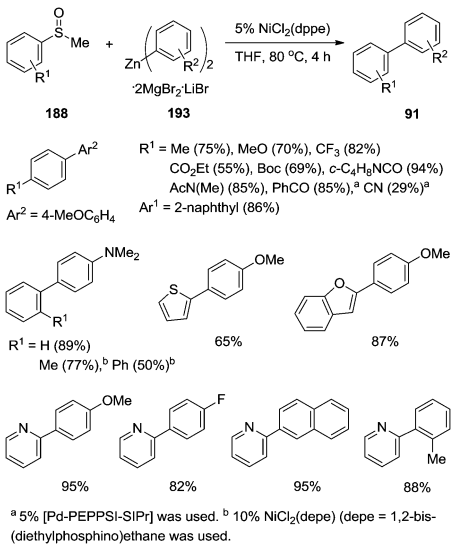
and electron-withdrawing 4-acetyl completely inhibited the desired reaction. These results have clearly suggested that the transition-metal complex catalyst as well as the ligand plays a crucial role in the alkyl C–S bond cleavage of the alkyl arylsulfoxides.[163,164]

In the presence of an air- and moisture-stable Nixantphos-based palladium catalyst (**190**) diaryl sulfoxides were efficiently synthesized from benzyl arylsulfoxides (**191**) and aryl chlorides through benzyl C–S bond cleavage of the sulfoxides.[165] The mechanistic studies have revealed that such a precatalyst promotes all the three sequential catalytic cycles and the key step is the *S*-arylation of a sulfenate anion (Scheme 63). Diverse functional groups such as those with acidic protons, F, OMe, NHAc, PhCO, ^{t}Bu, Me, CN, Me_2N, and CF_3 were tolerated. Under similar conditions by using 5% $Pd(dba)_2$/7.5% Nixantphos/NaO^{t}Bu (3 equiv.) as the catalytic system in CPME (cyclopentyl methyl ether) at 80 °C, benzyl arylsulfoxides (**191**) efficiently reacted with aryl bromides to give the corresponding diaryl sulfoxides **189** (85–95%).[166] Benzyl heteroaryl sulfoxides and heteroaryl bromides could also be used in the reaction. Such a catalytic system was effectively extended to the reaction of methyl phenyl (**188a**), dibenzyl (**191a**), and dimethyl sulfoxides (DMSO) with phenyl bromide, affording the diaryl sulfoxide product, that is, diphenyl sulfoxide (**189a**) in 88%, 73%, and 54% yields, respectively. With 5% $Pd(dba)_2$ as the precatalyst, 10% Xantphos as the ligand, and K_3PO_4 (2 equiv.) as the base, *tert*-butyl arylsulfoxides (**192**) underwent the cross-coupling reaction with aryl bromides and iodides as well as triflates in toluene or a toluene/H_2O mixture solvent at 90–120 °C, giving the diaryl sulfoxides of type **189** in up to 99% yields *via* the sulfenate anions generated *in situ* through the *tert*-butyl C–S bond cleavage[167] (Scheme 63). In a similar manner, di-*tert*-butyl sulfoxides reacted with aryl iodides to undergo double arylation by stepwise C–S bond cleavage, affording symmetrical and unsymmetrical diaryl sulfoxides, respectively. This method was applied for the diastereoselective construction of [2.2]paracyclophane-4-yl phenylsulfoxide in 91% yield, as a separable mixture of two diastereoisomers in a 75 : 25 molar ratio. Phenyl trifluoromethyl sulfoxide acted as a trifluoromethylation reagent in the presence of stoichiometric CuCl and KO^{t}Bu base in DMF at room temperature.[168] They reacted to cleave the alkyl C–S bond, *in situ* generating "$CuCF_3$" species which then interacted with aryl bromides and iodides or terminal alkynes under an air atmosphere to give the trifluoromethylated arene and alkyne products, respectively.

In order to cleave the aryl C–S bond in methyl arylsulfoxides (**188**) arylzinc reagents were employed. With 5% $NiCl_2$(dppe) as the catalyst Negishi-type cross-coupling of compounds **188** and arylzinc reagents **193** proceeded in THF at 80 °C, affording biaryl products **91** in moderate to excellent yields (Scheme 64).[169] Arylzinc reagents prepared from arylmagnesium bromide, zinc bromide, and lithium bromide were optimal to form the target products, while those arylzinc reagents prepared through other procedures exhibited lower reactivity. By consuming the catalyst-oxidizing methane-sulfenate anion ($MeSO^-$) through oxidative homocoupling of the arylzinc reagent, smooth catalyst turnover could be executed. The electronic effect varied from the 4-substituents on the aryl moiety of the sulfoxides, and the cyano group remarkably diminished the product yield to 29%, while the substituents on the aryl moiety of the arylzinc



Scheme 63 Palladium-catalyzed benzyl and *tert*-butyl C–S cleavage in sulfoxides.



[a] 5% [Pd-PEPPSI-SIPr] was used. [b] 10% $NiCl_2$(depe) (depe = 1,2-bis-(diethylphosphino)ethane was used.

Scheme 64 Nickel-catalyzed aryl C–S cleavage in sulfoxides.

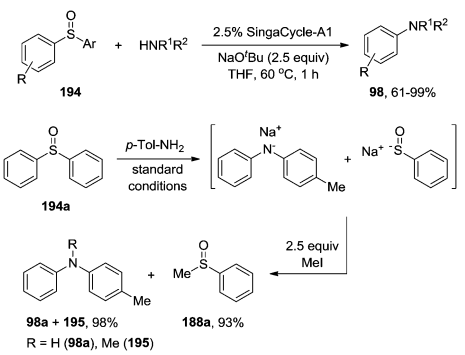
reagents facilitated the reaction, efficiently resulting in the target products. The $MeSO^-$ anion could be trapped by benzyl bromide during the nickel-catalyzed cross-coupling reaction of methyl phenylsulfoxide (**188a**) with 4-methoxyphenylzinc reagent at 80 °C. The control experiments demonstrated that the 4-CF_3 group facilitated the cross-coupling of **188** more efficiently than the 4-OMe group.

Palladium-catalyzed amination of diaryl sulfoxides **194** efficiently proceeded with anilines and alkylamines, forming the corresponding higher-order amine products **98** (61–99%) (Scheme 65).[170] SingaCycle-A1 was found to be the most efficient catalyst among the screened palladium sources, SingaCycle-A1, Pd–PEPPSI–IPr, $Pd(PPh_3)_4$, and XPhos Pd G2. The product yields were usually >80% with tolerance of functional groups such as silyl, boryl, methylsulfanyl, halogens, alkoxy, alkyls, CF_3, COOH, and OH. The regioselective amination of unsymmetrical diaryl sulfoxides was also executed by means of the steric bias. For example, the amination of sterically biased 2,6-dimethyl-phenyl 4-methoxyphenyl sulfoxide (**194b**) with *p*-toluidine proceeded at the less hindered C–S(=O) bond exclusively, giving the corresponding *N*-(4-methoxyphenyl)-*N*-(*p*-tolyl)amine (**98b**). Although this amination was applied to more accessible alkyl arylsulfoxides such as methyl phenylsulfoxide (**188a**) and *tert*-butyl *p*-tolylsulfoxide (**192a**), their reactions with *p*-toluidine occurred sluggishly to give the target products in 10–22% yields within 3 h. The more electron-donating alkylsulfinyl groups may diminish the oxidative addition and transmetalation steps in the catalytic cycle, and the *in situ* generated alkanesulfenate anions may be labile and catalyst-poisonous to interfere with the catalyst turnover. Generation of the arenesulfenate anions was confirmed by an electrophilic trapping experiment as shown in Scheme 65. After amination of **194a** with *p*-toluidine was complete under the standard conditions, the mixture was treated with 2.5 equiv. of MeI. Thus, the desired methyl phenylsulfoxide (**188a**) was obtained in 93% yield accompanied by a mixture of the target amination product **98a** and its methylated derivative **195** in a 98% total yield. Borylation of the C–S bonds in diaryl sulfoxides with bis(pinacolato)diboron (B_2pin_2) was achieved by means of a palladium–SPhos complex catalyst with $LiN(SiMe_3)_2$ as the base.[171] Both of the aryl rings in the diaryl sulfoxides were converted into the corresponding borylated products (ArBpin) in up to 81% yields. In the presence of the Pd–PEPPSI–SIPr catalyst and LiO^tBu base, Sonogashira–Hagihara-type alkynylation of diaryl sulfoxides with unactivated terminal alkynes was realized, affording the corresponding arylated alkyne products in up to 100% yields.[172]

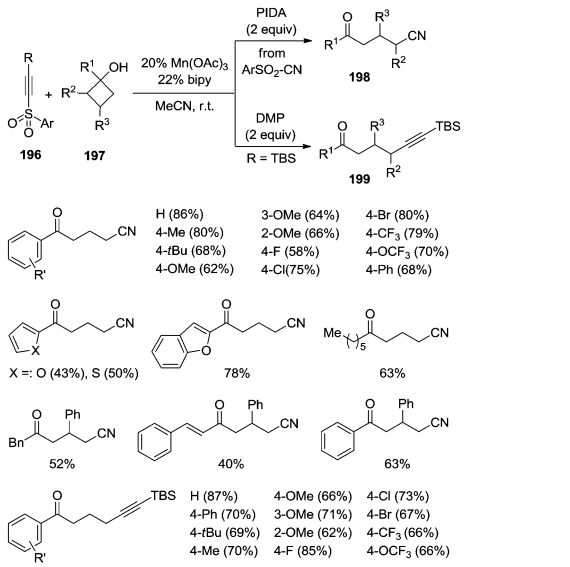
4.3 Sulfones

Sulfones feature more polar and labile C–S bonds than their sulfoxide analogs that they can be applied as the coupling partners in the desulfitative cross-coupling reactions. Manganese(III)-catalyzed desulfitative ring-opening cyanation and ethynylation of alkynyl arylsulfones (**196**) with cyclobutanol derivatives (**197**) were achieved under mild conditions, giving the target products in moderate to excellent yields (34–87%) (Scheme 66).[173] At room temperature, the cyano and ethynyl groups were regioselectively introduced to the γ-position of the resultant ketones as a C1 or C2 unit, respectively. Such transformations are based on a common sequence: (a) oxidative ring-opening of cyclobutanol through C–C bond cleavage; (b) radical addition to the triple bond bearing an arylsulfonyl group; and (c) radical-mediated C–S bond cleavage. By means of the one-carbon-chain growth strategy rare aliphatic nitriles **198** and alkynes **199** were accessed, respectively. Heteroaryl sulfones were also used in the reaction. This protocol features broad substrate scopes with tolerance of a variety of functional groups such as halogens, aryls, alkyls, CF_3, OMe, and OCF_3, regioselectively affording γ-cyanated and -alkynylated alkyl ketones, and providing mild but powerful methods for the production of elusive aliphatic nitriles and alkynes.

Using a combination of 2.5% Pd–NHC/1.3% $[RhCl(cod)]_2$ precatalysts the Suzuki–Miyaura arylation of aryl trifluoromethyl sulfones with arylboronic acid neopentylglycol esters proceeded smoothly in refluxing THF in the presence of LiO^tBu base (2 equiv.), giving the corresponding biaryls in moderate to excellent yields.[174] The mechanistic investigation has suggested that the rhodium catalyst mediates the aryl transfer from the arylboronate to the palladium center, resulting in acceleration of the transmetalation step, and the C–C bond-forming reductive elimination step is the turnover-limiting step. In a similar

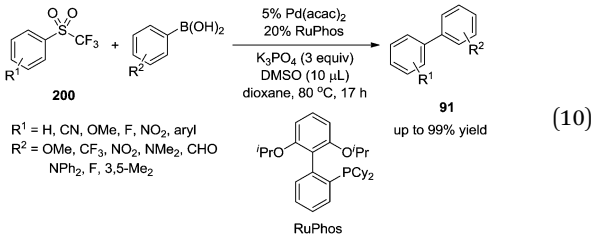


Scheme 65 Electrophilic trapping of arenesulfenate anions.



Scheme 66 Mn(III)-Catalyzed C–S bond cleavage in sulfones.

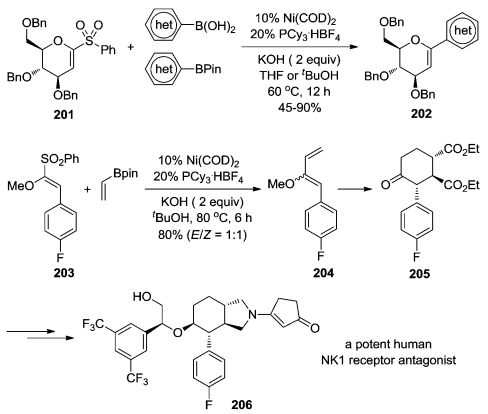
fashion using arylboronic acids, the same reaction of aryl trifluoromethyl sulfones (**200**) proceeded more efficiently to give diverse functionalized biaryls **91** (eqn (10)).[175] A wide range of functional groups were tolerated. 2-Pyridyl and biphenyl-based CF_3-sulfones, and 1-naphthyl and 2-thienyl boronic acids were also the suitable substrates for the reaction. The target functionalized biaryl products were obtained in moderate to high yields.



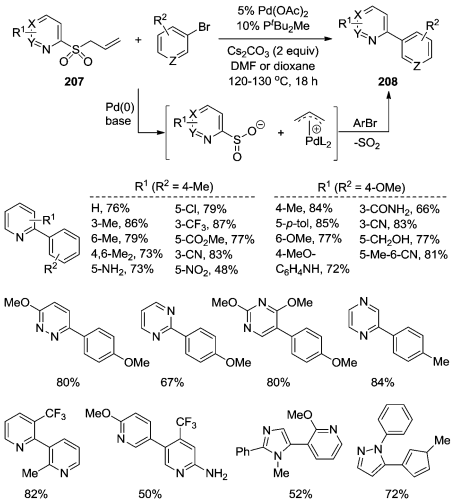
(10)

Nickel-catalyzed Suzuki–Miyaura cross-coupling of α-oxo-vinylsulfones was recently documented for the preparation of *C*-aryl glycals and acyclic vinyl ethers.[176] With 10% $Ni(COD)_2$ as the catalyst and 20% $PCy_3{\cdot}HBF_4$ as the ligand in the presence of KOH base (2 equiv.) the reaction of vinylsulfones, that is, sulfonyl glycals **201**, with (hetero)arylboronic acids or boronates in THF or ^{t}BuOH at 60 °C gave the target (hetero)arylated glycals **202** (Scheme 67). Vinylsulfone **203** reacted with the vinylboronate at an elevated temperature (80 °C) to efficiently afford acyclic vinyl ether **204** (80%) which was used as an intermediate for the synthesis of **206**, a potent human NK1 receptor antagonist. These reactions employ readily available starting materials and reagents, proceed under mild conditions, and tolerate various functional groups and heterocycles. Such a protocol has demonstrated a synthetic potential to prepare pharmaceutically relevant aryl gylcals and synthetically useful acyclic vinyl ethers.

Heterocyclic sulfinates are effective reagents in palladium-catalyzed coupling reactions with aryl and heteroaryl halides, often providing high yields for the target biaryl products. However, the preparation and purification of complex heterocyclic sulfinates is usually problematic, and they can not tolerate many synthetic conditions. Fortunately, heterocyclic allylsulfones

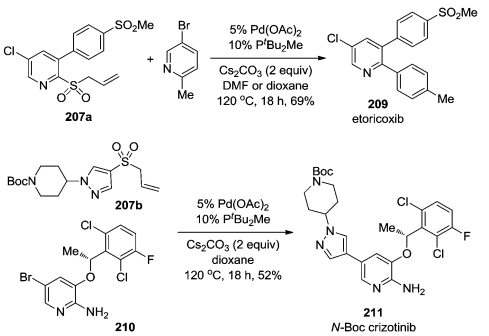


Scheme 67 Ni(0)-Catalyzed Suzuki–Miyaura cross-coupling of vinylsulfones.

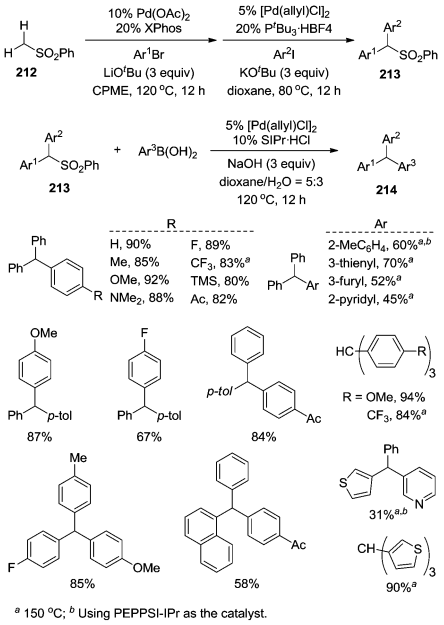


Scheme 68 Pd(II)-Catalyzed deallylation/desulfitative cross-coupling cascade of sulfones.

can act as latent sulfinate reagents to be involved in palladium-catalyzed reactions with aryl halides through a deallylation/desulfitative cross-coupling cascade (Scheme 68).[177] Thus, by means of 5% $Pd(OAc)_2$ as the catalyst, P^tBu_2Me as the ligand, and Cs_2CO_3 as the base in DMF or dioxane at 120–130 °C, heterocyclic allylsulfones **207** were used for this purpose. Pyridyl and other N-heterocyclic sulfones efficiently reacted with aryl and N-heteroaryl bromides to give the target biaryl products **208** in good to excellent yields, and only in a few cases including 5-NO_2-substituted phenyl bromide were the products obtained in *ca.* 50% yields. Functional groups amino, chloro, trifluoromethyl, ester, nitro, amido, methoxy, cyano, and hydroxy, *etc.* were tolerated. Pyridyl, pyrimidyl, pyridazinyl, pyrazinyl, imidazolyl, pyrazolyl, quinolinyl, isoquinolinyl, and isoxazolyl-based substrates were suitable for the cross-coupling reaction. These allylsulfones were also successfully coupled with a variety of medicinally relevant substrates, demonstrating their applicability in demanding cross-coupling transformations. Furthermore, the synthetic protocol was applied in the multiple-step synthesis, and the present cross-coupling strategy was utilized for the late-stage elaboration of pharmaceutically important agents, *i.e.*, etoricoxib and crizotinib (Scheme 69).

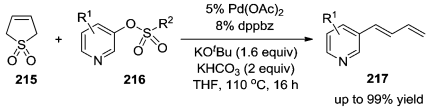


Scheme 69 Late-stage elaboration of etoricoxib and crizotinib.



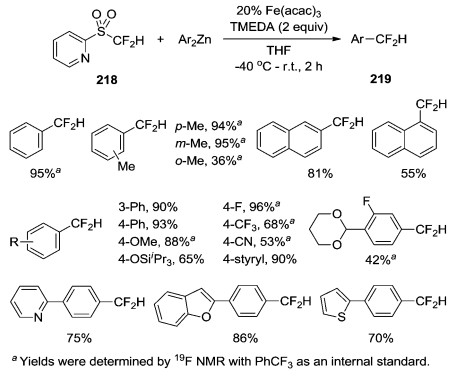
Scheme 70 Sequential arylation of methyl phenylsulfone.

Starting from readily available methyl phenylsulfone (**212**) a new strategy was developed to synthesize triarylmethanes **214**, which are valuable structures in materials, sensing compounds and pharmaceuticals, through three sequential palladium-catalyzed arylations.[178] This method involves two types of catalytic transformations: two stepwise C–H arylation reactions and a simultaneous benzylic C–S cleavage/arylation process through desulfonylation (Scheme 70). The arylative desulfonation of diphenylmethyl phenylsulfone (**213a**) was conducted in the presence of 5% $[PdCl(allyl)]_2$ as the catalyst, SIPr·HCl as the NHC ligand precursor, and NaOH as the base in refluxing dioxane/H_2O mixture solvent. A variety of electronically and structurally diverse aryl and heteroaryl boronic acids including 3-thienyl, 3-furyl, and 3-pyridyl boronic acids could be used in the reaction, giving the target diphenylarylmethanes in high yields. Aryl boronic acids bearing an electron-donating group such as *p*-methyl, *p*-methoxy, or *p*-*N*,*N*-dimethylamino reacted to form the products in 85–92% yields. The electron-withdrawing *p*-F group did not obviously affect the reaction efficiency, reaching 89% yield. Although electron-deficient *p*-CF_3-substituted phenylboronic acid exhibited a lower reactivity under the standard conditions, simply elevating the temperature to 150 °C led to the target product in a high yield (83%). Trimethylsilyl (TMS) and acetyl groups were also well tolerated. The sterically hindered *o*-tolylboronic acid showed a negative impact on the reaction efficiency, which could be improved by using the commercially available Pd–NHC catalyst. Heteroaryl functionalities, that is, 3-thienyl, 3-furyl, and 3-pyridyl, were also well installed in moderate to good yields (45–70%). With the same synthetic protocol diverse unsymmetrical triarylmethanes were programmably prepared (31–94%). In particular, triarylmethanes containing a thienyl, furyl, or pyridyl group, which are difficult to install using the typical Friedel–Crafts reaction procedure, were readily synthesized. In this manner, tris(3-thienyl)methane was accessed in 90% yield. It is noteworthy that sulfonenes (**215**) underwent palladium-catalyzed desulfitative C–O and C–I dienylation to stereoselectively give functionalized dienes **217** (eqn (11)).[179] Aryl, heteroaryl, and vinyl triflates, nonaflates, and iodides were suitable for the reaction. Functionalized sulfonenes could also be applied in the reaction, leading to multisubstituted dienes.

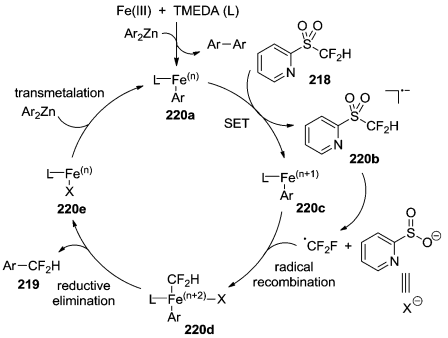


(11)

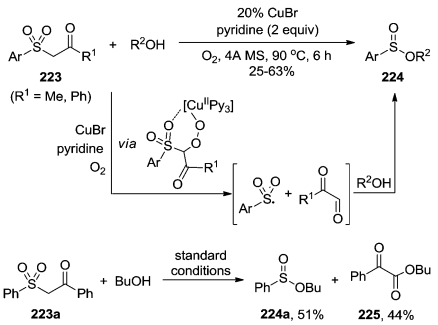
Although pyridyl allylsulfones **207** can undergo palladium-catalyzed deallylation/desulfitative cross-coupling with (hetero)aryl bromides to form biaryls,[177] 2-pyridyl difluoro-methylsulfone (**218**) reacted with arylzincs to afford difluoromethylarenes **219** through alkyl C–S bond cleavage under iron catalysis (Scheme 71).[180] A difluoromethyl group (CF_2H) has been used as a structural mimic to a hydroxy group in bioactive molecules.[181] However, conventional methods to directly introduce a CF_2H group onto an aryl moiety are limited. With 20% $Fe(acac)_3$ as the catalyst and TMEDA as the ligand in THF at −40 °C to room temperature, the aromatic difluoromethylation was conducted by means of **218** and arylzinc reagents. In the case of using diphenylzinc, the target difluoromethylarene **219a** was obtained in 95% yield. Arylzincs with an *ortho*-substituent gave inferior yields (36% and 55%), while reactions with *meta*- and *para*-substituted arylzincs attained excellent yields (81–95%). The electron-neutral, electron-rich, and electron-poor arylzincs were all suitable for the difluoromethylation reaction. The C=C double bond (styryl group) was tolerated under the stated conditions. A 1,3-propanediol acetal-bearing substrate was also successfully difluoromethylated in a moderate yield (42%). Heteroaryl-functionalized arylzincs efficiently underwent the difluoromethylation reaction to give the target products in high yields. It was found that the reaction was completely suppressed by the addition of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) and 1,4-benzoquinone (BQ), and the addition of 1,4-dinitrobenezene, a single electron transfer (SET) inhibitor, substantially inhibited the reaction, suggesting that a SET process and radical intermediates were involved in the reaction. A radical mechanism was proposed (Scheme 72), suggesting that the reaction is initiated by the formation of a reduced iron species **220a**,



Scheme 71 Iron-catalyzed difluoromethylation *via* CF_2H-sulfones.

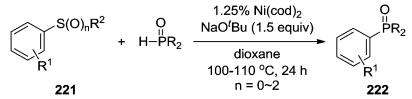


Scheme 72 Proposed mechanism for iron-catalyzed difluoromethylation of CF_2H-sulfones.



Scheme 73 Cu(I)-Catalyzed radical C–S bond cleavage in sulfones.

which is generated from the reduction of the precatalyst $Fe(acac)_3$ with arylzinc reagent in the presence of TMEDA. A SET process occurs between **220a** and 2-$PySO_2CF_2H$ (**218**) to form radical anion **220b** which undergoes fragmentation to result in a difluoromethyl radical. The radical recombination proceeds to form intermediate **220d** by interaction with the *in situ* generated iron complex **220c**. Subsequent reductive elimination gives product **219**. The catalytically active iron species **220a** is then regenerated through the transmetalation of species **220e** by Ar_2Zn, finishing a catalytic cycle.

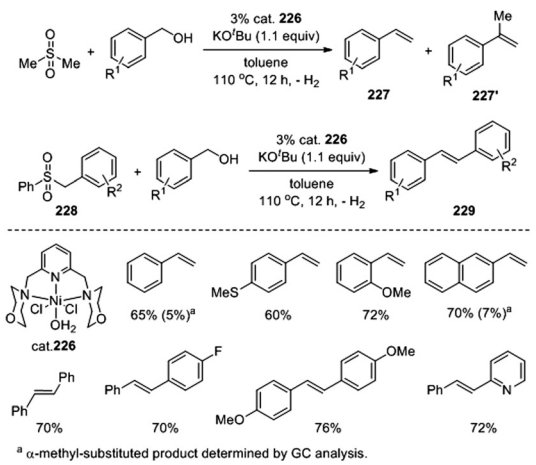


(12)

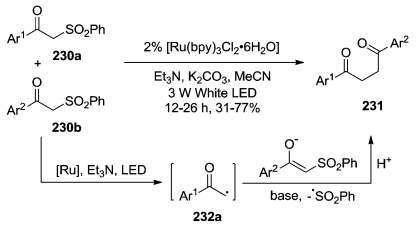
Nickel(0)-catalyzed phosphinylation of aryl sulfones and sulfoxides was realized with diaryl, dialkyl, or dialkoxyphosphine oxides through aromatic C–S bond cleavage (eqn (12)).[182] In the presence of 1.25% $Ni(cod)_2$ as the precatalyst and NaO^tBu as the base in dioxane, a variety of arylsufones **221** readily underwent the desulfitative C–S/P–H cross-coupling with the P(O)–H compounds, efficiently giving the target phosphinylation products **222** in 91–98% yields. Dialkoxyphosphine oxide $(^iPrO)_2P(O)H$ exhibited a reactivity much lower than its phenyl and *n*-butyl-based analogs. Thienyl and pyrimidinyl substituents on the aryl moiety of the arylsulfone substrates diminished the reaction efficiency. Both alkyl aryl and diarylsulfones nearly exhibited the same reactivity to form the target products in 97–98% yields. However, methyl phenylsulfoxide (**188a**) exhibited only a low reactivity even at an elevated temperature (120 °C), forming the product in 38% yield. Unexpectedly, the phosphinylation reaction of methyl arylthioethers **89** proceeded smoothly, affording the products in 30–98% yields.

A Cu(I)-catalyzed oxidative radical process of β-keto sulfones **223** with alcohols was established by using oxygen as the oxidant, giving the sulfinate esters **224** *via* alkyl C–S bond cleavage (Scheme 73).[183] Among the selected aliphatic alcohols, methanol, ethanol, propanol, *n*-butanol, *tert*-butanol, pentanol, 2-ethoxyethanol, benzyl alcohols, and cyclic alcohols, only *tert*-butanol exhibited a negative steric effect on the reaction with benzenesulfonylacetone, giving the target product in 25% yield. In other cases, the products were obtained in moderate to good yields (43–63%). However, neither 1-(benzylsulfonyl)propan-2-one nor 2-(phenylsulfonyl)acetonitrile reacted with *n*-butanol to give the target product under the stated conditions, implicating the crucial role of the aryl and carbonyl functionalities in the sulfone substrates. 1-Phenyl-2-(phenylsulfonyl)ethanone (**223a**) was chosen to react with *n*-butanol to form the target sulfinate ester product **224a** (51%) as well as *n*-butyl 2-oxo-2-phenylacetate (**225**, 44%), revealing that the arylsulfonyl-acetone carbonyl group is incorporated into the respective ketoester in the reaction. Experimental and computational studies have suggested that the reaction proceeds through the formation of a four-coordinated Cu(II) intermediate, O–O bond homolysis induced C–S bond cleavage, and Cu-catalyzed esterification to form the final product.

With Ni(II) complex **226** as the precatalyst in the presence of KO^tBu base direct olefination of sulfones with benzyl alcohols was achieved to afford olefins and release of dihydrogen (Scheme 74).[184] In the case of using dimethylsulfone, terminal olefins styrenes **227** were obtained in 40–76% yields with the branched styrenes **227′** (5–20%) as the minor products. When aryl benzylsulfones (**228**) were used, functionalized internal olefins **229** were generated in 45–90% yields. N- and O-heteroaryl groups were tolerated, but aryl alkyl sulfones did not undergo the reaction under the stated conditions. A combination of $NiBr_2$/neocuproline/KOH as the catalyst system was



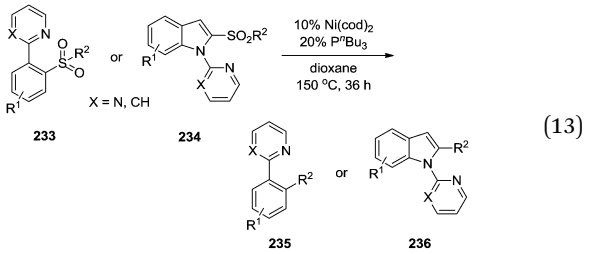
Scheme 74 Ni(II)-Catalyzed radical C–S bond cleavage in sulfones.



Scheme 75 Visible-light-induced C–S bond cleavage in sulfones.

applied for the same purpose.[185] This protocol provides a direct method to access olefins from readily available starting materials and base-metal complex catalysts.

A visible light-driven strategy was applied for the C–S bond cleavage of sulfones. Such a visible-light-induced alkyl C–S bond cleavage was conducted to access 1,4-diketones **231** from β,β-keto arylsulfones **230** (Scheme 75).[186] Symmetrical and unsymmetrical 1,4-diketones were conveniently prepared in 31–77% yields. A plausible mechanism indicates that the excited state of the photoredox catalyst Ru(II)* is reductively quenched by Et_3N to deliver the strong reductant Ru(I) species which then reduces β-keto sulfone **230a** by a SET process, forming the key radical intermediate **232a**. Radical **232a** reacts with the enolic anion of **230b** generated *in situ* or another molecule of **230a** affords the target unsymmetrical or symmetrical product of type **231**. $Ni(cod)_2$-catalyzed intramolecular desulfonylation of aromatic, heteroaromatic, and aliphatic sulfones was achieved to give the corresponding biaryls or alkylated (hetero)arenes (eqn (13)).[187] The target products **235** and **236** were obtained in up to 82% yields. The N-heterocyclic directing groups (2-pyridyl and 2-pyrimidyl) in the substrates are crucial for the success of the reaction. These results offer an atom-economical route to conversion of the sulfonyl groups in organic synthesis.



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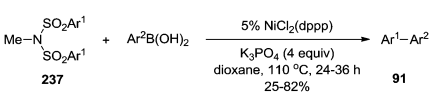


(14)

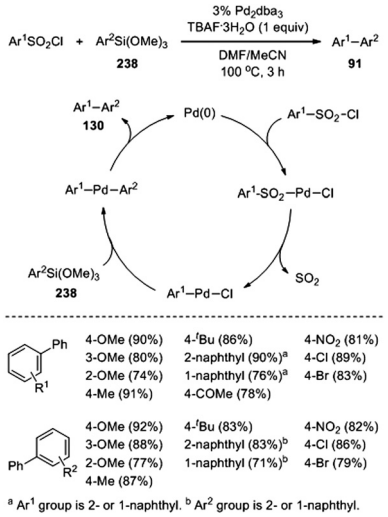
A nickel-catalyzed approach was documented for the synthesis of biaryls from *N*,*N*-disulfonylmethylamines **237** and arylboronic acids through aryl C–S bond cleavage of amino-based sulfones. The desulfitative Suzuki–Miyaura cross-coupling reaction afforded the corresponding biaryl products of type **91** (eqn (14)).[188] The unsymmetrical biaryls were not the sole products, and symmetrical biaryls were detected in most cases due to the desulfitative homocoupling of the sulfonyl group. Primary sulfonamides have recently been reported as a new class of coupling partners for the direct synthesis of unsymmetrical thioethers through copper-catalyzed aryl C–S bond cleavage.[189] By means of 10% CuI as the catalyst and Na_2CO_3 (2 equiv.) as the base in DMF at 100 °C, primary 2-nitro benzenesulfonamides efficiently coupled with aryl or alkyl thiols to give the corresponding unsymmetrical thioethers (ArSR) in up to 98% yields. In this case, the Ar–SO_2NH_2 bond was regioselectively cleaved. With CuCl as the catalyst in the presence of LiO^tBu base a heteroaryl C–H/sulfone C–S cross-coupling was realized to access functionalized heteroarenes, in which copper carbene was proposed as the reaction intermediate.[190]

5. C–S bond cleavage in sulfonyl chlorides and sulfinates

5.1 Sulfonyl chlorides

Sulfonyl chlorides are readily available and versatile reagents for both catalytic cross-coupling and C–H functionalization reactions.[191,192] The C–S bond in sulfonyl chlorides is considered as an activated bond, and considerable work has recently been documented for their catalytic desulfitative C–C cross-coupling reactions.[193–195] It has been well known that desulfonylation of arylsulfonyl chlorides can be achieved by stoichiometric transition-metal complexes.[196] In the presence of a transition-metal catalyst, a sulfonyl chloride substrate is usually oxidatively added to the transition-metal center, followed by desulfonylation to release SO_2, and then the other coupling partner is oxidatively added to the newly generated metal center in the catalytic cycle. Subsequently, reductive elimination proceeds to give the desulfitative cross-coupling product. Aryl-, arylmethyl-, and alkenylsulfonyl chlorides underwent palladium-catalyzed Suzuki–Miyaura cross-coupling reaction with aryl, heteroaryl, and alkenylboronic acids in THF at reflux, giving the corresponding biaryls and analogs.[197] Aryl trifluoroborates ($ArBF_3K$) were applied for the same purpose.[198] Palladium-catalyzed desulfitative Heck reaction of (poly)halo-substituted arylsulfonyl chlorides with terminal alkenes was realized in the presence of a phosphine-free palladium catalyst, affording the corresponding β-arylated Heck-type products with complete regio- and stereoselectivities.[199] Using 4-bromophenylsulfonyl chloride as the central unit, consecutive desulfitative Heck-type reaction followed by palladium-catalyzed direct arylation allowed preparation of heteroarylated stilbene derivatives in only two steps.

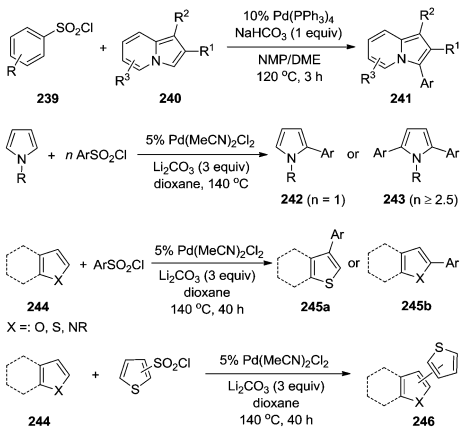
Palladium-catalyzed desulfitative Hiyama cross-coupling of arylsulfonyl chlorides with aryltrimethoxysilanes (**238**) was conducted to give biaryls **91** in good to excellent yields (71–92%),[200] following a typical palladium(0)-catalyzed oxidative addition/desulfonylation/transmetalation/reductive elimination mechanism[197] (Scheme 76). The reaction tolerated a range of functional groups at the *para*-position with coupling occurring in the presence of methoxy, acetyl, or nitro group. The ability to incorporate chloro and bromo groups makes this reaction particularly attractive for further transition-metal-catalyzed transformations. However, the substituents on the aryl moieties of the substrates affected the reaction. The electron-withdrawing groups such as nitro and acetyl usually diminished



Scheme 76 Hiyama cross-coupling of sulfonyl chlorides.

the product yields, and the steric hindrance from 2-methoxy and 1-naphthyl obviously reduced the reaction efficiency. Importantly, naphthyl groups were also applicable to the reaction conditions in high yields (71–90%) no matter whether naphthylsulfonyl chlorides or trimethoxy(naphthyl)silanes were used.

Palladium-catalyzed direct C3 desulfitative arylation of indolizines **240** with arylsulfonyl chlorides **239** was achieved, giving 3-arylation products **241** (38–50%)[201] (Scheme 77). Mono- and diarylations of pyrroles were performed to give **242** and **243** under palladium catalysis, respectively, by varying the amount of the arylsulfonyl chlorides.[202] When thiophenes **244** were used as the C–H substrates, the arylation reaction selectively occurred at the C3 or C4-position to form the arylated thiophene derivatives **244a**, whereas the reaction occurred at the C2(5)-position for furans and pyrroles, and at the C2-position for benzofurans, affording compounds of type **245b**.[203–205] Heteroarylation could also be established between heteroarenes **244** and heteroaryl-sulfonyl chlorides, such as 3-thienyl, 2-thienyl, 2-pyrrolyl, 3-pyridyl, and 2-pyrrolylsulfonyl chlorides, producing bi(hetero)aryls **246** under Pd(II) catalysis[206] (Scheme 77).



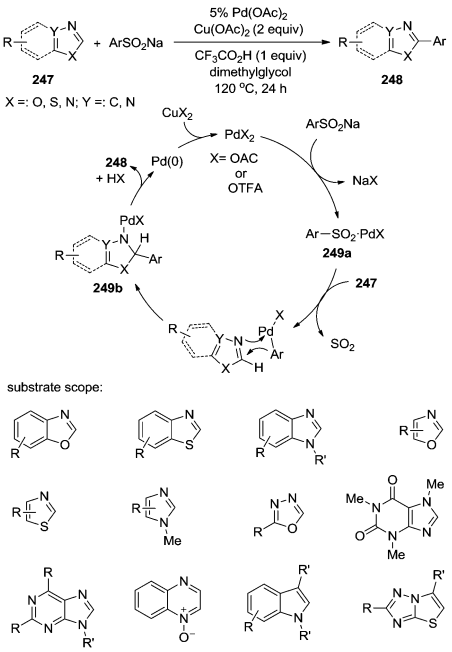
Scheme 77 C–H arylation of heteroarenes *via* C–S bond cleavage of sulfonyl chlorides.

5.2 Sulfinates

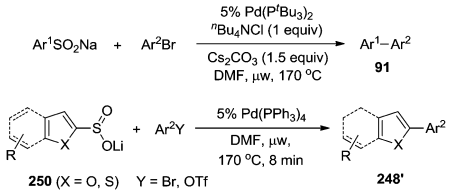
Sulfinates and their analogs have recently emerged as versatile coupling partners to access diverse aryl, heteroaryl, and carbocyclic compounds due to their dual capacity for acting as both nucleophilic and electrophilic reagents as well as ready manipulations.[207] They are usually applied as the surrogates of sulfonyl chlorides in the desulfitative cross-coupling to form new C–C bonds under relatively mild conditions.[195]

Sulfinate salts can undergo versatile cross-couplings for C–C bond construction. By using the palladium catalyst/copper(II) oxidant systems desulfitative C–H arylation of heteroarenes **247** at the 2-position readily occurred with sodium arylsulfinates[208] (Scheme 78). Azoles including benzoxazoles, benzothiazoles, benzimidazoles, oxazoles, thiazoles, imidazoles, 1,3-oxadiazoles, caffeine and derivatives, quinoxaline *N*-oxide, *N*-protected indoles, and thiazolo[3,2-*b*]-1,2,4-triazoles were reacted with sodium arylsulfinates to give the corresponding 2-arylated products **248** in good to excellent yields. A typical mechanism for such a palladium-catalyzed C–H arylation of heteroarenes with sodium arylsulfinates is proposed. The first step is presumably a ligand exchange between PdX_2 and sodium arylsulfinate to generate a Pd(II)-sulfinate intermediate **249a**, followed by desulfonylation to release SO_2 and form complex ArPdX. The heteroaryl C=N bond insertion of heteroarene **247** into the Pd–C bond of complex ArPdX leads to species **249b** *via* a possible carbopalladation. Subsequent β-hydride elimination from **249b** affords the target C–H arylation product **248**. Regioselective C-5 desulfitative arylation of thiazolo[3,2-*b*]-1,2,4-triazoles with sodium arylsulfinates also occurred under palladium catalysis.

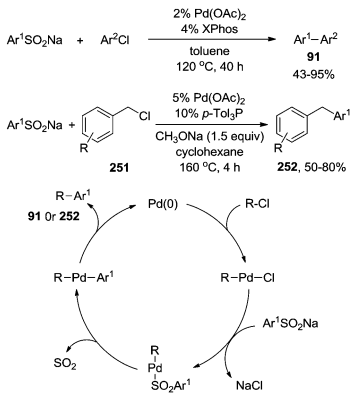
Sulfinates of a metal usually act as the nucleophilic partners in the cross-coupling reaction with organic reagents. Thus, palladium(0)-catalyzed desulfitative cross-coupling of sodium



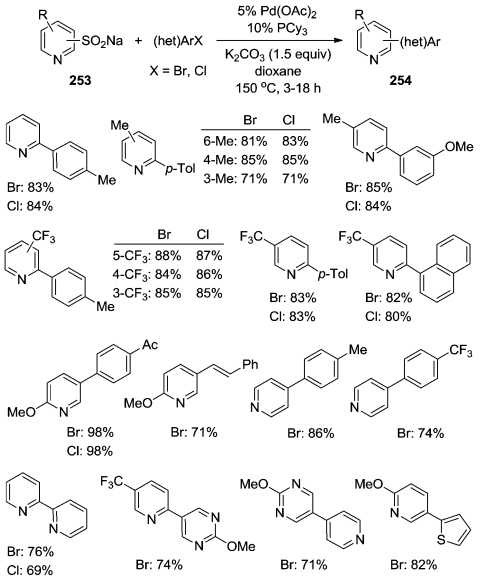
Scheme 78 C–H arylation *via* C–S bond cleavage of sodium sulfinates.



Scheme 79 Sulfinates as nucleophilic coupling partners.



Scheme 80 Cross-coupling of sodium sulfinates with aryl (benzyl) chlorides.

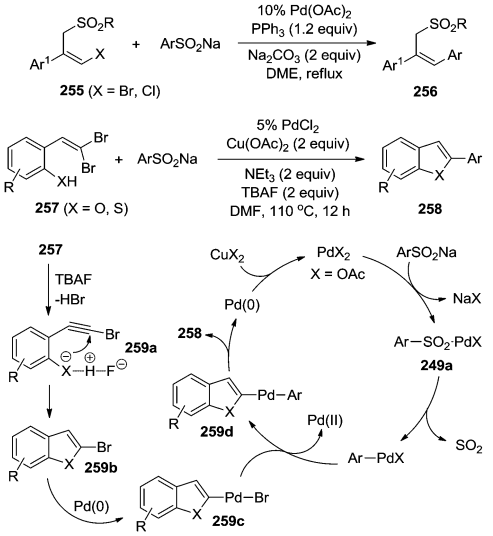


Scheme 81 Cross-coupling of sodium pyridylsulfinates with N-heteroaryl halides.

arylsulfinates with aryl bromides was conducted to produce the corresponding biaryl products **91** in the presence of a base under microwave irradiation (Scheme 79).[209,210] With 2.5% $Pd(dppf)Cl_2$/5% $P(OPh)_3$/K_2CO_3 (2 equiv.) as the catalyst system in DMF at 150 °C, the reaction of sodium arylsulfinates with aryl bromides or iodides efficiently proceeded to afford the target symmetrical or unsymmetrical biaryl products (78–92%).[211] The alternative sulfinate salts, that is, lithium sulfinates **250**, was applied for the same purpose.[212–214] Less reactive aryl chlorides[215] and reactive benzyl chlorides[216] as well as aryl tosylates[214] were used in such palladium-catalyzed desulfitative cross-coupling reactions. A plausible mechanism is proposed in Scheme 80. The precatalyst interacts with the phosphine ligand to generate the catalytically active Pd(0) species. Initial oxidative addition of the aryl or benzyl halide to the Pd(0) species forms the Pd(II) intermediate (R–Pd–Cl). Next, ligand exchange with the arylsulfinate substrate gives the Pd(II) sulfinate ($R–Pd–SO_2Ar^1$). Then, desulfonylation proceeds to release SO_2 and generate intermediate $R–Pd–Ar^1$. Subsequent reductive elimination from the $R–Pd–Ar^1$ species forms the target product **91** or **252** with regeneration of the Pd(0) species, establishing a catalytic cycle.

Sodium heteroarylsulfinates were also used to couple with aryl and heteroaryl bromides or chlorides under palladium catalysis (Scheme 81).[217] In the presence of 5% $Pd(OAc)_2$ catalyst, 10% PCy_3 ligand, and K_2CO_3 (1.5 equiv.) as the base in dioxane at 150 °C, functionalized sodium pyridylsulfinates **253** reacted with diverse aryl and heteroaryl bromides and chlorides to give the target (hetero)arylated pyridines **254** in good to excellent yields (69–98%). Sodium 2-, 3-, and 4-pyridylsulfinates, and functionalized aryl and N-heteroaryl bromides and chlorides were employed in the reaction. In the case of using aryl halides the product yields were comparable for the bromides and chlorides, while the heteroaryl chlorides exhibited a reactivity lower than their bromide analogs to give the products in 69–90% yields (*vs.* 76–95% yields by using the corresponding bromides). Styryl and 2-thienyl bromides were used in the reaction to produce the desired products (71–82%). This cross-coupling method was successfully applied for the derivatization of medicinally relevant molecules such as Cl-varenicline and mepyramine by means of N-heteroaryl sulfinates and bromides, respectively.

Sodium arylsulfinates were used to construct Heck-type products from the cross-coupling reaction with vinylic bromides. $Pd(OAc)_2$ catalyzed the desulfinative cross-coupling of sodium arylsulfinates with (*Z*)-β-bromostyrenes (**255**) in the presence of the PPh_3 ligand and Na_2CO_3 base at reflux to yield the stereocontrolled products **256** in good yields[218] (Scheme 82), and the relevant methodology was successfully applied for the synthesis of Tamoxifen. In a similar fashion, a regioselective palladium-catalyzed desulfitative Heck-type reaction of Baylis–Hillman adducts and sodium arylsulfinates was used to access α-benzyl-β-keto-esters.[219] Palladium-catalyzed tandem elimination/cyclization/desulfinative arylation of 2-*gem*-arylsulfinates formed benzofuran and benzothiophene derivatives **258**, respectively[220] (Scheme 82). The reaction may proceed through HBr elimination from **257** to form bromoalkynyl intermediate **259a** which then undergoes intramolecular nucleophilic addition to generate 2-bromo-benzofuran or -thiophene (**259b**). Palladium-catalyzed desulfitative arylation with sodium arylsulfinate proceeds to give Pd(II) complex **259d** presumably *via* (hetero)ArPdBr complex **259c**. Reductive elimination of **259d** affords the target product **258** and a Pd(0) species which is oxidized by $Cu(OAc)_2$ to Pd(II) to catalyze the next reaction. It should be noted that both aryl and heteroaryl halides and vinyl bromides could execute nickel-catalyzed sulfonylation with sodium arylsulfinates under photoredox conditions,

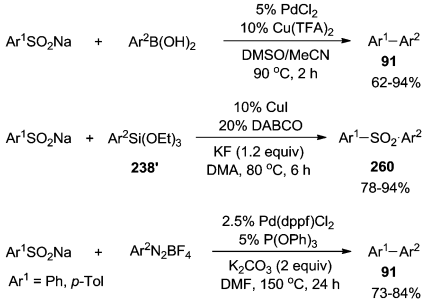


Scheme 82 Tandem cross-coupling of sodium arylsulfinates.

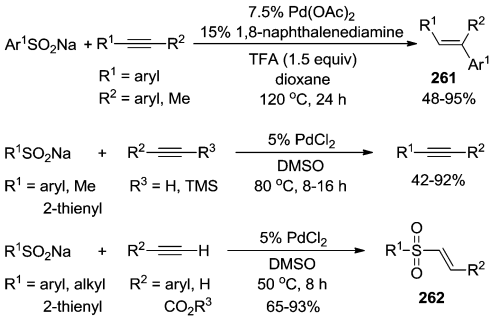
giving biaryl or aryl heteroaryl sulfones in moderate to good yields.[221]

Other coupling partners such as arylboronic acids, arylsilanes, Grignard reagents, and aryldiazonium salts were also documented for the cross-coupling with sodium aryl and heteroarylsulfinates, forming new C–C bonds to give biaryls. Palladium-catalyzed desulfinative Suzuki-type cross-coupling of sodium arylsulfinates with arylboronic acids was applied to make new C–C bonds for the synthesis of biaryls **91**[222] (Scheme 83). In the absence of the Pd(II) catalyst, the same reaction afforded the corresponding diaryl sulfone products ($ArSO_2Ar$). However, copper(I)-catalyzed desulfinative Hiyama-type reaction of sodium arylsulfinates with aryltri(ethoxy)silane (**238′**) did not occur, and the reaction only gave the corresponding sulfone products **260.**[223] With 2.5% $Pd(dppf)Cl_2$ as the catalyst in the presence of $P(OPh)_3$ as the ligand and K_2CO_3 as the base in DMF at 150 °C, sodium arylsulfinates efficiently reacted with aryldiazonium tetrafluoroborates to give biaryls **91** in 73–84% yields, further extending the scopes of the coupling partners for arylsulfinates in the cross-coupling reactions[224] (Scheme 83).

Desulfitative hydroarylation of alkynes with sodium arylsulfinates was achieved by using $Pd(OAc)_2$ as the catalyst and



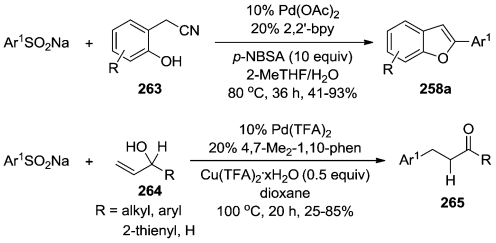
Scheme 83 Diverse cross-couplings of sodium (hetero)arylsulfinates.



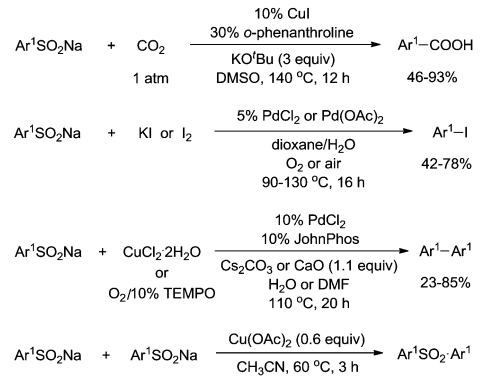
Scheme 84 Reactions of sodium arylsulfinates with alkynes.

1,8-naphthalenediamine as the ligand[225] (Scheme 84). Alkyne is proposed to insert into the Pd–C bond of the ArPd(II)X intermediate generated *in situ* from the interaction of the sulfinate with the catalyst, followed by hydrolysis to afford the target hydroarylation product **261.** In this case, only internal alkynes could be applied in the reaction. Interestingly, the reaction pathway was altered by using $PdCl_2$ as the catalyst in the absence of a ligand that the desulfitative reaction of terminal or TMS-functionalized internal alkynes with sodium arylsulfinates proceeded smoothly in DMSO at 80 °C, giving the internal alkyne products in 67–92% yields, while sodium methylsulfinate reacted with 1-ethynyl-4-methoxybenzene at 100 °C to form the target product in 42% yield.[226] However, in the absence of a ligand at 50 °C desulfonylation could not occur in the reaction sequence that the reaction of sodium aryl, alkyl, and 2-thienylsulfinates with terminal alkynes or even acetylene generated vinyl sulfones **262** in high yields (65–93%). At 100 °C the reaction of the same sodium sulfinates with 3-phenylpropiolic acid underwent decarboxylative cross-coupling, also forming the vinyl sulfone products.

Sodium arylsulfinates were used to react with phenol or alcohol derivatives under transition-metal catalysis. A palladium-catalyzed tandem reaction of 2-hydroxyarylacetonitriles (**263**) with sodium arylsulfinates produced 2-arylbenzofuran derivatives **258a**[227] (Scheme 85). *p*-Nitrobenzenesulfonic acid (*p*-NBSA) was crucial to promote the reaction. The plausible mechanism involves desulfitative addition and intramolecular annulation. The reaction was readily scaled up without any difficulty, which provides a practical and convenient method to access benzofuran derivatives. By means of 10% $Pd(TFA)_2$ as the catalyst, 4,7-dimethyl-1,10-phenanthroline as the ligand, and $Cu(TFA)_2{\cdot}xH_2O$ as the oxidant in dioxane at 100 °C, a highly regioselective Heck-



Scheme 85 Reactions of sodium arylsulfinates with phenols or alcohols.

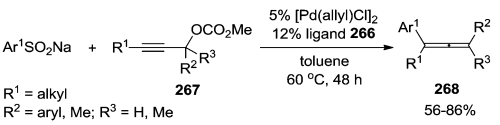


Scheme 86 Reactions of sodium arylsulfinates with versatile reagents.

type reaction of sodium arylsulfinates with allylic alcohols **264** was conducted to yield β-aryl ketones and aldehydes **265** (25–88%).[228] Functional groups such as halogens (I, Br, and F), OMe, and OCF_3 were tolerated, rendering the possible post-functionalization of these C–X bonds. The deuterium labeling experiments implicate that this transformation may proceed *via* a [1,2-H] shift process.

With CuI as the catalyst sodium arylsulfinates underwent desulfitative carboxylation with carbon dioxide, yielding the corresponding carboxylic acids in good to excellent yields (46–93%) (Scheme 86).[229] Sodium 2,4,6-triisopropylarenesulfinate did not exhibit any reactivity to CO_2 due to the steric hindrance under the stated conditions, while sodium 2,4,6-trimethylarene-sulfinate coupled with CO_2 to form the corresponding product in 82% yield. Desulfitative iodination of sodium arylsulfinates proceeded in the presence of KI or I_2 in air or under an oxygen atmosphere.[230] Palladium-catalyzed homocoupling of sodium arylsulfinates proceeded by using stoichiometric $CuCl_2{\cdot}2H_2O$ as the oxidant or using O_2 with a cocatalyst TEMPO.[231] The steric effect from the *ortho*-substituents on the aryl functionality was obvious to diminish the reaction efficiency. By means of a Cu(II) catalyst, desulfitative cross-coupling occurred between two sulfinate molecules, giving the symmetrical diaryl sulfones.[232] This homocoupling reaction was tolerant with various functional groups and occurred under relatively mild conditions.

Very recently, palladium-catalyzed desulfitative cross-coupling of sodium sulfinates with propargylic carbonates was reported for the synthesis of allenes (eqn (15)).[233] With 5% $[Pd(allyl)Cl]_2$ as the catalyst and tris[2,6-bis(methoxy)-phenyl]-phosphine (**266**) as the ligand sodium aryl sulfinates were desulfitatively coupled with propargylic carbonates **267**, affording tri- or tetrasubstituted allenes **268** in 56–86% yields. Use of the electron-rich and bulky phosphine ligand **266** is crucial for the reaction to regioselectively form the target products. The reaction features good substrate scopes and functional group tolerance, providing an alternative route to highly functionalized allenes.



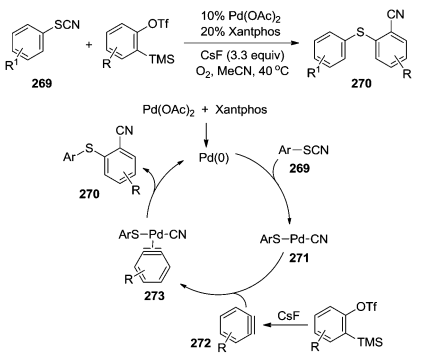
(15)

6. C–S bond cleavage in thiocyanates, sulfonium salts, sulfonyl hydrazides, and sulfonates

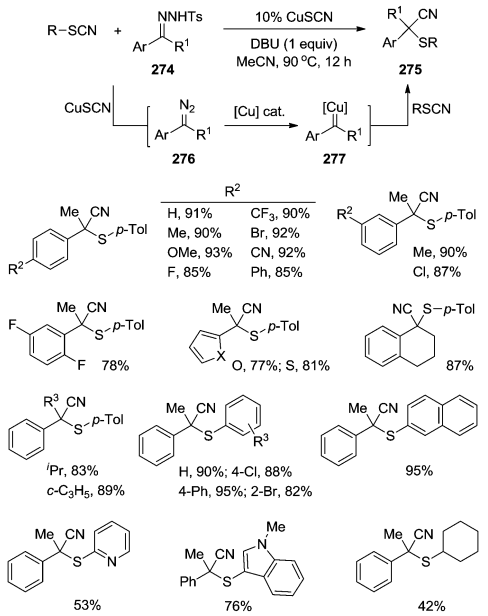
6.1 Thiocyanates

Transition-metal-catalyzed C–S bond cleavage often offers routes to specific organosulfur compounds. Under Liebeskind–Srogl coupling conditions, benzyl thiocyanates were desulfitatively coupled with aryl and alkenyl boronic acids, giving nitriles in good to excellent yields.[234] Other alkyl and arylthiocyanates were also used as effective coupling partners for such a $C(sp^3)$–S bond cleavage reaction. In this regard, palladium-catalyzed activation and C–S bond cleavage of arylthiocyanates **269** followed by aryne insertion was achieved to produce 1,2-thiobenzonitriles (**270**) in moderate to good yields (25–81%) through formation of new C–SAr and C–CN bonds (Scheme 87).[235] An oxygen atmosphere dramatically increased the product yields, minimized the side reactions, and significantly shortened the reaction time. Halogens (F, Br, and Cl), OMe, and CF_3 were tolerated on the aryl rings of the substrates. This method provides a straightforward access to 1,2-thiobenzonitriles from readily available arylthiocyanates and aryne precursors, serving as an alternative route to diaryl thioethers.

Copper(I)-catalyzed cyanothiolation of thiocyanates with *N*-tosylhydrazones **274** was conducted to construct α-aryl-thioalkanenitriles **275** bearing a sulfur-substituted quaternary carbon center (Scheme 88).[236] In the presence of 10% CuSCN catalyst and DBU base in acetonitrile at 90 °C, the reaction efficiently afforded the target products **275** (42–95%). The steric hindrance from the alkyl functionality and the electron-withdrawing group(s) on the aryl moiety of compounds **274** only slightly diminished the reaction efficiency. 2-Bromophenyl-thiocyanate showed a negative steric effect on the product yield (82%). In the case of 2-thiocyanatonaphthalene, the product was obtained in 95% yield. Furyl and thienyl-based substrates exhibited good reactivity to give the products in 77–90% yields. N-Heteroaryl thiocyanates such as 2-pyridyl and 3-(*N*-methyl)-indolylthiocyanates, and the alkylthiocyanate, that is, cyclohexyl-thiocyanate, reacted with phenyl methyl *N*-tosylhydrazone (**274a**), giving the target products in moderate to good yields (42–76%). Such a reaction involves the formation of a copper carbene species **277** from the initially generated diazo intermediate **276**, which



Scheme 87 C–S bond cleavage in arylthiocyanates.



Scheme 88 Carbene insertion into the C–S bond in aryl thiocyanates.

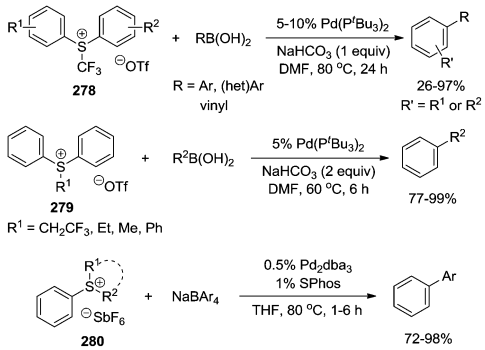
promotes the S–CN bond cleavage and C–CN/C–S bond reconstruction. This cyanothiolation reaction has demonstrated great potential for the synthetic utility of carbenoid species as new entries for the construction of diverse heteroatom-containing nitriles *via* cyanofunctionalization of metal–carbene species.

Potassium thiocyanate (KSCN) was reported for the synthesis of diaryl thioethers (ArSAr) from the reaction with aryl halides under palladium catalysis. By means of an air- and moisture-stable Pd(II) complex containing 1-benzyl-3-(1-benzyl-1-methylpyrrolidin-1-ium-2-yl)pyridin-1-ium ([DBNT][$PdCl_4$]), the reaction of aryl and pyridyl halides with KSCN was performed in the presence of KOH in DMSO at 120 °C, efficiently affording the corresponding diaryl thioethers (62–95%).[237] This protocol provides a convenient route to symmetrical diaryl thioethers from readily available (hetero)aryl halides and KSCN, avoiding use of foul-smelling thiols and air- and moisture-sensitive or costly catalysts and ligands. In particular, the iodo group of an aryl halide can be selectively coupled with a thiol in the presence of a bromo group, leaving a possibility for the late-stage functionalization of the functionalized diaryl thioether products.

6.2 Sulfonium salts

Liebeskind *et al.* developed the so-called ''alkylative activation'' strategy to cleave a C–S bond in thioethers or thioesters by means of palladium- or nickel-catalyzed cross-coupling reactions of the readily available or *in situ* generated benzyl tetramethylenesulfonium salts with organometallic reagents for the first time.[30] In these cases, sulfur was removed in the form of tetrahydrothiophene which acted as an effective leaving group during the reaction. Other kinds of sulfonium salts have also been developed as the reaction intermediates for further transformations through C–S cleavage.[27,238–241]

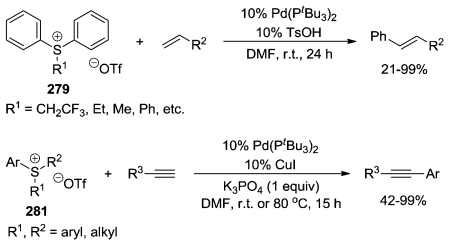
Recently, arylsulfonium salts have been applied as versatile arylation reagents for the synthesis of functionalized compounds.[242]



Scheme 89 Suzuki–Miyaura cross-coupling with arylsulfonium salts.

Yagupolskii–Umemoto reagents **278** were documented as the arylation reagents in palladium-catalyzed desulfitative Suzuki–Miyaura cross-coupling with aryl, heteroaryl, and vinyl boronic acids (Scheme 89).[243] Usually, these reagents are used as the electrophilic CF_3 transfer reagents. In contrast to copper-catalyzed trifluoromethylation,[244] the palladium-catalyzed reaction of **278** with boronic acids gave the arylation products in moderate to excellent yields (26–97%) through aryl C–S bond cleavage. The relatively electron-poor aryl groups in unsymmetrical sulfonium salts [$Ar^1Ar^2SCF_3$][OTf] were more favorably transferred than the relatively electron-rich ones in the reaction. In a similar fashion, symmetrical fluoroalkyl and alkyl(diphenyl)-sulfonium triflates [Ph_2SR^1][OTf] and triphenylsulfonium triflates **279** were applied in the Suzuki–Miyaura cross-coupling with arylboronic acids, giving the target products in 77–99% yields.[245] It was found that perfluoroalkyl(diphenyl)sulfonium triflates did not participate in the desired reaction, which underwent S–R_{fn} bond cleavage rather than S–Ph bond breakage due to the strong electron-withdrawing ability of the perfluoroalkyl group R_{fn}. Polyfluoro-alkyl(diphenyl)sulfonium triflates reacted with arylboronic acids much less efficiently to produce the biaryl products due to the deprotonation and β-F elimination of the sulfonium ions during the reaction. Both acyclic and cyclic aryl(dialkyl)sulfonium hexafluoroantimonates **280** underwent the cross-coupling reaction with sodium tetraarylborates under base-free conditions, yielding the corresponding biaryl products in high yields (72–98%).[246]

With 10% *p*-toluenesulfonic acid (TsOH) as the promoter a $Pd(P^tBu_3)_2$-catalyzed Heck-type reaction of compounds **279** with terminal alkenes at room temperature gave the phenylation products in 21–99% yields[247] (Scheme 90). The bases that usually benefit the Heck-type reaction severely inhibited the phenylation reaction with [Ph_2SR^1][OTf] (R^1 = CF_3, CH_2CF_3), while acids significantly promoted the reaction. Triaryl, aryl(dialkyl), and alkyl(diaryl)sulfonium salts **281** acted as versatile arylation reagents with various terminal aryl and alkyl alkynes in the palladium(0)/copper(I)-catalyzed Sonogashira cross-coupling reaction, affording the target internal alkyne products in 42–99% yields[248] (Scheme 90). Diphenyl(fluoroalkyl)sulfonium triflates were also suitable for the reaction, with [$Ph_2SCH_2CF_3$][OTf] being the most powerful one, which could react with alkynes at room temperature. This method



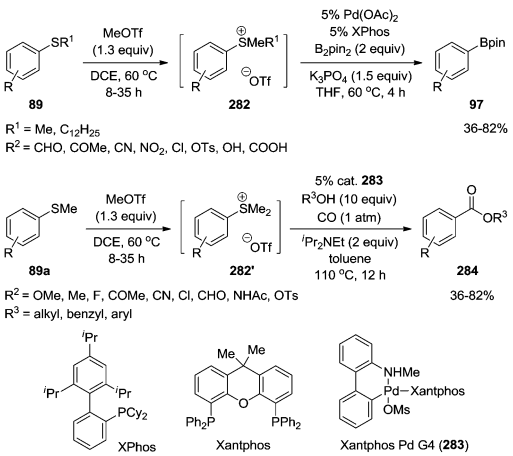
Scheme 90 Heck and Sonogashira-type cross-couplings with arylsulfonium salts.

features good tolerance of functional groups and easy access to the sulfonium reagents.

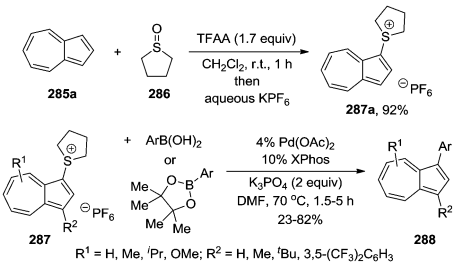
One-pot cross-coupling of arylthioethers could be executed by *in situ* generation of the more reactive sulfonium salts than their parent thioethers as the reaction intermediates (Scheme 91). Thus, arylboronate esters **97** were prepared by a one-pot, two-step protocol involving *in situ* formation of arylsulfonium salts **282** from the interaction of arylthioethers **89** with methyl triflate (MeOTf) followed by palladium-catalyzed cross-coupling of the sulfonium salts with bis(pinacolato)diboron (B_2pin_2).[249] In a similar fashion, palladium-catalyzed alkoxycarbonylation of arylsulfonium salts was achieved to give benzoates **284**.[250] Diverse functional groups such as CHO, COMe, CN, NO_2, Cl, F, OTs, OH, COOH, NHAc, Me, and OMe were tolerated. Both the ligands and bases are crucial for the success of the reactions. The above-mentioned methods have demonstrated great potential for further elaborating functionalized molecules.

Azulene (**285a**) is a non-alternant aromatic hydrocarbon and its derivatives have attracted much attention in medicinal chemistry, materials science, and organic electronics. For the potential application of an azulene derivative, introduction of substituents onto the azulene skeleton in a controlled manner is crucial. Thus, a strategy by means of azulenesulfonium salts was developed to functionalize the azulene skeleton (Scheme 92).[251]

The parent azulenesulfonium salt **287a** was synthesized in 92% yield from the reaction of azulene (**285a**) with readily



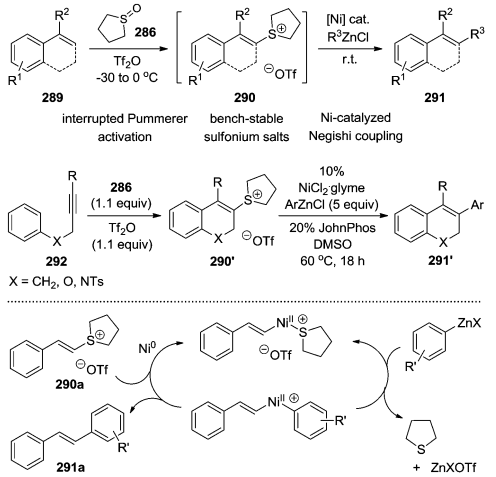
Scheme 91 The reactions of *in situ* generated arylsulfonium salts.



Scheme 92 Suzuki–Miyaura cross-coupling with azulenesulfonium salts.

available and inexpensive tetramethylene sulfoxide (**286**) (5.5 equiv.) and trifluoroacetic anhydride (TFAA) (1.7 equiv.) in CH_2Cl_2 at room temperature, followed by anion exchange with KPF_6 and recrystallization. The analogs of **287a** were prepared from substituted azulenes in 68–96% yields. DMSO could also be used to prepare the substituted azulenesulfonium salt of **285a**, but with a relatively poor efficiency (68% yield). The azulenesulfonium salts **287** underwent Suzuki–Miyaura cross-coupling with organoboron reagents, giving the arylated products **288** in 23–82% yields. In some cases, use of an aryl boronic acid led to the formation of a quantity of the corresponding boroxine cyclotrimer which could coelute with the target products, so aryl pinacolboranes were sometimes utilized in preference. Various functional groups were tolerated, including OH and CHO groups, as well as heterocycles. The present azulenesulfonium salts have exhibited several distinct advantages over the corresponding halides, that is, more straightforward preparation and purification, as well as obviously improved stability.

Activated sulfoxides are excellent electrophiles and can be used for the selective introduction of a functionality onto an aromatic system by replacement of a C–H bond through interrupted Pummerer processes.[251,252] However, analogous interrupted Pummerer reactions of alkenes, which generate alkenylsulfonium salts, have seldom been documented. Styrenes were envisioned to form alkenylsulfonium salts upon treatment with an activated sulfoxide and then could be used as the electrophilic coupling partners for C–C bond formation. Thus, a relevant interrupted Pummerer/nickel-catalyzed cross-coupling strategy was developed to elaborate styrenes (Scheme 93).[253] A more economical procedure than that for azulene derivatives[251] was applied to synthesize the bench-stable styrylsulfonium triflates **290** in excellent yields (89–91%) by treating styrenes **289** with compound **286** (1.1 equiv.) or DMSO in the presence of Tf_2O (1.1 equiv.) in CH_2Cl_2 at −30 to 0 °C for one hour. For convenience, a one-pot procedure for the interrupted Pummerer/nickel-catalyzed cross-coupling was employed to transform the *in situ* generated sulfonium salts **290** by means of 5% $Ni(PPh_3)_2Cl_2$ as the catalyst, aryl, heteroaryl, benzyl, alkyl, and alkynylzinc chlorides (1.5 equiv.) as the coupling partners, and K_2CO_3 as the base at room temperature, giving the target coupling products **291** in moderate to excellent yields. Subjecting the aryl-functionalized alkynes **292** to the interrupted Pummerer reaction conditions also efficiently formed the corresponding alkenylsulfonium salts **290′**, which underwent the Negishi-type

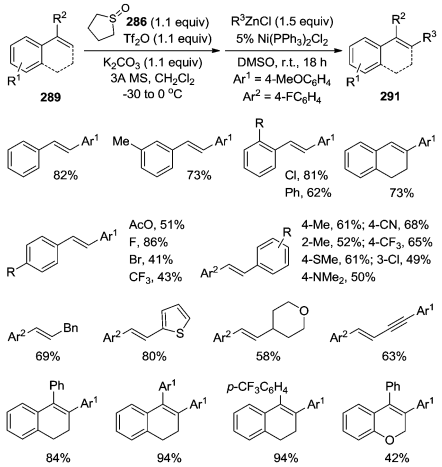


Scheme 93 Suzuki–Miyaura cross-coupling with styrylsulfonium salts.

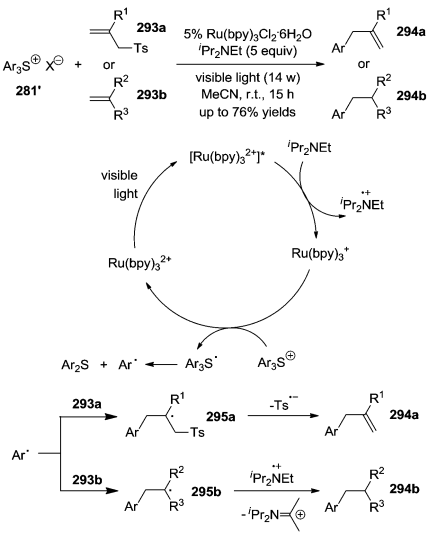
cross-coupling under the modified conditions by using 10% $NiCl_2$·glyme as the catalyst and 20% JohnPhos as the ligand in DMSO at 60 °C. The reaction pathway could be understood by oxidative addition of the sulfonium salt to the Ni(0) species generated *in situ* by the organozinc reagent, forming a styryl Ni(II)–S complex intermediate through alkenyl C–S bond cleavage. The subsequent transmetalation with the organozinc reagent produces the styryl arylnickel complex species. Finally, reductive elimination gives the coupling product. By means of the two routes as shown in Scheme 93, diversely functionalized styrene derivatives **291** were prepared in moderate to excellent yields (Scheme 94). The one-pot sequence involves the direct formation of the stable alkenylsulfonium salt intermediates from styrenes or aryl-functionalized alkynes and a readily available sulfoxide, and uses sp, sp^2, and sp^3-hybridized organozinc chlorides as the coupling partners, giving the functionalized styrene products under mild conditions. Such an interrupted Pummerer/cyclization protocol can also be used to synthesize carbo- and heterocyclic alkenylsulfonium salts for cross-coupling. It is noteworthy that alkylsulfonium halides have been widely used as the precursors to sulfur ylides, but the relevant chemistry is not discussed in this review.[254]

Photoredox catalysis is emerging as a promising research area in organic synthesis.[255] Under visible-light photocatalytic conditions, triarylsulfonium salts $Ar_3S^+X^-$ (**281′**, X =: OTf, BF_4, PF_6) reacted with allyl sulfones (**293a**) or activated alkenes (**293b**) to give the addition or addition/elimination products of type **294** in up to 76% yields (Scheme 95).[256] In the presence of 5% $Ru(bpy)_3Cl_2·6H_2O$ (bpy = 2,2′-bipyridine) as the photosensitizer, the reaction proceeded smoothly through a radical pathway. Under visible-light irradiation, the excited state of the Ru(II) complex, that is, $[Ru(bpy)_3^{2+}]^*$, is reduced by $^iPr_2NEt$ to generate the stronger reductant $Ru(bpy)_3^+$, which then transfers an electron to the triarylsulfonium salt substrate **281′**. The resultant triarylsulfuranyl radical decomposes into diaryl thioether and an aryl radical. Subsequently, the latter interacts with an allyl sulfone or activated alkene molecule to form radical intermediate **295**, which undergoes β-fragmentation of the *p*-tosyl radical anion to give the addition/elimination product **294a** or H-abstraction from the amine radical cation to produce the addition product **294b**.

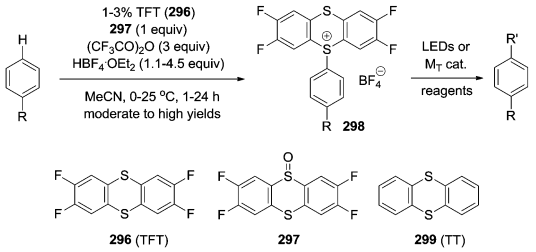
Very recently, Ritter *et al.* developed a new class of sulfonium salts for site-selective and versatile aromatic C–H functionalization by thianthrenation.[257–260] In the presence of tetrafluorothianthrene (**296**, 1–3%) and trifluoroacetic acid anhydride (TFAA), the reaction of arenes with the new thianthrene sulfoxide **297**, which can be prepared on scale in two steps from 1,2-difluorobenzene and disulfur dichloride *via* **296**, gave arylsulfonium salts **298** after anion exchange in moderate to high yields (Scheme 96).[257] In a similar fashion, the non-fluorinated thianthrene **299** could also be used to make the corresponding arylsulfonium salts. The tetrafluorothianthrene radical cation generated *in situ* by comproportionation of **296** and **297** was identified by an EPR experiment and it could react chemoselectively to functionalize arenes in preference to



Scheme 94 Interrupted Pummerer/nickel-catalyzed cross-coupling of styrenes.



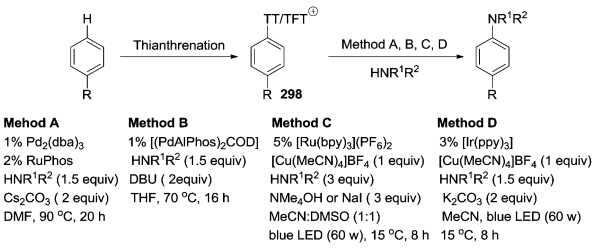
Scheme 95 Photoredox reaction of arylsulfonium salts.



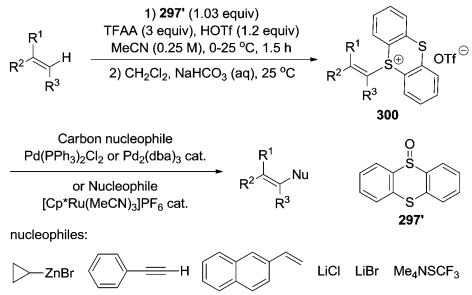
Scheme 96 Thianthrenation of aromatic C–H bonds with TFT or TT.

undergoing deleterious side reactions. The thianthrenation proceeded on arenes as electron-rich as aniline derivatives to those as electron-poor as 1,2-dichlorobenzene, exhibiting a wide substrate scope with a high degree of *para*-functionalization. Arenes that are more electron-rich than anisole underwent unproductive oxidation with **297**. Thus, **299** was applied to prepare the sulfonium salts for all the arenes which are more electron-rich than anisole. These arylsulfonium salts (**298**) underwent diverse transformations under photocatalytic or transition-metal-catalyzed conditions, including borylation with B_2pin_2, phosphonylation with $P(OPh)_3$, cyanation with NBu_4CN, pseudohalogenation with NMe_4SCF_3, chlorination with $CuCl/NH_4Cl$, iodination with LiI, sulfonylation with $PhSO_2Na$, Heck reaction with styrene, Negishi coupling with alkylzinc bromide or chloride, Sonogashira coupling with 1-hexyne, Suzuki–Miyaura coupling with cyclohexylvinylboronic acid, and carbonylation. Such transformations differ fundamentally from all the known aromatic C–H functionalization reactions in which it provides direct access to various derivatives of complex small molecules, quickly establishing functional diversity with high site-selectivity that is not achievable by other methods.

By means of the same strategy and using Pd(0) catalysts or under photocatalysis conditions in the presence of $[Cu(MeCN)_4]BF_4$, aryl thianthrenium salts of type **298** were reacted with a wide range of primary and secondary alkyl and aryl amines, and various N-containing heterocycles for the late-stage functionalization of complex, drug-like small molecules through C–N bond formation,[258] exhibiting diverse applicability (Scheme 97). Photoredox-catalyzed cross-coupling of the aryl thianthrenium salts proceeded with a copper-based trifluoromethylation reagent "$CuCF_3$" by using $[Ru(bpy)_3](PF_6)_2$ as the catalyst, enabling the site-selective late-stage trifluoromethylation of arenes.[259] The site-selective late-stage aromatic fluorination was also realized in acetone at 30 °C under photocatalysis by means of



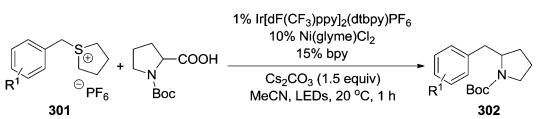
Scheme 97 C–N cross-coupling of aryl thianthreniums.



Scheme 98 Thianthrenation of vinyl C–H bonds with TT-*S*-oxide.

1% $Ir[dF(CF_3)ppy]_2(dtbpy)PF_6$ as the photosensitizer, 20% $[Cu(MeCN)_4]BF_4$ as the catalyst, and CsF as the fluorine source.[260] In a fashion similar to the preparation of aryl thianthrenium salts **298** and under the slightly modified conditions, alkenyl thianthrenium salts **300** were efficiently prepared (Scheme 98),[261] which could undergo palladium-catalyzed C–C cross-coupling with alkylzinc bromides, phenylacetylene, and 2-naphthylethylene, or ruthenium-catalyzed chlorination with LiCl, bromination with LiBr, and trifluoromethylthiolation with Me_4NSCF_3, respectively. This protocol provides an alternative method to functionalize olefins.

Under photocatalysis alkylsulfonium salts also underwent cross-coupling to form C–C bonds. Using a well-established dual Ni–Ir system benzylsulfonium salts (tetramethylenesulfonium salts) **301** coupled with proline through radical CO_2 extrusion (eqn (16)).[262] The combination of 1% $Ir[dF(CF_3)ppy]_2$-(dtbpy)PF_6, 10% Ni(glyme)Cl_2, and 15% bpy acted most efficiently in the presence of Cs_2CO_3 base. The alkylsulfonium salts were conveniently prepared from the reaction of benzyl bromides and tetrahydrothiophene (THT), followed by anion exchange with NH_4PF_6.[30] This method enabled the simple one-step synthesis of 2-benzylpyrrolidines (**302**) from the readily available stable and cheap starting materials.

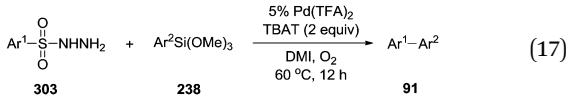


(16)

6.3 Sulfonyl hydrazides

The analogs of sulfonyl chlorides and sodium sulfinates, that is, sulfonyl hydrazides, can also undergo the cross-coupling reactions for C–C bond formation.[195] In this regard, palladium-catalyzed Hiyama-type cross-coupling of the surrogates of arylsulfonyl chlorides and sodium arylsulfinates, that is, arylsulfonyl hydrazides **303**, with aryltri(methoxy)silanes (**238**) afforded the corresponding biaryl products **91** (eqn (17)).[263] By using 5% $Pd(TFA)_2$ as the catalyst and TBAT (tetrabutylammonium-difluorotriphenylsilicate) as the additive in DMI (1,3-dimethyl-2-imidazolidinone) solvent, the Hiyama-type coupling reaction of aryl and heteroarylsulfonyl hydrazides with aryl and heteroaryl trimethoxysilanes was conducted at 60 °C under an oxygen atmosphere, giving the target biaryl products **91** in good to excellent yields (72–95%). The reaction did not require stoichiometric Ag(I)

or Cu(II) oxidants, tolerated the common functional groups such as methoxy, free hydroxy and amino, cyano, nitro, and halogens (F, Cl, Br, and I), and could be accelerated by TBAT. The hindrance from 2-methyl and 1-naphthyl exhibited a negative steric effect on the product yields. For the heteroaryl-based substrates, their reactions usually afforded the aryl-heteroaryl coupling products in good yields (72–83%). This protocol offers a supplementary route to the traditional palladium-catalyzed cross-coupling approaches.

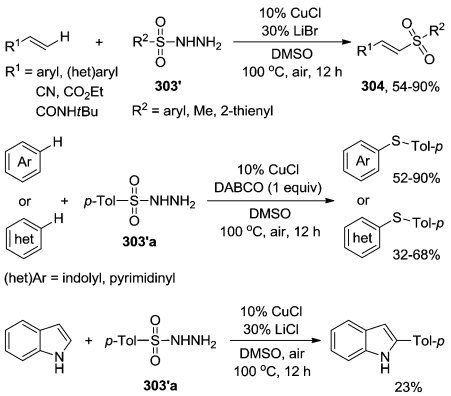


(17)

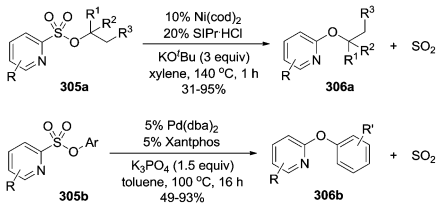
The desulfitative coupling of sulfonyl hydrazides strongly relies on the reaction conditions. In the presence of 10% CuCl as the catalyst and 30% LiBr as the additive in DMSO at 100 °C under an air atmosphere, the reaction of arylsulfonyl or methylsulfonyl hydrazides (**303′**) with styrenes, 2-vinylthiophene, and acrylate derivatives (esters, nitriles, and amides) gave the corresponding aryl or methyl vinylsulfone products **304** (54–90%), undergoing no desulfitative cross-coupling (Scheme 99).[264] Under similar conditions by replacement of LiBr with DABCO (1,4-diazabicyclo[2.2.2]octane), the reaction of the aryl and heteroaryl C–H bonds with *p*-tosyl hydrazide (**303′a**) formed the diaryl and di(heteroaryl)thioethers in 52–90% and 32–68% yields, respectively. Only in the reaction of indole with **303′a** through modification of the reaction conditions by replacing LiBr with 30% LiCl did the desulfitative cross-coupling reaction occur to produce 2-(*p*-tolyl)-indole in 23% yield. Arylsulfonyl hydrazides acted the same way as arylsulfonium salts did in the palladium-catalyzed reaction with KI and I_2, giving the corresponding aryl iodides *via* carbon–heteroatom bond formation.[230] It is noteworthy that the chemistry of arylsulfonyl hydrazones is not discussed in this review although these compounds have been extensively utilized in organic synthesis,[265] or they can react with arylsulfonium salts under palladium catalysis.[266]

6.4 Sulfonates

Versatile coupling partners have been developed for transition-metal-catalyzed cross-coupling reactions, including organosulfur compounds. Although ester-type tosylates and triflates have been extensively used as the surrogates of organic halides as the electrophilic coupling partners, sulfonates have been rarely documented in this area, in particular for desulfitative reactions due to their relatively low reactivity. Iron-[267] and nickel-catalyzed[268] cross-coupling of arylsulfonates and polymer-bound arylsulfonates with Grignard reagents was documented to access alkylated arenes or biaryls and terphenyl products. Nickel-catalyzed intramolecular desulfonylation of alkyl (aryl) heteroarylsulfonates **305** was recently achieved to give the corresponding heteroaryl alkyl (aryl) ethers **306** (Scheme 100).[269] In the presence of 10% Ni(cod)$_2$ catalyst and 20% NHC ligand precursor SIPr·HCl and KO^{t}Bu base, alkyl heteroarylsulfonates **305a** were desulfonylated in xylene at 140 °C, giving the heteroaryl alkyl ethers **306a** in 31–95% yields. Change of the catalytic system to 5% Pd(dba)$_2$/5% Xantphos/K_3PO_4 (1.5 equiv.) rendered the desulfonylation of aryl heteroarylsulfonates (**305b**) proceed smoothly in toluene at 100 °C, forming biaryl ethers **306b** in 49–93% yields. Both arylsulfonates and 4-pyridylsulfonates did not react under the stated conditions. The secondary and tertiaryl *O*-alkyls exhibited obvious negative steric effects on the yields of **306a**, while the electron-withdrawing groups on the aryl and heteroaryl rings usually facilitated the reaction. Methyls on the 2-pyridyl ring benefited the reaction for **305b** more than for that of **305a**. The 2-pyridyl group acted as a directing functionality to execute the desired reaction. This work provides a new route to aryl ethers and has demonstrated the applicability of sulfonates in cross-coupling reactions. It should be noted that ester-type tosylates and triflates usually undergo transition-metal-catalyzed C–O cleavage reactions to construct C–C bonds, and thiosulfonates such as Ts–SR undergo a copper-catalyzed S–S cleavage reaction to transfer an alkylthio or (hetero)arylthio group.[270]



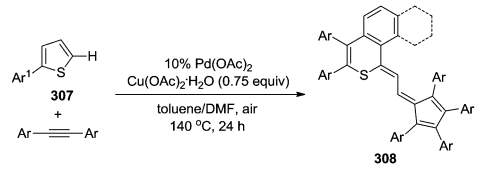
Scheme 99 Copper-catalyzed C–S bond formation and cleavage with sulfonyl hydrazides.



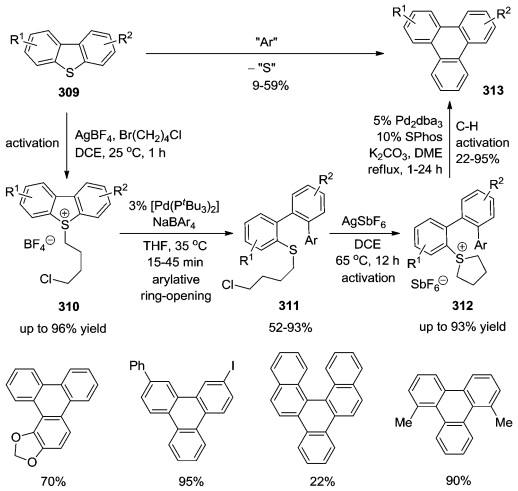
Scheme 100 Catalytic C–S bond cleavage in heteroarylsulfonates.

7. C–S bond cleavage in thiophene-based compounds

Thiophene, benzothiophene (BT), dibenzothiophene (DBT), and their derivatives are the problematic organosulfur compounds for sulfur removal in the HDS process.[1] Investigation of the relevant C–S bond cleavage by transition-metal complexes may provide mechanistic insights into the sulfur removal during a refinery process. In this area, considerable attention has been paid to their C–S bond cleavage/cross-coupling reactions under transition-metal catalysis. With 10% Pd(OAc)$_2$ as the catalyst and Cu(OAc)$_2$·H$_2$O as the oxidant the reaction of thiophenes **307** with



Scheme 101 C–S bond cleavage of thiophene derivatives.

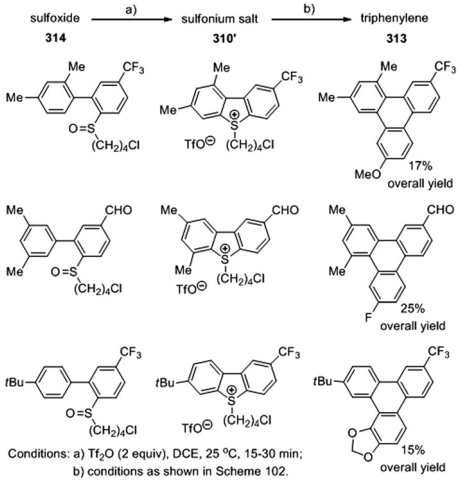


Scheme 102 Aromatic metamorphosis of DBTs into triphenylenes.

internal diaryl alkynes gave the diene products of type **308** through double C–H and C–S bond cleavages (Scheme 101).[271]

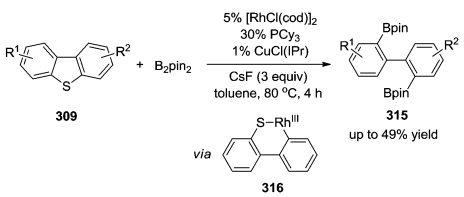
The sulfur in dibenzothiophenes (DBTs) can be catalytically removed by the strategy using palladium-assisted aromatic metamorphosis of DBTs into triphenylenes (Scheme 102).[272] Such a strategy begins with the activation of DBT **309** as sulfonium salts **310** through diminishment of the Lewis basicity of the sulfur atom by alkyl bromide $Br(CH_2)_4Cl$. The activated sulfonium salt **310** then undergoes cross-coupling with an aryl nucleophile.[17] The ring-opening product, 4-chlorobutylteraryl thioether **311**, is thus activated again through formation of the corresponding cyclic sulfonium salt **312**. Subsequent intramolecular arylation of **312** finalizes the aromatic metamorphosis to form triphenylene **313**. All the intermediates **310–312** were efficiently synthesized in up to 96% yields under mild conditions, and the total yields for the four-step procedure ranged from 9% to 59%. For the last step synthesis as shown in the selected examples (Scheme 102), good to excellent yields (70–95%) were reached. This protocol provides an ''aromatic metamorphosis'' of DBTs into triphenylenes by subjecting to two palladium-catalyzed arylation reactions. Due to the importance of the polycyclic aromatic cores, aromatic metamorphosis may play an important role in the construction of potentially useful molecules in organic chemistry and materials science.

Dibenzothiophene sulfonium salts were alternatively obtained by the cyclization of 2-arylphenyl sulfoxides (**314**) under Pummerer-like conditions.[251–253] Thus, sulfoxides **314**, readily prepared by cross-coupling biaryl synthesis, underwent Tf_2O-promoted



Scheme 103 Synthesis of multisubstituted triphenylenes *via* Tf_2O-promoted sulfonium formation.

electrophilic cyclization to efficiently form sulfonium triflates **310′**. These sulfonium salts were then converted to triphenylenes of type **313** in 15–25% overall yields from the five-step procedure (Scheme 103).[272] The present strategy is useful for the preparation of multisubstituted triphenylenes in a precisely controlled manner. Rh(I)/Cu(I)-cocatalyzed ring-opening diborylation of DBTs **309** was established through aromatic metamorphosis to form diborylated biaryls **315** (eqn (18)).[273] In the presence of B_2pin_2 (3 equiv.) and CsF (3 equiv.) as the base in toluene at 80 °C, two C–S bonds of DBTs underwent a couple of sequential borylation reactions co-catalyzed by the Rh(I) and Cu(I) complex catalysts, giving the corresponding 2,2′-diborylbiaryls (**315**) in up to 49% yields *via* thiarhodacycle species **316**. Compounds **315** could be converted to extended π-systems such as potentially useful molecules fulvenes (82–97%) from two-fold palladium-catalyzed cross-coupling reactions of 2,2′-diborylbiphenyl (**315a**) with *gem*-dibromoethylenes, and dibenzofuran (49%) from the formal Cu(II)-mediated replacement of the sulfur atom of DBT with an oxygen atom under basic conditions. This rhodium-catalyzed, copper-assisted ring-opening diborylation reaction of DBTs offers diborylbiaryls as useful building blocks, exhibiting the diversity for further transformations.



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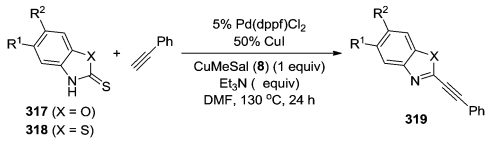
8. C═S bond cleavage

8.1 Cyclic thioamides and thioureas

Thioamides, thioureas, and thiones can undergo catalytic desulfitative cross-coupling with electrophilic or nucleophilic reagents *via* C═S bond cleavage, forming new C–C bonds. Mercapto-benzoxazoles (**317**) and -benzothiazoles (**318**) underwent

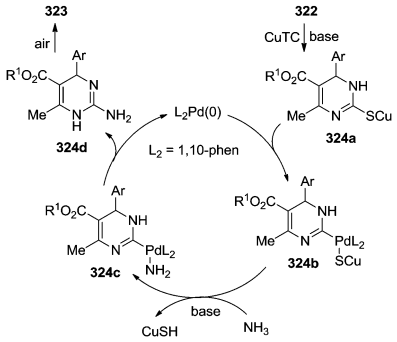
Table 7 Sonogashira-type cross-coupling of mercapto-heteroarenes



Entry	X	R^1	R^2	Yield (%)
1	O	H	H	60
2	O	MeO	H	30
3	O	F	H	Trace
4	O	Cl	H	—
5	O	Br	H	—
6	S	H	H	70
7	S	H	EtO	75
8	S	Cl	H	38

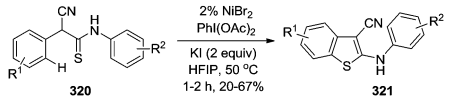
palladium-catalyzed, Cu(I)-mediated desulfitative Sonogashira-type cross-coupling with phenylacetylene (Table 7).[274] In the presence of 5% $Pd(dppf)Cl_2$, 50% CuI, CuMeSal (**8**) (1 equiv.), and Et_3N base in DMF at 130 °C under an air atmosphere, **317a** reacted with phenylacetylene (3 equiv.) to result in 2-alkynylated benzoxazole **319a** in 60% yield. For the cross-coupling of other 2-mercapto-benzoxazoles bearing a MeO, F, Cl, or Br group, only the methoxy-functionalized 2-mercapto-benzoxazole reacted to form the target product in 30% yield, and the halo-functionalized substrates did not undergo the reaction. Unsubstituted or electron-donating group-substituted 2-mercaptobenzothiazoles reacted well with phenylacetylene to yield the target products in good yields (70–75%), while a chloro functional group diminished the yield to 38%. This method provides an alternative route to 2-alkynylated benzoxazole and benzothiazole derivatives through the desulfitative cross-coupling of mercapto-heteroarenes. A nickel-catalyzed intramolecular site-selective C–H functionalization of α-arylthioamides gave the corresponding 2-aminobenzothiophenes (eqn (19)), demonstrating the formation of C–S bonds from the C=S bond.[275]

Under oxidative conditions and in the presence of a base, palladium-catalyzed, copper-mediated desulfitative amination occurred for 3,4-dihydropyrimidine-2-thiones (**322**) to give the corresponding 2-aminopyrimidine derivatives (**323**) through Biginelli reaction (eqn (20)).[276] 2-Aminopyrimidine is a common core motif in a variety of natural products and pharmaceuticals, and its construction is of high importance in organic synthesis. With 5% $Pd(OAc)_2$ as the catalyst, CuTC (1.1 equiv.) as the mediator, 10% 1,10-phen as the ligand, K_2CO_3 (2 equiv.) as the base in refluxing toluene, the reaction of **322** with ammonia was conducted under an air atmosphere, forming 2-aminopyrimidines (**323**) in 63–83% yields. The electronic properties of the substituents did not significantly affect the reaction efficiency, while the steric effect was obvious from 1-naphthyl group. The reaction did not proceed in the absence of a base, and toluene was superior to DMSO, dioxane, DMF, or NMP as the solvent. The plausible mechanism suggests that the Cu(I) mediator CuTC initially interacts with thiourea **322** to form Cu(I) thiolate **324a** in the presence of a base (Scheme 104). Oxidative addition of species **324a** to the Pd(0) center *in situ*



Scheme 104 Desulfitative amination of pyrimidine-2(1*H*)-thiones.

generated intermediate **324b** in which the C–S bond is activated. The reaction of **324b** with ammonia *via* a transmetalation step in the presence of the base produces intermediate complex **324c**, from which reductive elimination affords intermediate **324d** and regenerates the catalytically active Pd(0) species. Finally, compound **324d** is oxidized by air to the target product **323**. This protocol provides a general, highly chemoselective, and efficient method to access 2-aminopyrimidines. Under the modified conditions using LiHMDS as the base, amination of 3,4-dihydropyrimidine-2-thiones with aliphatic and (hetero)-arylamines was achieved to give 2-aminopyrimidine derivatives (**323′**) in moderate to excellent yields (eqn (21)).[277]



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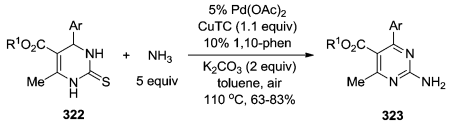

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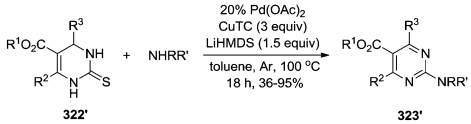
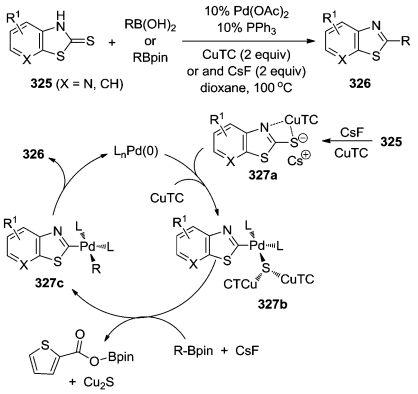


(21)

An efficient palladium-catalyzed, copper-mediated desulfitative C–C cross-coupling of fused thiazolidine-2-thiones (**325**) with boronic acids or acid pinacol esters was also established to prepare fused thiazoles (**326**) (Scheme 105).[278] The former reaction was carried out under the neutral Liebeskind–Srogl coupling conditions, while the latter occurred under basic conditions by using CsF as the base.

8.2 Thiourea

It has been well known that sulfur-containing functional groups and heterocycles are ubiquitous structural elements in pharmaceuticals and functional materials. In this area, sulfur incorporation-based C–S bond formation plays an important role, and the development of versatile sulfurizing agents has

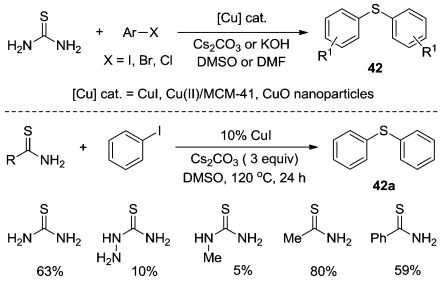


Scheme 105 C═S bond cleavage in thiazolidine-2-thiones.

attracted much attention.[279,280] In this area, unsubstituted thiourea has been paid considerable attention as the surrogate of H_2S for thiolation.

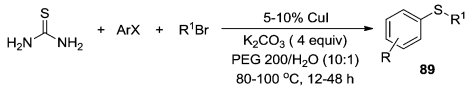
Versatile homogeneous and heterogeneous copper catalysts were documented for the preparation of thioethers by using thiourea as the sulfur source. The copper-catalyzed two-component reaction of aryl halides with thiourea usually gives symmetrical diaryl thioethers of type **42** (Scheme 106). CuI with DMAP (4-(dimethylamino)pyridine),[281] 2-methoxy-1-phenylethanone functionalized MCM-41 supported Cu(II) complex (Cu(II)-2-MPE@MCM-41),[282] and CuO nanoparticles[283] can be used for the same purpose. A base such as K_2CO_3, Cs_2CO_3, or KOH is usually required to promote the C–S coupling reaction. Although aryl chlorides could be used in the reaction,[282] aryl iodides and bromides have been found to act as more effective coupling partners. Diaryl thioethers **42** were obtained in good to excellent yields with a good tolerance of functional groups such as methoxy, dimethylamino, amino, nitro, cyano, trifluoromethyl, halogens, and acetyl, as well as alkyls and other substituents, which offers a possibility for further transformation of the functionalized diaryl thioether products. A glycerol Cu(II) complex supported on Fe_3O_4 magnetic nanoparticles was also used for the same reaction.[284]

The same strategy was utilized to access unsymmetrical aryl alkyl thioethers by means of the three-component reaction of thiourea, an aryl halide, and an alkyl halide under copper(I) catalysis.[285] In a similar fashion by using phenolic esters such as aryl acetates, triflates, tosylates, and phosphonates to replace



Scheme 106 Synthesis of symmetrical diaryl thioethers from thioureas and aryl halides.

the aryl halides, the three-component reaction with thiourea and benzyl, octyl, cyclohexyl, cyclopentyl, hexyl, and butyl iodides, bromides, chlorides, or tosylates also efficiently gave the aryl alkyl thioethers **89** in high yields (≥80% yields) (eqn (22)).[286] This method was applicable for the gram-scale preparation of the desired aryl alkyl thioethers, featuring use of an eco-friendly reaction medium PEG 200 and thiourea as the sulfur source to avoid less commercially available foul-smelling thiols which are used in the traditional procedures for the synthesis of thioethers.

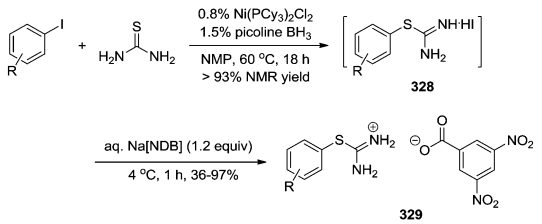


(22)

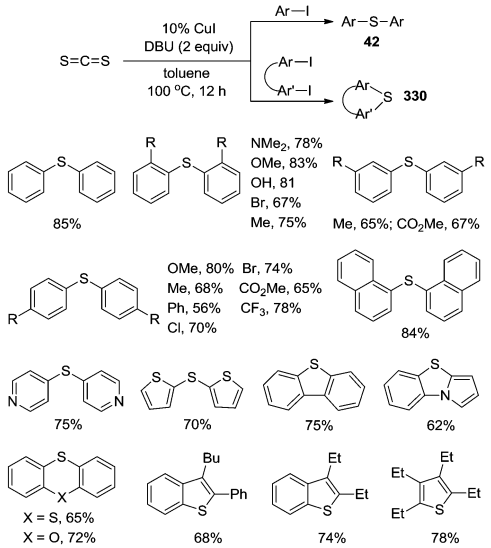
Thiourea has usually been used as a sulfur source. However, the use of relatively harsh conditions and presence of a base result in *in situ* decomposition of the initially formed isothioureanium salt, and the resultant thiophenol(ate) then undergoes the cross-coupling reaction. However, base-free thiourea cross-coupling has rarely been reported. With a combination of 0.8% $Ni(PCy_3)_2Cl_2$ and 1.5% picoline·BH_3 as the catalyst the reaction of aryl iodides and thiourea was conducted in *N*-methylpyrrolidinone (NMP) at 60 °C to afford the thiophenol surrogates **329** *via* the formation of intermediate isothioureanium iodide (**328**) (Scheme 107).[287] The air-stable and odorless thiophenol surrogates were thus obtained by work-up with 2,5-dinitrobenzoic acid (NDB). Thiophenols were liberated from the corresponding isothioureanium salts upon treatment with a weak base, enabling an *in situ* release/S-functionalization strategy which does not require isolation, purification, and manipulation of these stinking reagents.

8.3 Carbon disulfide

Exploration of sulfur sources has attracted much attention in synthetic chemistry. Although considerable progress has been achieved in use of thiourea, thiolates, and metal sulfides as the sulfur sources, limitations are always encountered, including specific catalyst systems, high temperature, and long reaction time. Therefore, the development of a foul-smell-free, cheap, and easy-to-handle method using a sulfur surrogate for the synthesis of thioethers is strongly desirable. In this regard, carbon disulfide is a potential candidate as the sulfur source.[288] CS_2 was thus successfully employed for the synthesis of diaryl thioethers and S-heterocyclic compounds (Scheme 108).[289] With 10% CuI as the catalyst, DBU as the mediator in toluene at 100 °C, the reaction of CS_2 with aryl iodides gave symmetrical



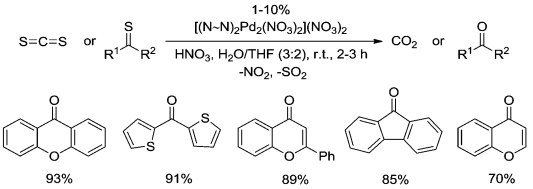
Scheme 107 Synthesis of isothioureanium salts from thiourea.



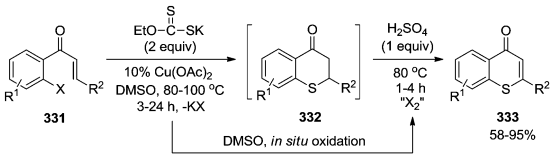
Scheme 108 Catalytic C═S bond cleavage in CS_2.

diaryl thioethers of type **42** in good to high yields (65–85%). DBU was crucial for the reaction, while other bases such as Cs_2CO_3, K_3PO_4, KOH, NaO^{t}Bu, and Et_3N were ineffective. DBU is proposed to activate CS_2 by forming a trisulfide and species $DBUH^+SH^-$ which then reacts with the CuI catalyst to generate CuSH. Oxidative addition of aryl iodide to CuSH forms Cu(III) complex Ar(I)CuSH from which aryl thiol (ArSH) is produced with regeneration of CuI. The second catalytic cycle starts from the interaction of ArSH and the catalyst in the presence of DBU base, giving ArSCu species which is then oxidatively added by another molecule of aryl iodide, forming complex Ar(I)CuSAr. Subsequently, reductive elimination gives the diaryl thioether product **42**. A variety of functional groups NMe_2, OMe, OH, Br, Cl, CF_3, and CO_2Me as well as phenyl and methyl were tolerated. S-Heterocyclic compounds **330** were accessed in 62–78% yields by using diiodoaryl compounds under the same conditions. This protocol provides an alternative efficient method to access symmetrical diaryl thioethers and S-heterocycles.

The C═S double bonds in CS_2 and thioketones were cleaved by means of dimeric palladium complex $[(N\text{–}N)_2Pd_2(NO_3)_2](NO_3)_2$ (N–N = 2,2′-bipyridine, 4,4′-dimethylbipyridine, 4,4′-bis(trifluoromethyl)bipyridine) at room temperature in one pot, affording carbon dioxide and ketones, respectively (Scheme 109).[290] The mechanistic investigations by kinetic NMR, isotope-labelled experiments, *in situ* ESI-MS, and DFT calculations reveal that the reaction involves a hydrolytic desulfurization process to



Scheme 109 Palladium-catalyzed C═S bond cleavage in CS_2 and thioketones.



Scheme 110 Copper-catalyzed C═S/C–S bond cleavage in xanthate.

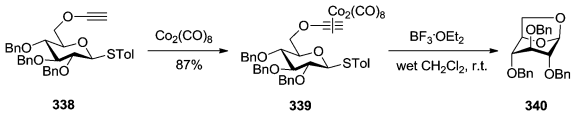
generate C═O bonds and a trinuclear cluster, which plays a crucial role in the catalytic cycle to regenerate the dimeric catalysts with nitric acid. This process features mild conditions, a broad substrate scope, and operational simplicity, providing mechanistic insight into the catalytic activation of C═S bonds.

Copper-catalyzed one-pot synthesis of 2-arylthiochromenones (**333**) was developed by using xanthate (KCS_2OEt) as the sulfur source from readily available 2′-halochalcones (**331**) (Scheme 110).[291] The iodides exhibited a reactivity higher than their bromide analogs, and the latter required a higher reaction temperature (100 °C) for the first-step reaction. A wide substrate scope was established to give the target products in 58–95% yields. This protocol was further extended for the synthesis of 3,3′-methylenebisthioflavone by means of DMSO as the methylene source.

9. C–S bond cleavage by stoichiometric transition-metal reagents

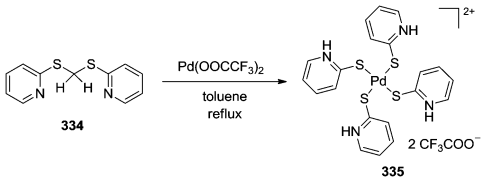
Transition metals usually exhibit high thiophilicity that they can readily insert into a C–S bond to form the corresponding sulfur-containing complexes,[22] which is not summarized here. In this section, only a brief overview of the selected examples of C–S bond activation/cleavage using stoichiometric transition-metal reagents is given. Transition-metal-free cross-couplings such as those of thioesters with vinyl Grignard reagents to access thioalkylated ketones[292] and (hetero)aryl thiols with arylzinc reagents for the synthesis of biaryl products[293] are not discussed either.

In refluxing toluene under a nitrogen atmosphere bis(2-pyridylthio)methane (**334**) reacted with a stoichiometric amount of palladium(II) trifluoroacetate to form tetrakis(pyridine-2-thio)palladium(II) complex **335** (eqn (23)).[294] Complex **335** could be further converted to a heterobimetallic Pd(II)–Fe(II) paddle-wheel complex upon treatment with iron(II) triflate in the presence of a base in acetonitrile at room temperature. In the first step of reaction akyl C–S bond cleavage occurred. However, $Pd(OAc)_2$ could only execute the akyl C–H bond activation reaction of **335** without cleavage of the akyl C–S bonds. Treatment of azo-functionalized aryl benzylthioether **336** with rhodium(I) complex $Rh(PPh_3)_3Cl$ in refluxing acetonitrile afforded Rh(III) complex **337** which could act as an efficient catalyst for the transfer hydrogenation of ketones in refluxing isopropanol (eqn (24)).[295] A benzyl C–S bond was cleaved during the formation of complex **337**. $Co_2(CO)_8$-propargyl cation was found to mediate the glycosylation reaction of thioglycoside **338** (Scheme 111).[296] It should be



Scheme 111 $Co_2(CO)_8$-mediated glycosylation.

noted that rare-earth phosphinidene complexes can also be used to cleave the C═S bonds of CS_2.[297]



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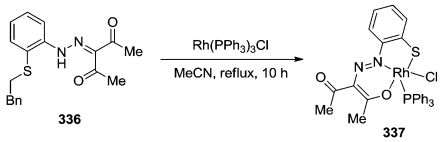
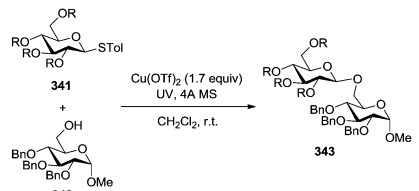


(24)

Transition-metal complexes can also act as the mediators to promote the C–S bond cleavage in organosulfur compounds. For example, stoichiometric $Cu(OTf)_2$ was used for the glycosylation of thioglycosides,[298] and a glycosyl coupling reaction *via* photoinduced direct activation of thioglycosides and subsequent *O*-glycosylation in the absence of a photosensitizer was thus developed under mild conditions (eqn (25)).[299] Such a photocatalytic reaction underwent a selectively homolytic C–S cleavage to generate a glycosyl radical, which was then oxidized to an oxocarbenium ion by $Cu(OTf)_2$, followed by a sequential *O*-glycosylation. Various glycosides **343** were efficiently prepared by means of sugars, amino acids, or cholesterol as the acceptors. In the presence of Ag_2CO_3 (1 equiv.) and Cs_2CO_3 base, tandem thien- and benzannulation reaction of α-alkenoyl-α-alkynyl ketene dithioacetals **344** with ethyl cyanoacetate proceeded to afford functionalized benzo[*b*]-thiophenes **345** (eqn (26)).[300] 3,4-Dihydropyrimidine-2-thiones (**322**) reacted with boric esters in the presence of stoichiometric amounts of copper(I) reagents CuTC and CuSCN, giving 2-alkoxypyrimidines (**346**) in moderate to high yields through a copper-mediated oxidative dehydrosulfitative C–O cross-coupling (eqn (27)).[301] All these methods offer alternative routes to C–S bond cleavage and transformations.



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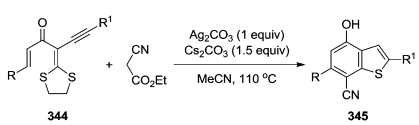

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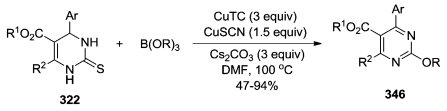

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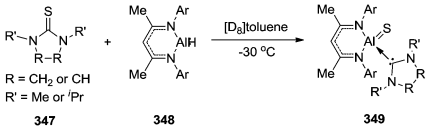


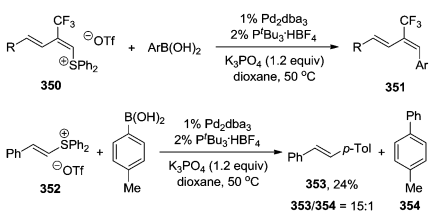
(28)

10. Theoretical studies

Theoretical studies have been conducted to explore the activation modes of C–S and C═S bonds by transition-metal complexes, which may guide the catalyst design for C–S bond cleavage in the cross-coupling reactions and organosulfur removal in the oil refinery process. CS_2 has usually been used as the model molecule for the theoretical investigation of C–S and C═S bond cleavages due to its diverse reactivity to transition metals, including insertion and disproportionation.[290] Density functional theory (DFT) calculations were used to evaluate the effectiveness of different ML_3 complexes to activate the C–S bonds in both CS_2 and CS with M = Mo, Re, W, and Ta, and L = NH_2.[302] Metal complexes can also be utilized to cleave the C–S bonds in other organosulfur compounds. Treatment of cyclic thioureas **347** with stoichiometric aluminum(I) compounds **348** at low temperature led to oxidative cleavage of the C═S bond and formation of Al(III)–NHC complexes **349** (eqn (28)).[303] It is noteworthy that C═S bond cleavage is usually achieved by means of stoichiometric transition-metal complexes,[304] but no further relevant summary and comments are given in this review.

Palladium-catalyzed Suzuki–Miyaura coupling reaction of (*E*)-(β-trifluoromethyl)vinyl-diphenylsulfonium salts (**350**) with aryl boronic acids was performed to afford the desulfitative cross-coupling products **351** in good to excellent yields (83–99%) (Scheme 112).[305] The CF_3 group plays a crucial role in facilitating the reaction. The reaction of (*E*)-(β-phenyl)vinyldiphenylsulfonium salt (**352**) with *p*-tolyl boronic acid only gave the target coupling product **353** in 24% yield, and the side product 4-methylbiphenyl (**354**) was observed (**353**/**354** = 15 : 1) from the phenylic C–S bond cleavage by GC-MS analysis. The DFT calculations have shown that the oxidative addition transition state of the vinyl C–S bond is much more favorable (11.7 kcal mol^{-1}) than the aryl C–S bond.

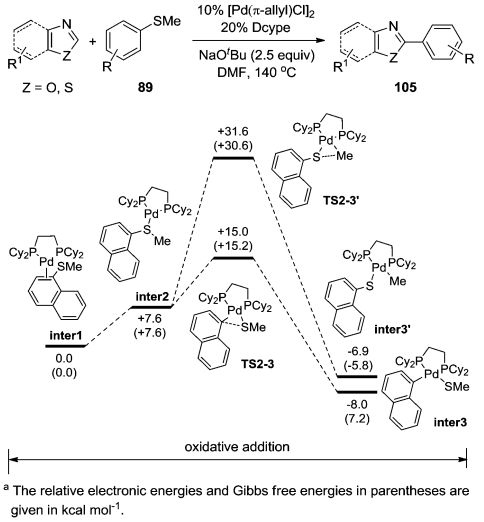
DFT calculations were well performed on palladium-catalyzed cross-coupling of azoles with methyl aryl thioethers



Scheme 112 C–S cleavage preference predicted by DFT calculations.

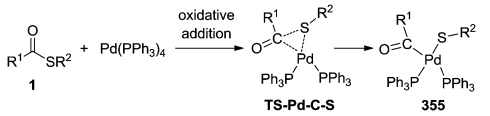
(**89**),[306] which reveals the origin of the chemoselectivity for the exclusive arene C(sp^2)–S bond cleavage in the presence of an alkane C(sp^3)–S bond, and suggests that the arene C(sp^2)–S bond activation is favored over that of the alkane C(sp^3)–S bond. Based on the plausible reaction mechanism,[307] the catalytic cycle is initiated by the ligation of the thioether to the palladium center, and the coupling process consists of three steps: C–S activation, NaO^{t}Bu mediated C–H palladation, and reductive elimination. The relevant DFT calculations of the possible oxidative addition pathways are presented in Scheme 113. These results indicate that coordination of the π-bond of the naphthyl group (or an aryl group) is thermodynamically more favored than that of the SMe group (**inter1** *vs.* **inter2**). **inter1** was chosen as the energy reference point to simplify the relevant discussion. The low energy gap (7.6 kcal mol^{-1}) suggests that **inter2** can be readily formed *via* the isomerization of **inter1**. From **inter1** the C–S oxidative addition may occur either on the arene C(sp^2)–S bond or on the alkane C(sp^3)–S bond. The relative energies of the related transition states are +15.0 kcal mol^{-1} for **TS2-3**, and +31.6 kcal mol^{-1} for **TS2-3′**, respectively. Thus, the C–S oxidative addition through the **TS2-3** pathway is kinetically more feasible than that through the **TS2-3′** pathway. According to the theoretical calculations di(hetero)aryls were the predicted products. Such a prediction is completely consistent with the observed experimental results, and compounds **105** were exclusively formed as the target products (23–99%).[307]

Transition-metal-catalyzed C–S activation and transformations have been paid more and more attention in organic synthesis, petroleum chemistry, and protein synthesis. However, the inherent structure–activity relationships are less well understood, limiting the future development and applications of the related synthetic methods and processes. The structure–activity relationships of a series of structurally independent thioesters **3** (R^1COSR^2) in palladium-catalyzed C–S activation were investigated



[a] The relative electronic energies and Gibbs free energies in parentheses are given in kcal mol^{-1}.

Scheme 113 Oxidative addition of arene C(sp^2)–S *vs.* alkane C(sp^3)–S bonds of methyl aryl thioethers by DFT calculations.



Scheme 114 C–S bond activation of thioesters with Pd(PPh_3)$_4$ by DFT calculations.

by DFT calculations.[308] The calculations reveal that the C–S bond dissociation energies (BDE) of all the thioesters bearing the alkyl thiol groups (SR^2) are similar (76–78 kcal mol^{-1}), while the BDE values are significantly decreased by about 10 kcal mol^{-1} to reach 62–70 kcal mol^{-1} when the alkyl thiol groups are replaced by the aryl thiol groups. These results suggest that the C–S bond strength in the thioester substrates is insensitive to the substituents (R^1) on the carbonyl groups (R^1CO), whereas the substituents in SR^2 moieties significantly affect BDE of the C–S bonds. It was found that the C–S BDE of thioesters (R^1COSAr) bearing an aryl thiol group exhibit good linear correlations with the substituent constants (σ_p) of the substituents in the SAr moieties, implicating that the C–S bond strength is primarily determined by the electronic effect of the thiol groups. The positive correlation suggests that the C–S bond is weakened by the electron-donating substituents, while it is strengthened by the electron-withdrawing groups. Based on the calculations, the oxidative addition pathway for palladium-catalyzed C–S bond activation of thioesters is proposed (Scheme 114). The oxidative addition of the carbonyl C–S bond to the palladium center prefers to occur *via* the transition state (**TS-Pd-C-S**) in which both the sulfur and carbonyl carbon atoms interact with the palladium center to cleave the C–S bond. The present theoretical studies may benefit the design of a catalytic system for thioester coupling.

11. Summary and outlook

Investigations of diverse C–S bond activation by transition-metal catalysts can provide a fundamental understanding of the C–S bond cleavage in organosulfur compound-involved cross-couplings. By designing suitable catalyst systems desulfitative cross-coupling of organosulfur compounds can be rendered catalytic. As more and more efforts are devoted to C–S transformations, organosulfur compounds are becoming a class of versatile coupling partners. However, in comparison to the well-documented traditional coupling partners, the following aspects are still challenging for organosulfur compounds to act as effective coupling partners through transition-metal-catalyzed C–S bond activation/cleavage. (a) Direct use of thiols and the problematic thiophene, benzothiophene, and dibenzothiophene derivatives as the coupling partners; (b) use of readily available alkyl aryl or heteroaryl thioethers as the coupling partners; (c) cross-coupling reactions using inexpensive base-metal catalysts or at low catalyst loadings; (d) asymmetric catalysis and synthesis *via* organosulfur compounds. It is expected that through the development of effective transition-metal catalytic systems, efficient C–C and C–heteroatom bond formation can be achieved *via* C–S bond activation/

cleavage, affording diverse functionalized organic compounds and providing deeper mechanistic insight into the cross-coupling processes.

Conflicts of interest

The authors declare no conflict of interest.

Acknowledgements

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