C–H Activation

International Edition: DOI: 10.1002/anie.201601540
German Edition: DOI: 10.1002/ange.201601540

C–H Coupling Reactions Directed by Sulfoxides: Teaching an Old Functional Group New Tricks

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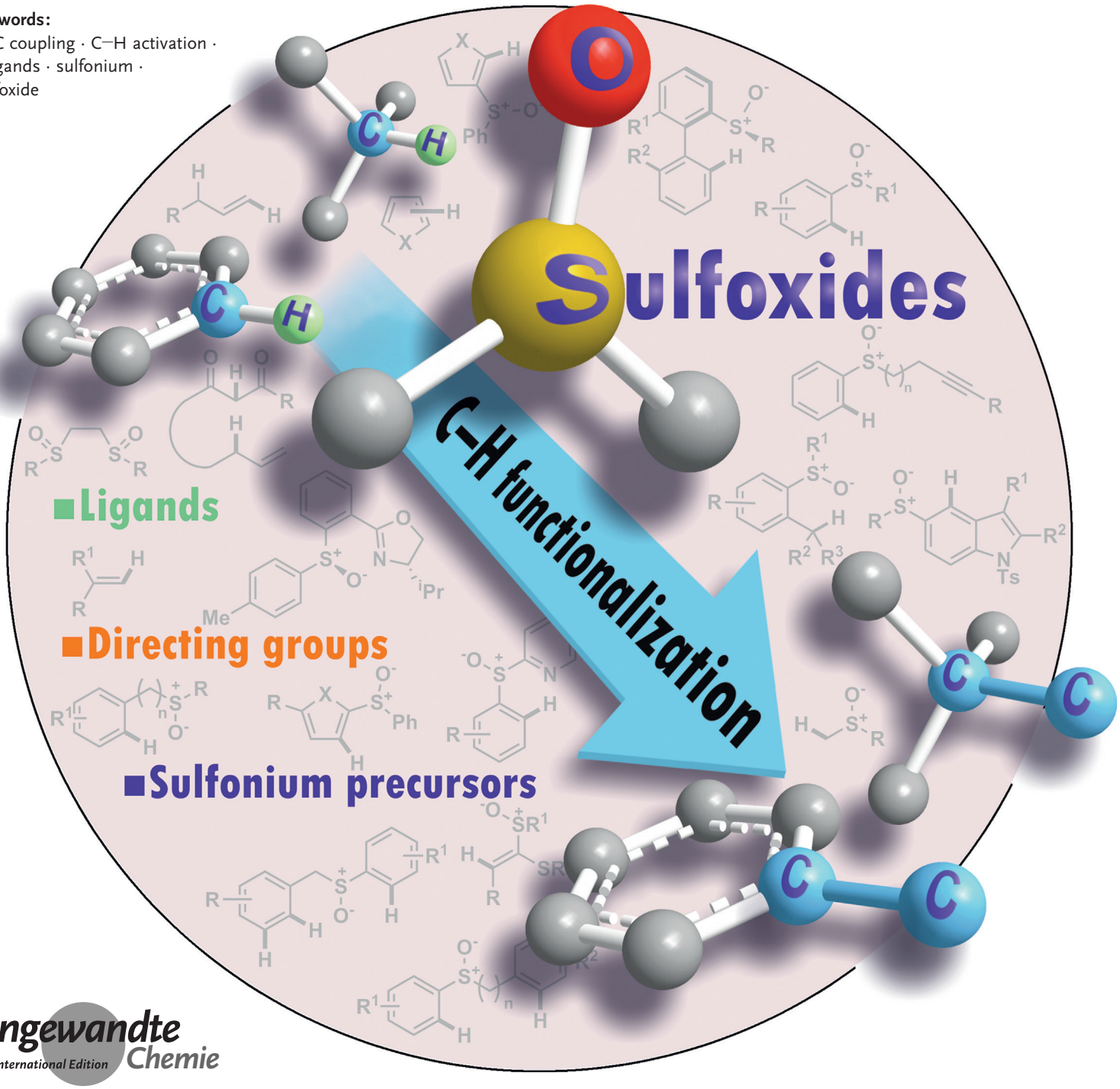
Keywords:
C–C coupling · C–H activation · S ligands · sulfonium · sulfoxide



Sulfoxides are classical functional groups for directing the stoichiometric metalation and functionalization of C–H bonds. In recent times, sulfoxides have been given a new lease on life owing to the development of modern synthetic methods that have arisen because of their unique reactivity. They have recently been used in catalytic C–H activation proceeding via coordination of an internal sulfoxide to a metal or through the action of an external sulfoxide ligand. Furthermore, sulfoxides are able to capture nucleophiles and electrophiles to give sulfonium salts, which subsequently enable the formation of C–C bonds at the expense of C–H bonds. This Review summarizes a renaissance period in the application of sulfoxides arising from their versatility in directing C–H functionalization.

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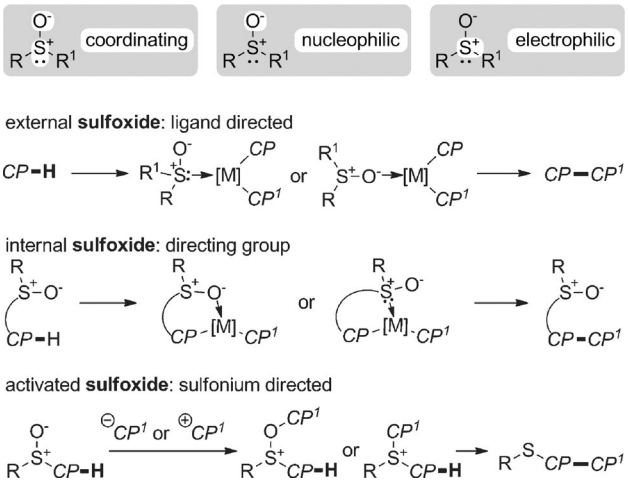
1. Introduction

Direct C–H bond functionalization is an attractive method for elaborating molecules owing to the high step and atom economy; a new C–C bond is formed at the expense of only a C–H bond. Directing groups are typically used to achieve the selective activation of one C–H bond in the presence of others. Sulfoxides are classical directing groups whose use is undergoing a renaissance as a result of their ability to control a range of very different C–H functionalization processes.

The ambivalent nature of sulfoxides allows them to be nucleophilic and coordinating at both oxygen and sulfur, whilst activation at the oxygen atom results in electrophilicity at the sulfur atom. This fascinating reactivity has led to a plethora of well-established sulfoxide-mediated methods, which are at the disposal of the synthetic chemist. In a classical sense, sulfoxides can direct metalation[1] and undergo Pummerer reactions.[2,3] However, sulfoxides have recently found a unique place in C–H bond functionalization owing to their various modes of reactivity, and herein, we describe recent advances in this area that shed new light on the utility of sulfoxides. These reactions include the use of sulfoxides in transition-metal-catalyzed C–H activation, either directed by a sulfoxide in the substrate or by a sulfoxide ligand attached to the metal, and as in situ precursors of sulfonium intermediates that can result in C–H functionalization under metal-free conditions (Scheme 1). These new reactions facilitate expedient access to a variety of organic scaffolds whereby C–C bonds, which result in the introduction of aryl, heteroaryl, alkenyl, allyl, propargyl, and α-carbonyl motifs, can be constructed at the expense of a C–H bond with high efficiency and site selectivity.

In this Review, we include the recent advances in sulfoxide-directed/mediated C–H functionalization that result in C–C bond formation where the sulfoxide has a clear and defined role. Along with each reaction, we include representative examples of the scope and discuss the mechanism where appropriate.



Scheme 1. Sulfoxides as directing groups in C–H bond functionalization and subsequent C–C bond formation. *CP* = coupling partner.

2. Sulfoxide-Directed Stoichiometric Metalation

The metalation of C–H bonds with alkali metals, particularly lithium, is a classical strategy for the formation of C–C bonds.[1] Owing to the Lewis basicity of oxygen and the ability of sulfur to stabilize carbanions, sulfoxides have long been used as efficient directors of stoichiometric C–H metalations.

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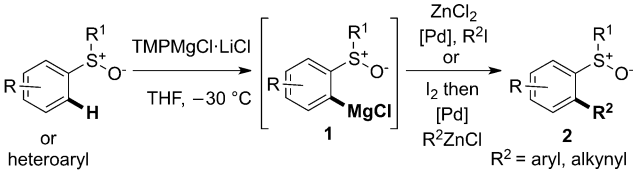
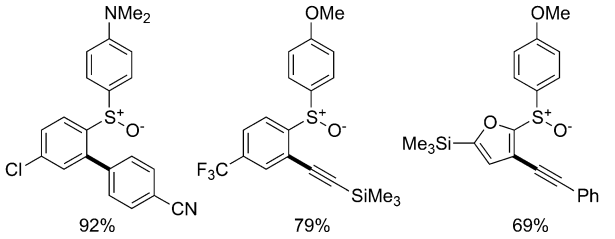
With sulfoxide direction, a variety of C–H bonds can be efficiently metalated, for example, in directed *ortho* metalation, lateral lithiation, and α-lithiation reactions. The generated metalated species can be reacted with a variety of electrophiles, resulting in the formation of C–C bonds. Given that enantiomerically enriched sulfoxides are readily available, it is unsurprising that a plethora of asymmetric transformations based on sulfoxide-directed C–H metalation have been reported. This is a relatively mature field, and as such we only wish to highlight a few recent examples in this area.

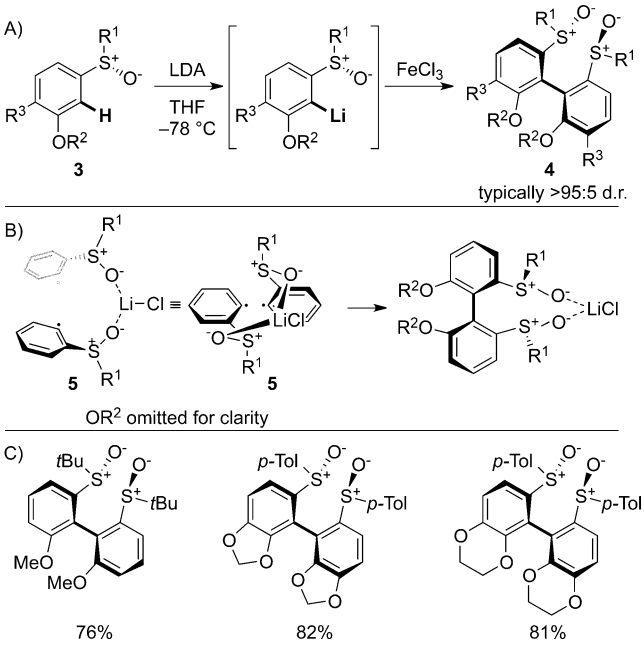
Knochel and co-workers have shown that the sulfoxide group enables the *ortho* magnesiation of aryl and heteroaryl C–H bonds using TMPMgCl·LiCl (Scheme 2).[4,5] Coordination of the magnesium ion to the sulfoxide directs the metalation to the *ortho* position of the most electron-deficient ring in the diaryl sulfoxide. The resultant organomagnesium intermediates **1** can then undergo Negishi cross-coupling after transmetalation to zinc, or are trapped with iodine before cross-coupling to yield arylated and alkynylated arenes **2**.





Scheme 2. Knochel's sulfoxide-directed *ortho* magnesiation. TMP = 2,2,6,6-tetramethylpiperidine.

Zhou, Li, and co-workers reported that the *ortho* lithiation of enantiopure sulfoxides **3** and subsequent atropodiastereoselective biaryl homocoupling mediated by inexpensive $FeCl_3$ gave biaryl bis-sulfoxides **4** (Scheme 3).[6] The *ortho* lithiation is mediated by LDA, and $FeCl_3$ causes a single-electron oxidation of the organolithium intermediate to form an aryl radical. LiCl is then thought to coordinate to two aryl radicals through the sulfoxide oxygen atoms in a transition-state structure (**5**) where the bulky R^1 groups point away from each other (Scheme 3 B). The resultant products are excellent ligands for asymmetric synthesis (Scheme 3 C).

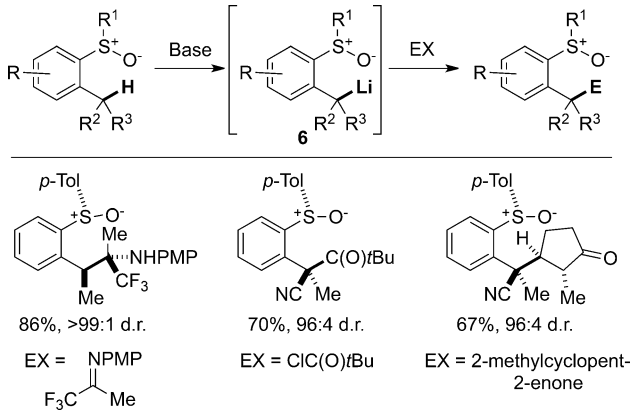


Scheme 3. Zhou and Li's sulfoxide-directed *ortho* lithiation and iron-mediated coupling (A), including the rationalization of the observed stereochemistry (B) and representative examples (C).

Ruano and co-workers have shown the power of the sulfoxide directing group in diastereoselective nucleophilic substitution and nucleophilic addition reactions of laterally lithiated sulfoxides **6** with a variety of electrophiles, including benzyl, allyl, and propargyl halides as well as ketones, imines, acid chlorides, chloroformates, and α,β-unsaturated carbonyl derivatives (Scheme 4). All reactions proceeded with generally high diastereocontrol.[7,8] When prochiral electrophiles were used, 1,2- and even 1,2,3-stereocenter arrays were formed with high stereocontrol, even when challenging quaternary stereocenters were constructed.

Alex Pulis completed his Ph.D. at the University of Bristol with Prof. Varinder K. Aggarwal in 2012. After postdoctoral work with Prof. Douglas W. Stephan at the University of Toronto, he moved to the University of Manchester in 2015 to take a position as Lecturer in Organic Chemistry within the group of Prof. David J. Procter. His current research interests lie in the reactivity of main-group elements and their application in synthesis.

David J. Procter obtained his Ph.D. from the University of Leeds in 1995 with Professor Christopher Rayner. He then spent two years as a Postdoctoral Fellow with Professor Robert Holton at Florida State University. In 1997, he took up a Lectureship at the University of Glasgow before moving to the University of Manchester in 2004. He was promoted to Professor in 2008 and currently is an EPSRC Established Career Fellow. His research interests lie in the development of new synthetic methods, catalysis, and the synthesis of natural and unnatural targets.



Scheme 4. Ruano's diastereoselective sulfoxide-directed lateral lithiation. PMP = *para*-methoxyphenyl.

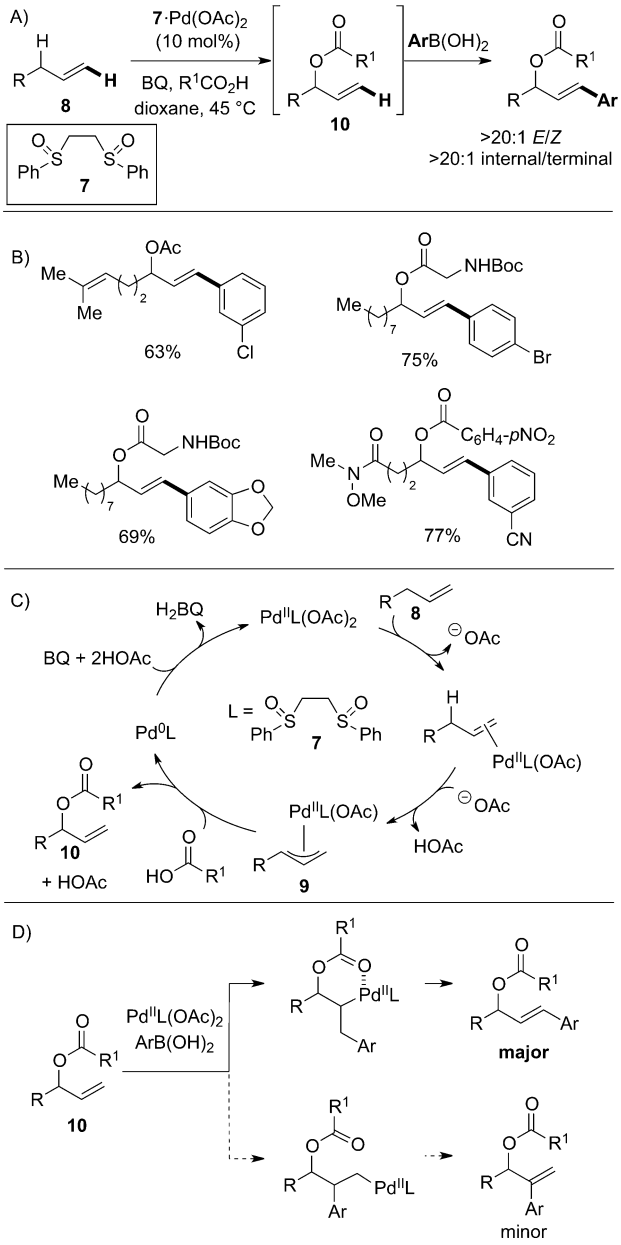
3. Sulfoxides as Ligands in C–H Functionalization

Owing to the lone pair at sulfur and the highly polarized S–O bond, sulfoxides are excellent ligands for metal catalysis and have been utilized in a variety of transformations. The binding mode (through oxygen or sulfur) that sulfoxides operate through is often dependent on the metal and its oxidation state, as well as the other ligands that are present, and both binding modes can be in operation within the same system. For a more in-depth discussion of this fascinating aspect of sulfoxide chemistry, we direct the reader to an excellent review by Dorta and co-workers.[9]

Sulfoxide ligands have been shown to impose unique reactivity on transition-metal-catalyzed reactions.[9,10] The following Section describes palladium-catalyzed processes—a metal that generally binds to sulfoxides through the sulfur atom. Sulfoxides, particularly DMSO, are a common additive in palladium-catalyzed reactions, but their role is often undefined. In this Section, we wish to only include those reactions where the sulfoxide ligand is critical to the success of the C–H functionalization reaction that results in C–C bond formation. These reactions include alkenyl C–H arylation and alkenylation, allylic C–H alkylations, and dehydrogenative couplings, all of which can be directed by a sulfoxide ligand.

Bis-sulfoxide **7** is a privileged ligand in allylic C–H functionalization reactions. White and co-workers first reported that a complex formed from bis-sulfoxide **7**[11] and $Pd(OAc)_2$ is an efficient catalyst for allylic C–H oxidation.[12] This system was utilized in a one-pot allylic C–H oxidation/vinylic C–H arylation reaction to couple an alkene **8** with a carboxylic acid and an aryl boronic acid (Scheme 5).[13] The scope of the reaction is broad and encompasses a variety of olefins, carboxylic acids, and boronic acids (Scheme 5B). Remarkably, single regio- and olefin isomers were formed despite the use of electronically unbiased olefins. It is also significant that this process tolerates aryl bromides in the boronic acid moiety, allowing for complementary downstream functionalization.

The reaction proceeds through two stages where C–O and C–C bonds are formed at the expense of two C–H bonds, enabling the elaboration of simple hydrocarbons into highly



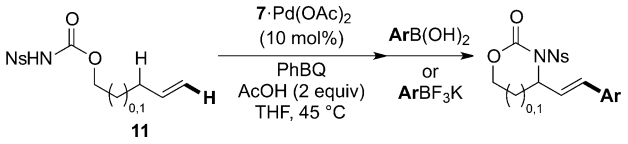
Scheme 5. White's sulfoxide-ligand-directed allylic C–H oxidation/vinylic C–H arylation catalyzed by **7** and Pd^{II} (A) with representative examples (B). Proposed catalytic cycle for the C–H activation event (C) and chelation-controlled regioselectivity in C–H bond arylation (D). Boc = *tert*-butoxycarbonyl, BQ = benzoquinone.

functionalized compounds. The mechanism of the initial C–H functionalization/C–O bond-forming event was studied by Fristrup and co-workers by using a combination of experimental and theoretical methods.[14] They found that C–H bond cleavage is the rate-limiting step in this cycle and occurs by action of an intermolecular acetate unit (or carboxylate) as the base in a proton-abstraction-type mechanism (Scheme 5C). Nucleophilic addition of the carboxylate onto the resultant π-allyl palladium complex **9** liberates the oxidized allyl species **10** and Pd^0, which is oxidized with benzoquinone to close the catalytic cycle.

The vinylic C–H coupling is likely to proceed through an electrophilic palladium(II)-mediated transmetalation/C=C bond insertion mechanism in an oxidative-Heck-type process.[15] Intramolecular chelation in the formed palladacycle is thought to be responsible for the exclusive regioselectivity observed in the C–C bond-forming step (Scheme 5D).

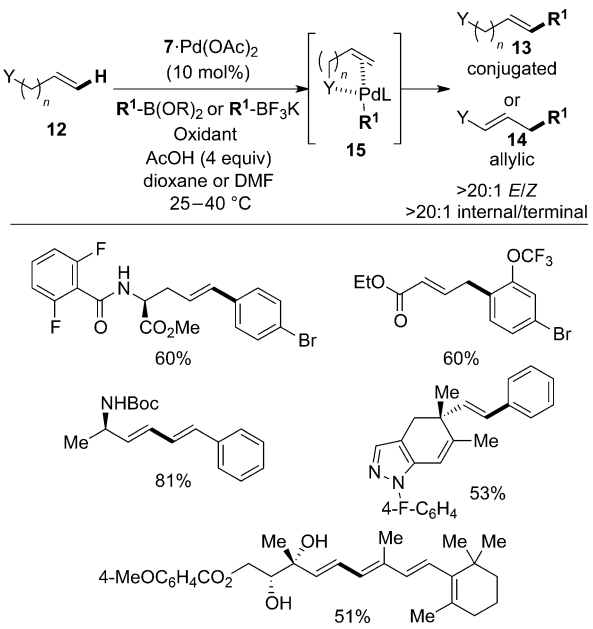
The exact nature and role of the bis-sulfoxide **7**/palladium interaction is unclear; no discernable difference was observed by NMR or IR spectroscopy between a mixture of **7** and $Pd(OAc)_2$ and the free ligand.[16] However, the sulfoxide ligand is critical in both steps of the reaction and is believed to impart favorable electronic properties at Pd that encourage C–H bond cleavage as coordination of Pd^{II} to the alkene decreases the pK_a value of the allylic hydrogen atoms.[14] Furthermore, the bis-sulfoxide ligand **7** ensures that the C–O bond formation proceeds with high regioselectivity. The use of DMSO and $Pd(OAc)_2$ yields linear carboxylates whereas the bis-sulfoxide **7**/Pd complex results in the almost exclusive formation of branched carboxylates **10**.[12] Remarkably, in the absence of the sulfoxide ligand, Wacker-type oxidation products are formed. Moreover, the vinylic C–H bond arylation is not efficiently catalyzed without the sulfoxide ligand.[13]

An analogous reaction mediated by bis-sulfoxide **7** and $Pd(OAc)_2$ that was reported by White and co-workers proceeds by sequential intramolecular allylic C–H amination and intermolecular vinylic C–H arylation starting from alkenyl *N*-nosyl carbamates **11** and aryl boronic acids or trifluoroborate salts (Scheme 6).[17] The mechanism is similar to that of White's C–H oxidation/vinylic C–H arylation discussed above (Scheme 5C,D).[14]



Scheme 6. White's sulfoxide-ligand-directed intramolecular allylic C–H amination/intermolecular vinylic C–H arylation. Ns = nosyl, PhBQ = 2-phenyl-1,4-benzoquinone.

To extend the oxidative Heck component of the reactions discussed above, White and co-workers developed a chelate-controlled oxidative Heck reaction of terminal olefins **12** with aryl and vinyl boron compounds mediated by the Pd^{II}/bis-sulfoxide **7** complex (Scheme 7).[18] In all cases, exemplary *E*/*Z* and regioselectivities were observed despite the use of electronically unbiased olefins. The formation of conjugated (**13**) or allylic products (**14**) was dependent upon the nature of the chelating group (Y) and its proximity to the alkene in the starting material: When a β,γ-unsaturated ester was used, the alkene moved into conjugation with the carbonyl group, resulting in the allylic coupling product. Other chelating groups gave alkenes that are in conjugation with the newly introduced aryl or alkenyl group. High selectivities were obtained in either case. The high regioselectivity during the insertion step, and thus the high internal alkene selectivity, originates from the chelated Pd^{II} species **15** (Scheme 7; see also Scheme 5D). The scope of this process is broad, and even enables the formation of challenging polyenes and the coupling of α-quaternary-carbon-substituted vinyl compounds. Impressively, no erosion in e.r. was observed when allylic stereogenic centers were present. Presumably, under these mild conditions, Pd–H-mediated isomerization is suppressed. Again, bis-sulfoxide ligand **7** is key to efficient catalysis, and the yields are greatly diminished in its absence.

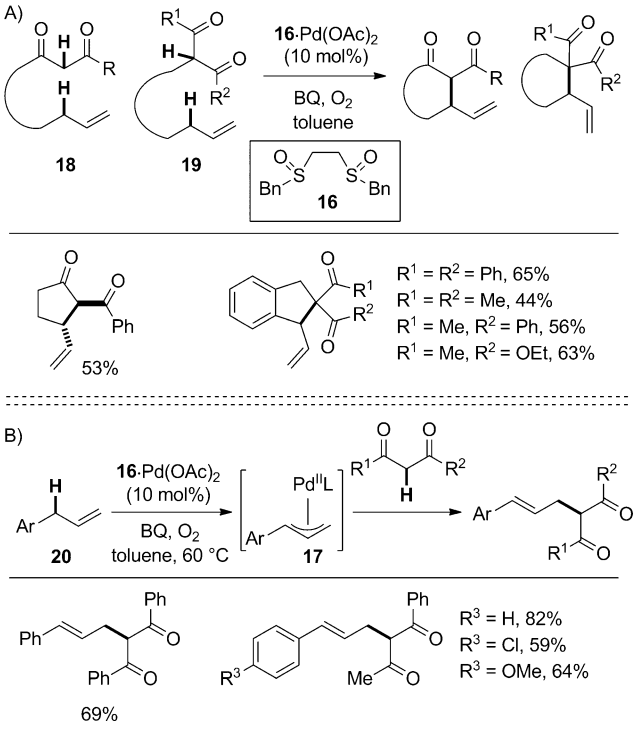


Scheme 7. White's sulfoxide-ligand-directed chelate-controlled intermolecular oxidative Heck reaction. Y = chelating group, oxidant = BQ or 2,6-dimethylbenzoquinone (DMBQ), $(OR)_2 = (OH)_2$ or pinacolato.

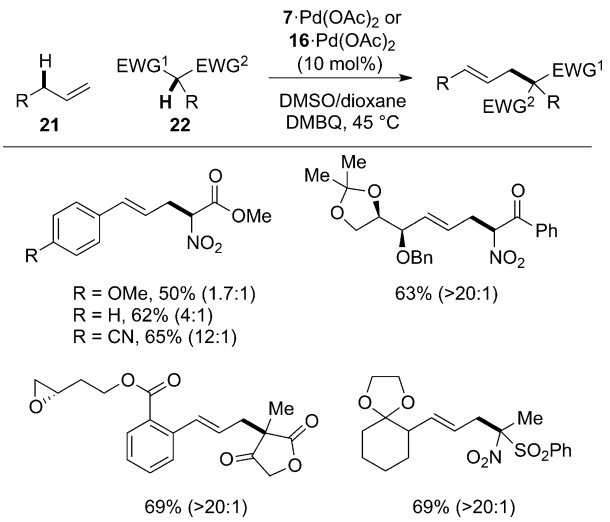
The groups of Shi[19] and White[20] independently reported the first direct allylic C–H alkylations using Pd complexes of bis-sulfoxide ligands **16** and **7** (Schemes 8 and 9, respectively). These reactions are akin to the Tsuji–Trost reaction in that a π-allyl Pd complex is reacted with a nucleophile. After acetate-mediated C–H bond cleavage (see Scheme 5C),[14] carbon nucleophiles react with the resultant π-allyl Pd complex (e.g., **17**) to yield the C–C coupled products and Pd^0. The net result is the formation of $C(sp^3)$–$C(sp^3)$ bonds from allylic C–H bonds.

In Shi's work, intramolecular allylic alkylation of 1,3-diketones or keto esters (**18** and **19**) delivers cyclic compounds with complete selectivity for the terminal alkene (Scheme 8A). In the intermolecular case, allylic aryl compounds **20** react with 1,3-diketones to exclusively give internal *E* alkenes (Scheme 8B).[19]

In White's allylic C–H alkylation, a variety of activated and unactivated allylic systems (**21**) were coupled with carbon nucleophiles (**22**) in the presence of bis-sulfoxides **7** or **16** (Scheme 9).[20] Remarkably, tertiary nucleophiles could be utilized to form challenging quaternary carbon centers. In all cases, only the *E* isomers were formed, and generally, the linear product prevailed. The scope of the allyl coupling partner was found to be broad, and the process tolerated both activated (e.g., aryl-substituted) and unactivated (e.g., alkyl-



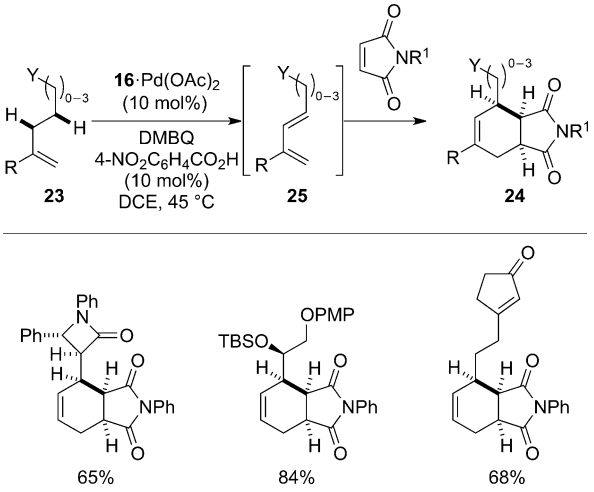
Scheme 8. Shi's sulfoxide-ligand-directed intramolecular (A) and intermolecular (B) allylic C–H alkylation. Bn = benzyl.



Scheme 9. White's sulfoxide-ligand-directed allylic C–H alkylation. Ratios in parentheses indicate linear/branched substitution. EWG = electron-withdrawing group.

substituted) allyl systems **21**. Furthermore, stereocenters proximal or distal to the allylic C–H bond did not undergo racemization. The presence of DMSO was found to be critical to the success of the reaction as there is a subtle interplay between DMSO and bis-sulfoxide ligation to Pd: The bis-sulfoxide is essential for the C–H activation event whereas DMSO is crucial to the C–C bond-forming step. The absence of either DMSO or the bis-sulfoxide adversely affected the efficiency of the reaction.

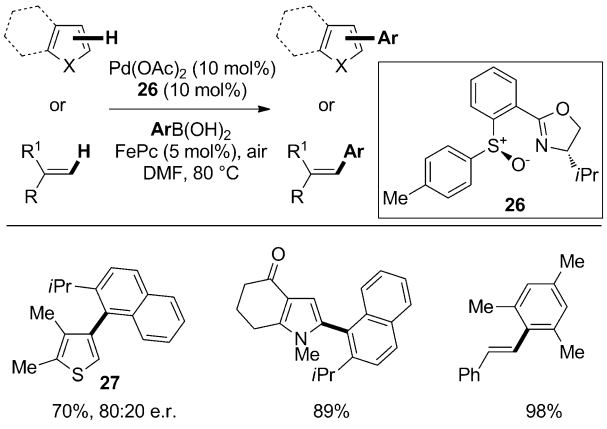
Allylic C–H functionalization mediated by bis-sulfoxide **16** and $Pd(OAc)_2$ was also utilized in dehydrogenative Diels–Alder reactions to couple terminal alkenes **23** and maleimides to form highly functionalized cyclohexenes **24** (Scheme 10).[21]



Scheme 10. White's sulfoxide-ligand-mediated dehydrogenative Diels–Alder reaction. DCE = 1,2-dichloroethane, TBS = *tert*-butyldimethylsilyl.

This process can be used for the dehydrogenation of a variety of simple and readily available terminal alkenes (via the corresponding π-allyl Pd complex followed by β-hydride elimination) and yields reactive 1,3-dienes **25** in situ. As the dienes are generated in low concentrations relative to that of the maleimide coupling partner, side reactions associated with the 1,3-dienes are greatly inhibited.

Recently, Yamaguchi, Itami, and co-workers reported the oxidative coupling of five-membered heterocycles and alkenes with aryl boronic acids mediated by sulfoxide-oxazoline **26** and Pd^{II} using air as the terminal oxidant (Scheme 11).[22] Whereas other ligands, such as DMSO, tetramethylene sulfoxide, and White's ligand **7**, were also effective, ligand **26** was found to be superior in terms of both activity and scope. The reaction exploits thiophenes, benzo-



Scheme 11. Yamaguchi and Itami's sulfoxide-ligand-directed aerobic oxidative C–H/C–B coupling. FePc = iron phthalocyanine.

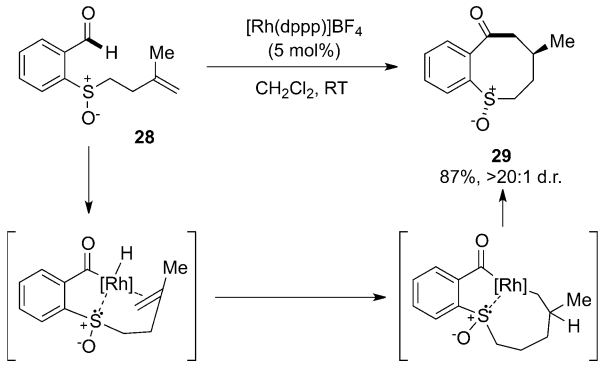
thiophenes, indoles, pyrroles, and furans as the C–H coupling partner in a highly regioselective manner. In addition, acrylates and styrenes can be used. Hindered coupling partners are well tolerated, which is remarkable considering that they often fail in other C–H/C–B couplings. Ligand **26** was shown to induce moderate enantioselectivity in one example (**27**, 80:20 e.r.).

4. Sulfoxide-Directed Transition-Metal-Catalyzed C–H Activation

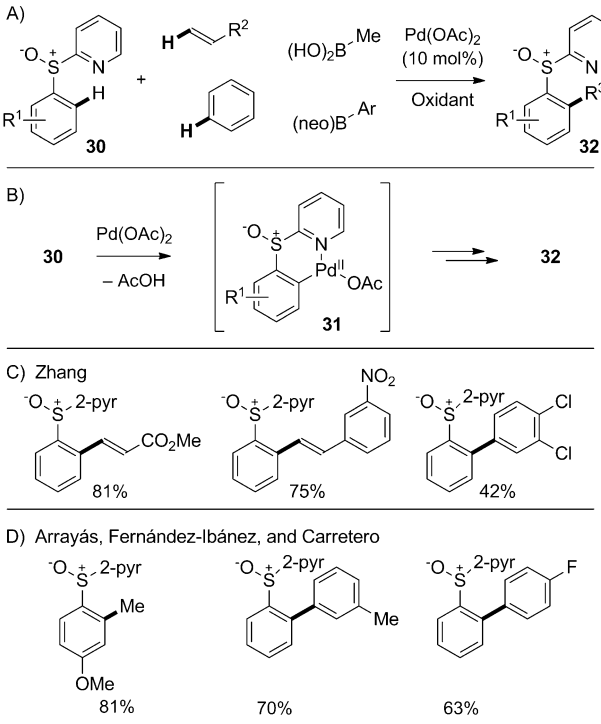
The most common strategy for addressing regioselectivity in C–H activation is the use of directing groups.[23] Only recently has the use of sulfoxides been explored for such purposes. In these reactions, aryl rings bearing either *ortho* or remote sulfoxide groups undergo C–H activation forming metalated aryl rings, which undergo subsequent C–C bond-forming events with alkenes, alkynes, and arenes. By far the most common transition metal used in conjunction with a sulfoxide directing group has been palladium but rhodium and ruthenium have also been employed. Many of the early examples were intramolecular processes, whereas more recent disclosures have revealed that sulfoxides are efficient directors in intermolecular C–H coupling reactions. In this Section, we describe the seminal reports of sulfoxide-directed catalytic C–H activation and showcase the development of this emerging directing group in transition-metal-catalyzed C–C bond-forming reactions.

In an early example of sulfoxide-directed transition-metal-catalyzed C–H activation, Dong and co-workers reported the Rh-catalyzed intramolecular alkene hydroacylation of **28** to give eight-membered heterocyclic ketone **29**.[24] The sulfoxide directing group coordinates to Rh and is thought to promote alkene hydroacylation over competing alkene isomerization, aldehyde decarbonylation, and catalyst decomposition (Scheme 12).

The first general studies on sulfoxide-directed metal-catalyzed C–H activation involved the 2-pyridyl sulfoxide directing group (**30**; Scheme 13). The key cyclopalladated intermediate **31** formed after C–H activation exists as the nitrogen-bound chelate (Scheme 13B). Zhang and co-workers showed that such intermediates enable the C–H/C–H



Scheme 12. Dong's sulfoxide-directed rhodium-catalyzed intramolecular alkene hydroacylation. dppp = 1,3-bis(diphenylphosphino)propane.

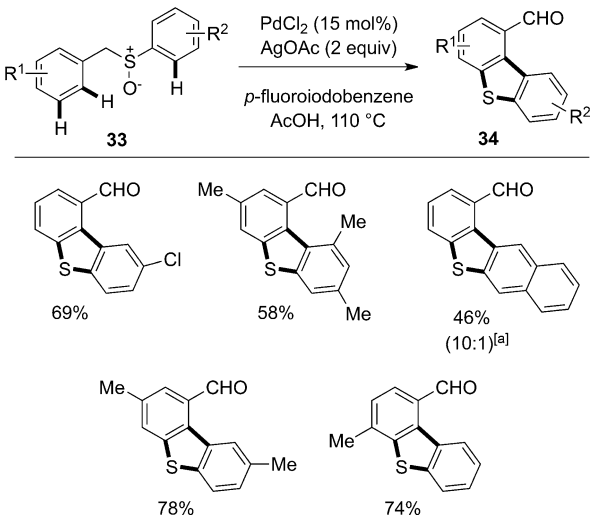


Scheme 13. 2-Pyridylsulfoxide-directed palladium-catalyzed C–H coupling reactions (A), showing the key palladated intermediate (B) and representative examples reported by Zhang (C) and Arrayás, Fernández-Ibánez, and Carretero (D). neo = neopentylglycolato, 2-pyr = 2-pyridyl.

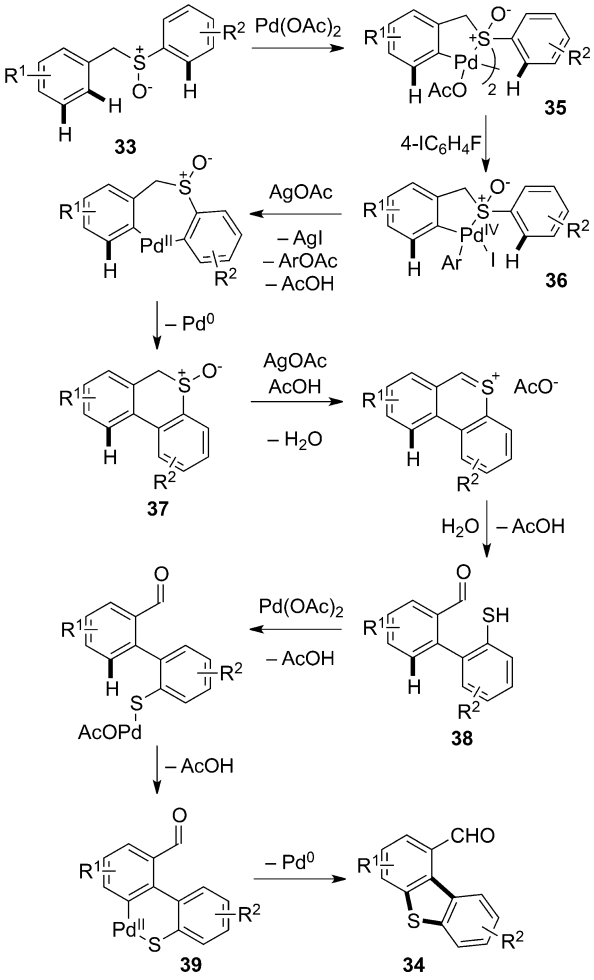
coupling of arenes **30** with electron-deficient alkenes, styrenes, and arenes (Scheme 13C).[25,26] Furthermore, the 2-pyridylsulfinyl directing group has also been employed by Arrayás, Fernández-Ibánez, Carretero, and co-workers to mediate a Pd^{II}-catalyzed C–H coupling of **30** with methylboronic acid and aryl boronic acid neopentyl esters (Scheme 13D).[27]

Antonchick and Samanta employed a sulfoxide as the directing group in a powerful Pd-catalyzed triple C–H activation approach for the conversion of aryl benzyl sulfoxides **33** into important dibenzothiophenes **34**.[28] Substitution at both the aryl and benzyl components in sulfoxides **33** was tolerated, and the desired products were isolated in good yield and high regioselectivity (Scheme 14). The use of an aryl iodide additive was important for catalyst turnover.

The triple C–H activation cascade process is thought to proceed by initial sulfoxide-directed C–H palladation to give dimeric Pd^{II} species **35**, in which the sulfur atom of the sulfoxide group is coordinated to Pd^{II} (Scheme 15). Oxidative addition to the aryl iodide additive to give a transient Pd^{IV} species **36** followed by reductive elimination may prelude C–H activation. Reductive elimination then delivers cyclic sulfoxide **37**, and Pd^{II} is regenerated from Pd^0 by AgOAc. In the next stage of the catalytic cascade, cyclic sulfoxide **37** undergoes a Pummerer rearrangement[3] and hydrolysis to give the thiol-containing aldehyde **38**. Coordination of Pd^{II} and C–H activation then forms palladacycle **39** before reductive elimination completes the cascade and furnishes **34**.[28]

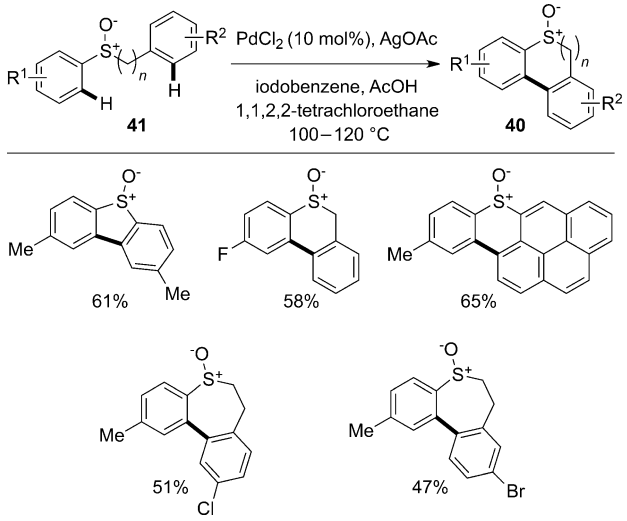


Scheme 14. Antonchick's sulfoxide-directed palladium-catalyzed triple C–H activation approach to dibenzothiophenes. [a] Ratio of the 3- and 1-substituted naphthalene.



Scheme 15. Proposed mechanism for Antonchick's sulfoxide-directed palladium-catalyzed synthesis of dibenzothiophenes.

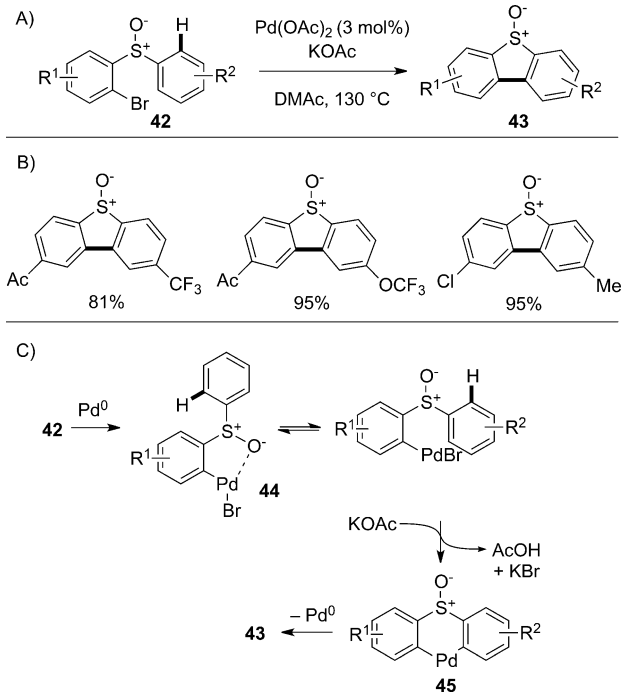
Inspired by Antonchick's ground-breaking studies, Zhang and co-workers described a sulfoxide-directed C–H activation approach to sulfoxide-containing polycycles **40** that also involves a Pd-catalyzed intramolecular C–H/C–H oxidative coupling (Scheme 16).[29] Varying the sulfoxide bridge between the two aryl rings in **41** enables the synthesis of five-, six-, and seven-membered sulfur heterocycles **40**.



Scheme 16. Zhang's sulfoxide-directed C–H activation approach to sulfoxide-containing polycycles.

Colobert and co-workers utilized aryl sulfoxide substrates in a related palladium-catalyzed C–H activation approach to dibenzothiophene *S*-oxides.[30] A range of 2-bromoaryl aryl sulfoxides **42** underwent cyclization upon treatment with $Pd(OAc)_2$ to give products **43** in good yield (Scheme 17). The process proceeds by Pd^0 insertion into the *ortho* C–Br bond of the aryl sulfoxide, rather than by C–H activation, to generate the key sulfoxide-bound Pd^{II} intermediate **44**, in which the sulfoxide oxygen atom is likely coordinated to Pd^{II} (Scheme 17C). C–H activation then gives the six-membered palladacycle **45**, which undergoes reductive elimination to afford **43** and Pd^0.

Colobert and co-workers also exploited an enantiopure compound containing a sulfoxide directing group in the intermolecular atropodiastereoselective Pd-catalyzed C–H alkenylation of biaryl sulfoxides **46** using methyl acrylate[31] and styrenes[32] (Scheme 18).[33] The alkenylated biaryl products **47** were obtained in good yield and diastereoselectivity. This approach is significant as the sulfoxide moiety is used as both a directing group and a chiral auxiliary in C–H activation. Furthermore, in most asymmetric C–H bond functionalizations, asymmetry is induced after C–H bond activation. In contrast, in Colobert's approach, the activation of the C–H bond is the diastereoselectivity-determining step. With 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) as the solvent, the amount of oxidant could be reduced, and the reactions could be run at ambient temperature, albeit with long reaction times. Under these conditions, high yields and high atropodiastereoselectivities were obtained.

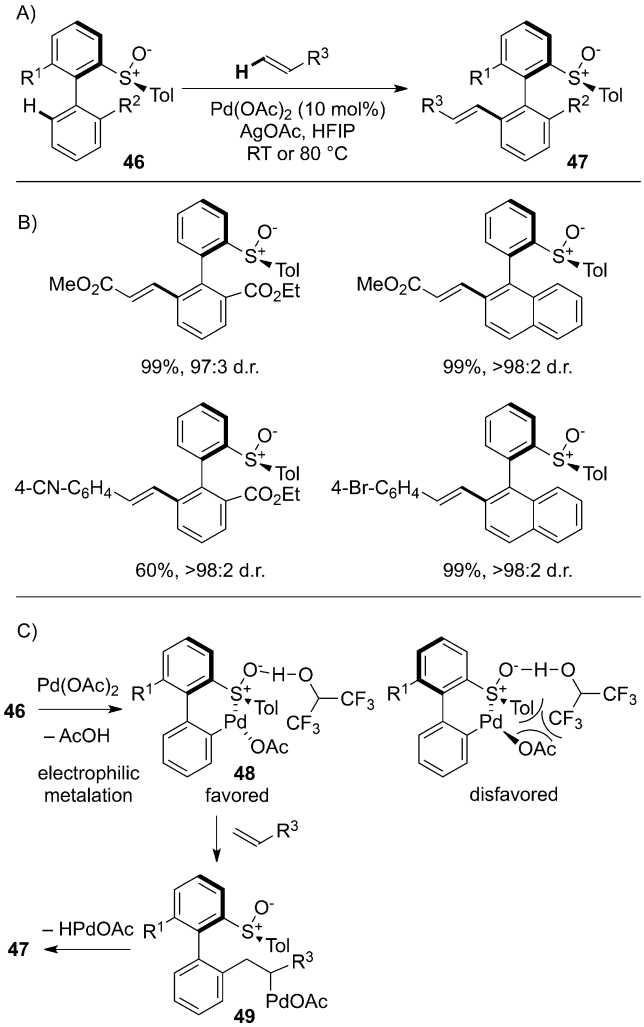


Scheme 17. Colobert's sulfoxide-directed palladium-catalyzed C–H activation approach to dibenzothiophene *S*-oxides (A), with representative examples (B) and the proposed mechanism (C). DMAc = dimethylacetamide.

The sulfoxide is thought to direct electrophilic C–H palladation via coordination to sulfur, resulting in a six-membered palladacycle intermediate (**48**; Scheme 18C). Subsequent insertion of the alkene partner into the Pd–C bond generates **49**. β-Hydride elimination and reductive elimination of AcOH then give the product and Pd^0, which is reoxidized to Pd^{II} by AgOAc. The atropodiastereoselectivity observed likely arises during the formation of palladacycle **48**. HFIP has an effect on both the efficacy and the atropodiastereoselectivity of the coupling. Using NMR and IR studies, Colobert and co-workers showed that the hydrogen-bond-donor solvent coordinates to the oxygen of the sulfoxide group. This coordination affects the electronics of the directing sulfoxide group and appears to enhance the rate-determining C–H activation step. This sulfoxide–HFIP interaction plays a key role in achieving high atropodiastereoselectivity, which may be due to the increased effective size of the sulfoxide directing group when coordinated to HFIP.

Zhang and co-workers assessed the generality of the sulfoxide-directed Pd^{II}-catalyzed *ortho* C–H alkenylation using arenes **50** and various acrylates (Scheme 19).[34] Directed C–H activation involving the sulfoxide in a five- and six-membered palladacycle through coordination of the sulfur atom to palladium was particularly effective, and remarkably, an analogous seven-membered palladacycle was also competent (**51**; Scheme 19C). The process tolerated a range of substituents at various sites on the aryl ring.

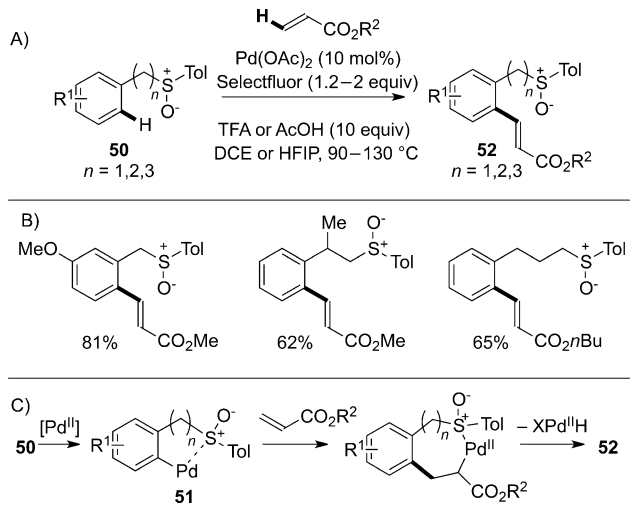
Satoh and Miura exploited a sulfoxide directing group to mediate the Rh-catalyzed *ortho* C–H alkenylation of aryl sulfoxides **53** using electron-deficient alkenes or aryl alkynes (Scheme 20).[35] The C–H alkenylation using alkenes pro-



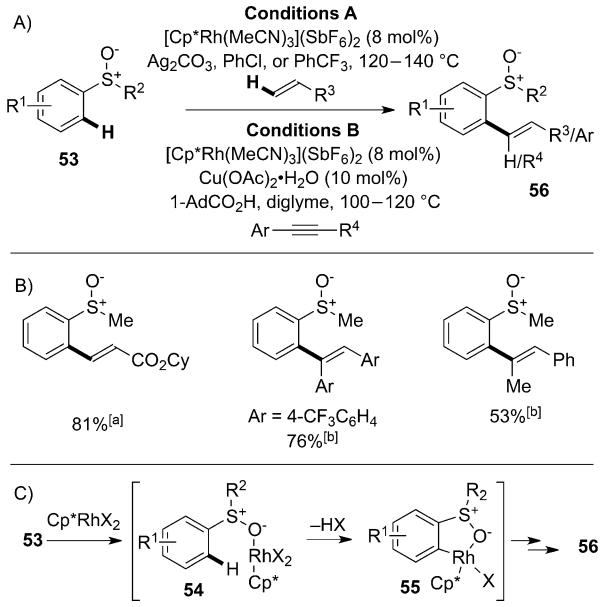
Scheme 18. Colobert's use of an enantiopure sulfoxide directing group in the intermolecular atropodiastereoselective palladium-catalyzed C–H alkenylation of biaryl sulfoxides (A), with representative examples (B) and the proposed stereochemical rationale (C). HFIP = 1,1,1,3,3,3-hexafluoropropanol.

ceeds by coordination of the sulfoxide oxygen atom to Rh^{III} (see intermediate **54**; Scheme 20C). This enables subsequent cyclometalation to give intermediate rhodacyle **55**, which then undergoes alkene insertion. β-Hydride elimination furnishes the alkenylaryl sulfoxide products **56**, and oxidation of Rh^I to Rh^{III} by Ag_2CO_3 closes the catalytic cycle.[35]

In a related transformation, Jeganmohan and Padala used a sulfoxide group to direct the Ru^{II}-catalyzed C–H alkenylation of aryl sulfoxides **53** with aryl alkynes as the cross-coupling partner (Scheme 21).[36] This Ru-catalyzed system is believed to operate solely at the Ru^{II} oxidation state (Scheme 21C). A cationic Ru^{II} species **57** coordinates to the oxygen atom of the sulfoxide directing group, resulting in *ortho* deprotonation/metalation and the formation of intermediate **58**. Subsequent alkyne insertion and protonation then delivers product **59** and regenerates the Ru^{II} catalyst **57**.



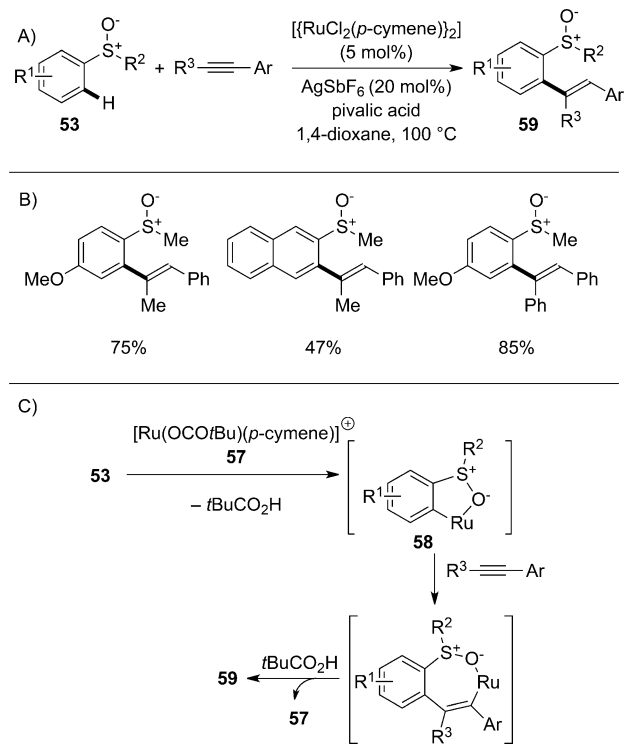
Scheme 19. Zhang's use of a remote sulfoxide directing group in the palladium-catalyzed C–H alkenylation of arenes (A), with representative examples (B) and the proposed mechanism (C). TFA = trifluoroacetic acid.



Scheme 20. Satoh and Miura's sulfoxide-directed rhodium-catalyzed *ortho* C–H alkenylation of aryl sulfoxides (A), with representative examples (B) and the proposed mechanism (C). [a] Conditions A. [b] Conditions B. Ad = adamantyl.

5. C–H Couplings via Sulfonium Intermediates Derived from Sulfoxides

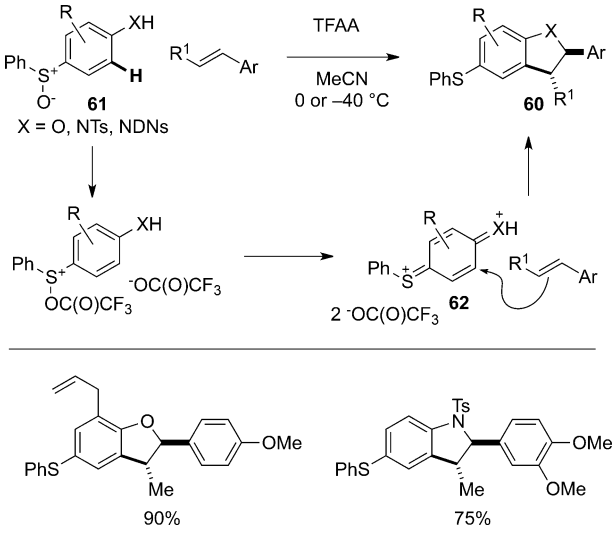
In recent times, sulfoxides have been employed as precursors to sulfonium salts[2,3] that have been exploited in metal-free C–H coupling processes. Once activated, sulfoxides react with nucleophilic coupling partners at the sulfur atom to afford sulfonium salts, which enables the union of a variety of carbon units in a site-selective manner. In contrast to the transition-metal-mediated reactions described in Sections 3 and 4, where a stoichiometric oxidant is used to regenerate the active metallic species for catalyst turnover, here, the sulfoxide is used as an internal redox-active director and is reduced to the sulfide upon C–C bond formation. This precludes any further C–H functionalization taking place, ensuring mono- and site-selective C–C bond formation. Early developments in this field employed a limited range of substrates; however, in recent years, this strategy has been greatly extended, and it now encompasses a variety of coupling partners. Moreover, unactivated sulfoxides are nucleophilic at oxygen and react with electrophilic coupling partners to form sulfoxonium salts. This facet of sulfoxide reactivity has recently been exploited in C–H functionalization reactions. Other strategies for sulfoxide direction in metal-free C–H bond functionalization have recently also come to light. These aspects are explored in the proceeding Section.



Scheme 21. Jeganmohan's sulfoxide-directed ruthenium(II)-catalyzed C–H alkenylation of aryl sulfoxides with aryl alkynes (A), with representative examples (B) and the proposed mechanism (C).

5.1. Reactions of Activated Sulfoxides with Nucleophilic Coupling Partners

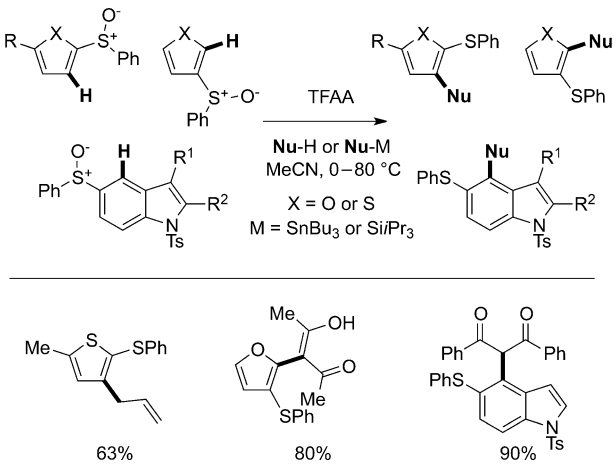
In the early 2000s, Kita and co-workers reported the synthesis of dihydrobenzofurans[37] and indolines[38] (**60**) through the C3–H functionalization of 4-sulfinyl phenols and anilines (**61**) with styrenes (Scheme 22). The reaction proceeds through an aromatic Pummerer-type mechanism; upon treatment of the aryl sulfoxide with trifluoroacetic acid anhydride (TFAA) and subsequent elimination of trifluoroacetate, the resulting thionium ion **62** undergoes 1,4-addition with a styrene nucleophile. The O or N atom then sponta-



Scheme 22. Kita's sulfoxide-mediated *meta* functionalization of phenols and anilines. DNs = *N*-(2,4-dinitrobenzenesulfonyl), Ts = *para*-toluenesulfonyl.

neously cyclizes onto the carbocation forming the five-membered ring. Complete regio- and diastereoselectivities were observed in all cases. The process is remarkable as it reverses the normal reactivity of electron-rich arenes: The position *ortho* to oxygen/nitrogen becomes electrophilic in nature.

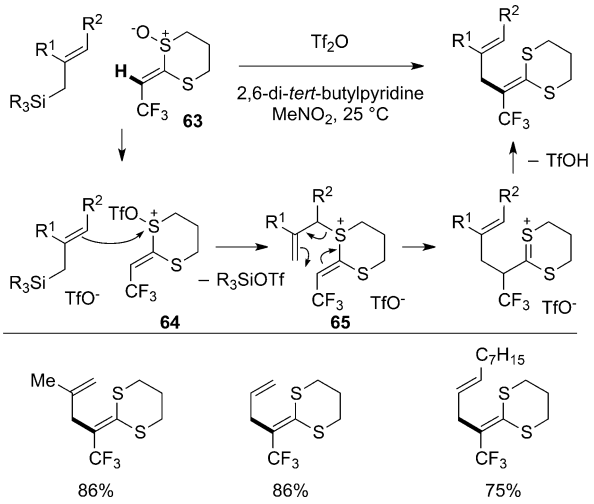
Kita and co-workers also reported a sulfoxide-directed aromatic C–H coupling of sulfinyl-substituted furans, thiophenes,[39] and indoles[40] with nucleophiles (Scheme 23). The sulfoxide moiety was activated with TFAA, triggering the coupling with a net loss of an aromatic C–H bond after formation of a new C–C bond. The authors proposed a direct addition mechanism whereby the nucleophile attacks at the carbon center with concomitant loss of trifluoroacetate. Allyl stannanes and acetylacetone were coupled with 2- or 3-sulfinyl thiophenes and furans. Aside from these nucleophiles, 5-sulfinyl indoles were also coupled with vinyl sulfides, allyl silanes, and other 1,3-dicarbonyl nucleophiles to give chal-



Scheme 23. Kita's sulfoxide-mediated *ortho* functionalization of sulfinyl furans, thiophenes, and indoles. TFAA = trifluoroacetic anhydride.

lenging C4-substituted indoles. Very high regioselectivity was observed in all cases.

Yorimitsu, Oshima, and Yoshida reported that ketene dithioacetal monoxides can direct a variety of C–H functionalization reactions.[41] In particular, they showed that trifluoromethyl-substituted ketene dithioacetal monoxides **63** could be coupled with allyl silanes (Scheme 24).[42]

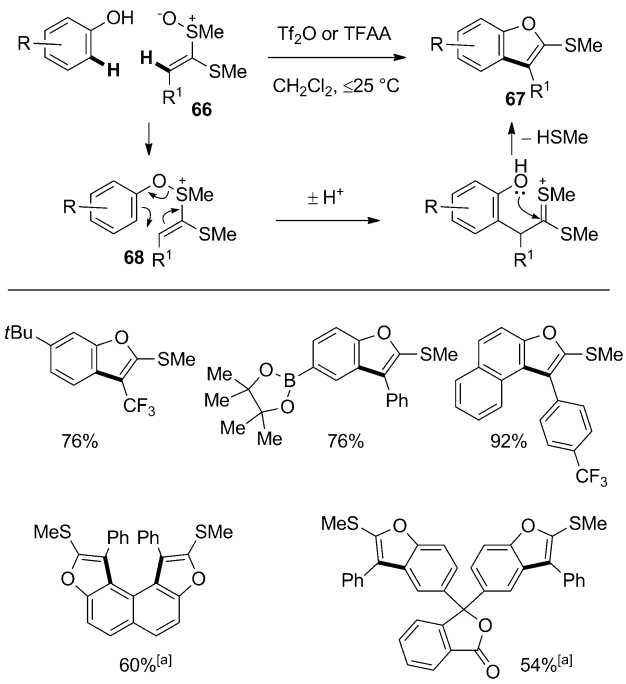


Scheme 24. Yorimitsu and Oshima's C–H coupling of ketene dithioacetal monoxides with allyl silanes. Tf = trifluoromethanesulfonyl.

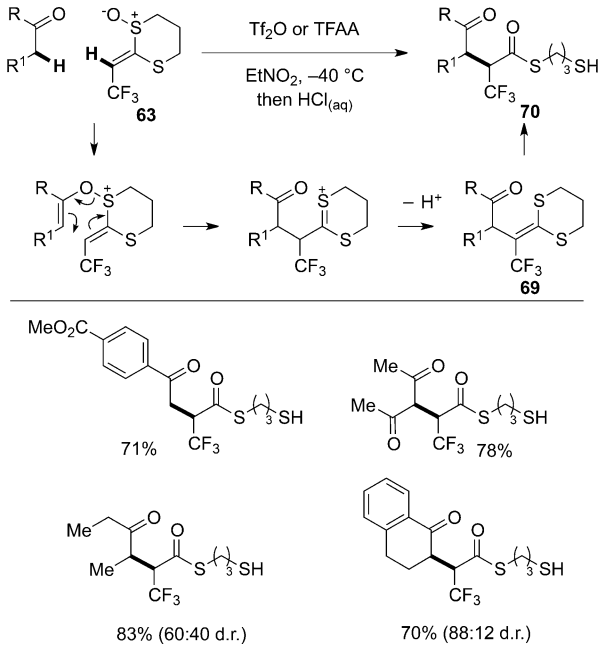
Addition of the allyl silane to the electrophilic sulfur atom in the activated ketene dithioacetal monoxide **64** results in a vinyl/allyl-substituted sulfonium salt **65** that is predisposed to facile [3,3]-sigmatropic rearrangement.[43] This concept of activating the sulfoxide director and then forming an initial sulfur–coupling partner bond prior to the delivery of the coupling partner has become a useful method for constructing C–C bonds from C–H bonds and has been generalized by Yorimitsu and Oshima, and others.

Yorimitsu, Oshima, and co-workers also developed a method for the C–H coupling between phenols and ketene dithioacetal monoxides **66** to form highly versatile benzofurans **67** (Scheme 25).[44] The reaction proceeds by addition of the oxygen atom to the cationic sulfur center of the activated ketene dithioacetal monoxide. The new C–C bond is formed during the resulting sigmatropic rearrangement of **68**. Impressively, the reaction gave very high regioselectivity when two inequivalent *ortho* positions were present in the phenol coupling partner. Furthermore, double C–H functionalization occurred when the aromatic partner contained two phenol units. The SMe moiety of the product **67** can be further transformed in Pd- or Ni-mediated coupling reactions.

The group of Yorimitsu and Oshima also reported the coupling of non-aromatic C–H bonds in the reaction between enolizable ketones and ketene dithioacetal monoxides **63** (Scheme 26).[45] The reaction yielded γ,γ-disulfanyl-β,γ-unsaturated carbonyl compounds **69**, which were hydrolyzed to 1,4-dicarbonyl derivatives **70**, important starting materials for



Scheme 25. Yorimitsu and Oshima's synthesis of benzofurans through the C–H coupling of phenols and ketene dithioacetal monoxides. [a] In a one-pot process from the corresponding diphenol.

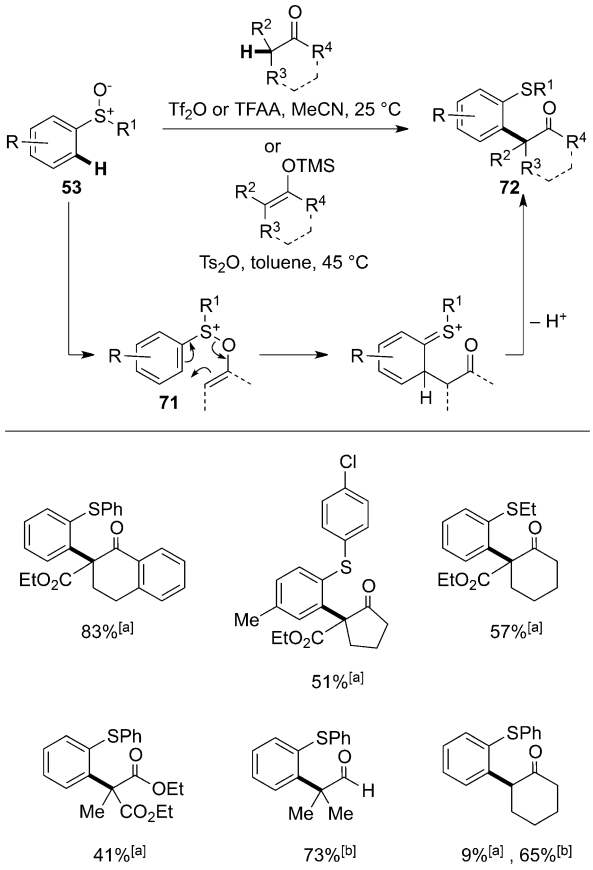


Scheme 26. Yorimitsu and Oshima's coupling of ketene dithioacetal monoxides and ketones for the synthesis of 1,4-dicarbonyl derivatives.

heterocycle formation. A similar mechanism to the reaction with phenols (Scheme 25) was proposed.

The groups of Maulide and Procter recently extended the concepts reported by Kita, Yorimitsu, and Oshima towards more general studies of sulfoxide-directed C–H functionalization reactions that proceed via sulfonium intermediates.

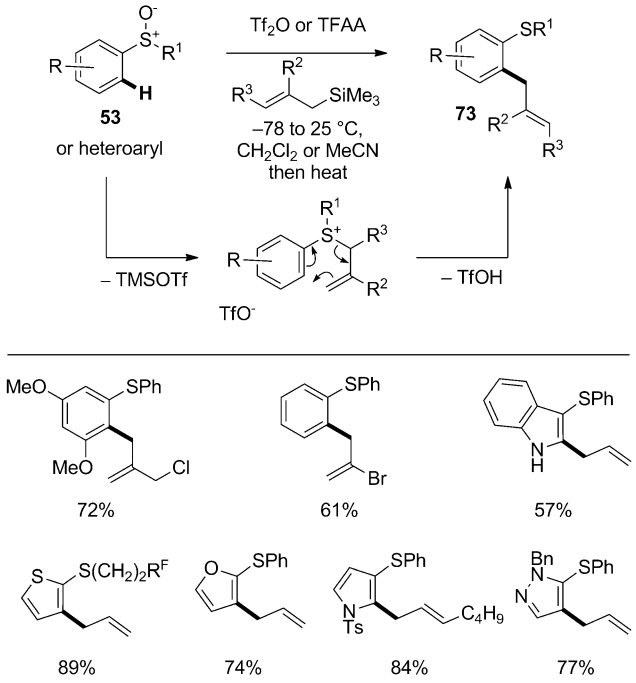
Maulide and co-workers reported the sulfoxide-directed C–H alkylation of arenes **53** with ketones or enol silanes (Scheme 27).[46] The sulfoxide was activated and subsequently



Scheme 27. Maulide's sulfoxide-directed synthesis of α-arylated ketones. [a] From the ketone. [b] From the enol silane. TMS = trimethylsilyl.

reacted with the nucleophilic coupling partners at the sulfur center. The resulting sulfoxonium salts **71** undergo a [3,3]-sigmatropic rearrangement, which, after rearomatization, gives α-arylated ketones **72**. Ketones or enol silanes gave *ortho*-monosubstituted products. Interestingly, when electronically different aryl groups were attached to the sulfur atom, substitution occurred preferentially at the more electron-rich ring. Furthermore, the reaction enabled the synthesis of carbonyl derivatives with quaternary carbon centers at the α-position. The use of enol silanes increased the efficiency of the α-arylation of simpler carbonyl derivatives.

Procter and co-workers reported the C–H coupling of aromatic and heteroaromatic compounds, such as furans, thiophenes, pyrroles, pyrazoles, and indoles, bearing sulfoxide directing groups with allyl silanes to give exclusively *ortho*-allylated products **73** (Scheme 28).[47] The sulfoxide moiety was activated using triflic anhydride or TFAA and reacted with various nucleophilic allyl silanes. After addition of the allyl silane to the activated sulfoxide, a [3,3]-sigmatropic rearrangement occurs. The C–H coupling products could be

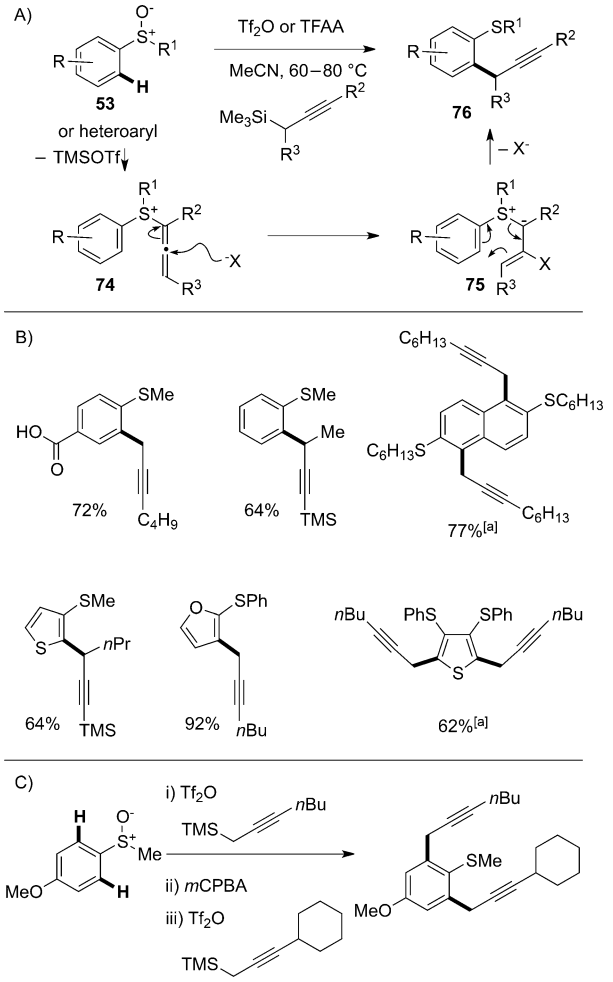


Scheme 28. Procter's sulfoxide-directed C-H coupling of arenes with allyl silanes. $R^F = C_8F_{17}$.

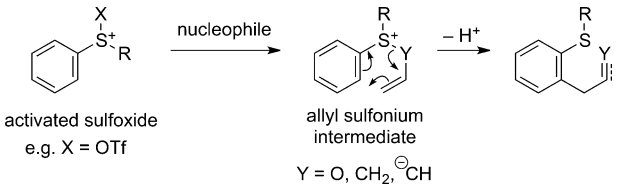
further functionalized by Ni catalysis to introduce a variety of aryl and alkyl groups in place of the SR^1 moiety.

Procter and co-workers also showed that the sulfoxide-directed coupling of propargyl silanes with arenes and heteroarenes proceeds with complete *ortho* regioselectivity (Scheme 29).[48] The propargyl silane adds to the activated sulfoxide to form the isolable allenyl intermediate **74**. Intermediate **74** is then thought to undergo a [3,3]-sigmatropic rearrangement directly or after addition of a nucleophile (e.g., base, triflate, solvent) to the electrophilic allenyl sulfonium to form ylide **75**. A sequence of propargylation, sulfur oxidation, and propargylation allows for controlled iterative double C–H functionalization (Scheme 29C). The propargylated products **76** were readily converted into important benzothiophenes upon treatment with iodine, and the combined approach can be used for the metal-free synthesis of benzothiophene-based organic materials.

Mechanistic features link the works of Yorimitsu and Oshima (Schemes 24–26), Maulide (Scheme 27), and Procter (Schemes 28 and 29). The sulfoxide, once activated, is electrophilic at the sulfur atom and reacts with the chosen nucleophile to form an aryl allyl sulfonium derivative (Scheme 30). For example, allyl and propargyl silanes react through the terminal carbon atom (Yorimitsu and Oshima, Procter), and ketones react through the enol oxygen atom (Yorimitsu and Oshima, Maulide). This key intermediate is predisposed for a charge-accelerated [3,3]-sigmatropic rearrangement,[43] which forms the new C–C bond. Rearomatization yields the C–H-functionalized products. This mechanistic hypothesis is backed up by the high regioselectivities (versus the direct addition pathway proposed by Kita; Schemes 22 and 23) and the isolation/observation of the key allyl sulfonium intermediates prior to rearrangement. Moreover,



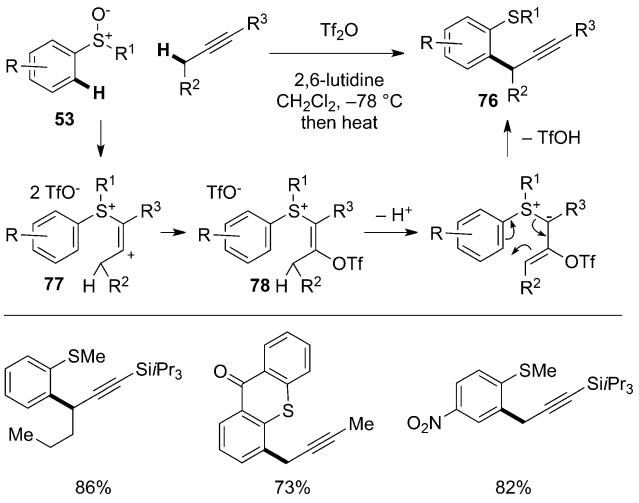
Scheme 29. Procter's sulfoxide-directed C–H coupling of arenes with propargyl silanes. [a] In a one-pot process from the bis(sulfinyl) arene.



Scheme 30. Proposed mechanism of the sulfoxide-directed C–H allylation, propargylation, and alkylation reactions.

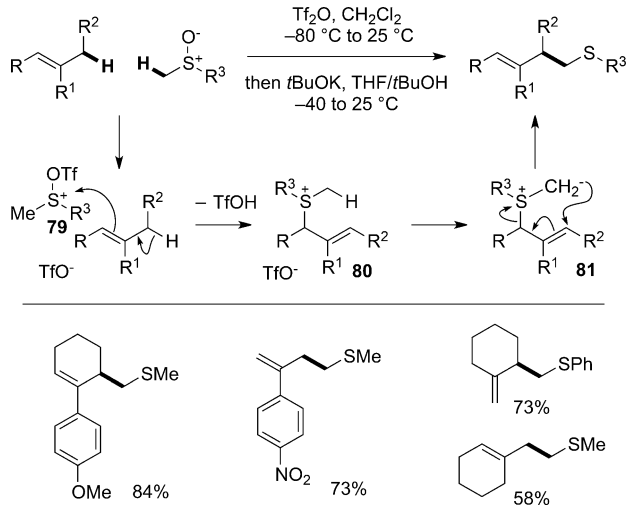
when allyl and propargyl silanes are coupled with arenes, double allylic inversion is observed, first upon addition to the sulfonium-derived sulfoxide, then upon delivery to the arene. Furthermore, Maulide and co-workers studied the reaction of ketones and activated sulfoxides computationally, and in this case, the transition state during C–C bond formation is best described as the intramolecular delivery of a nucleophile. Thus the sulfoxide moiety has a dual directing role: In capturing the nucleophilic coupling partner, it ensures complete regioselectivity as the C–C bond-forming event can only occur at the *ortho* position, and because of its reduction to the sulfide, overfunctionalization is impossible.

Recently, Procter and co-workers showed that the sulfoxide group can direct C–H/C–H couplings of alkynes and arenes **53**, and deliver propargylated arenes **76** with complete site selectivity for the *ortho* position (Scheme 31).[49] Surprisingly, even an alkyne is a competent nucleophile in this sulfoxide-directed process. After nucleophilic attack at the sulfur atom of the activated sulfoxide, the resultant vinyl cation **77** is subsequently trapped by triflate to form observable intermediate **78**. Deprotonation of **78** followed by [3,3]-sigmatropic rearrangement and elimination of triflic acid yields the coupled product **76**.

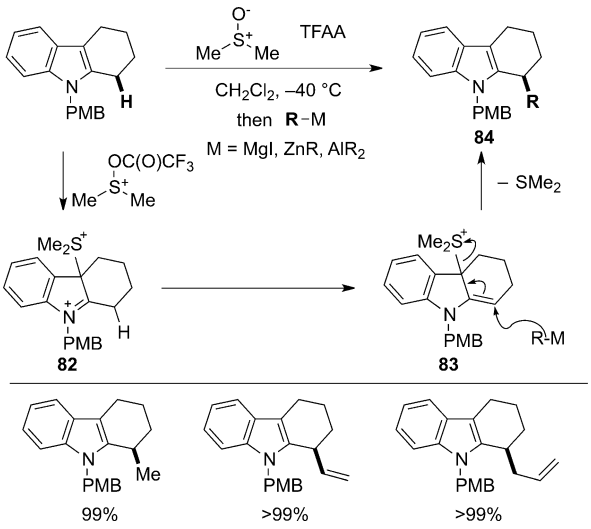


Scheme 31. Procter's sulfoxide-directed C–H/C–H coupling of arenes and alkynes.

In a different approach to sulfoxide-directed C–H coupling reactions, Xu, Li, and Hu recently reported the coupling of two sp^3-hybridized carbon atoms in a C–H/C–H allylic alkylation (Scheme 32).[50] The reaction is thought to proceed through an ene-like addition of the alkene to the activated sulfoxide **79**. The allyl sulfonium intermediate **80** is deprotonated, and the resulting ylide **81** undergoes a [2,3]-sigmatropic rearrangement to accomplish C–C bond formation.



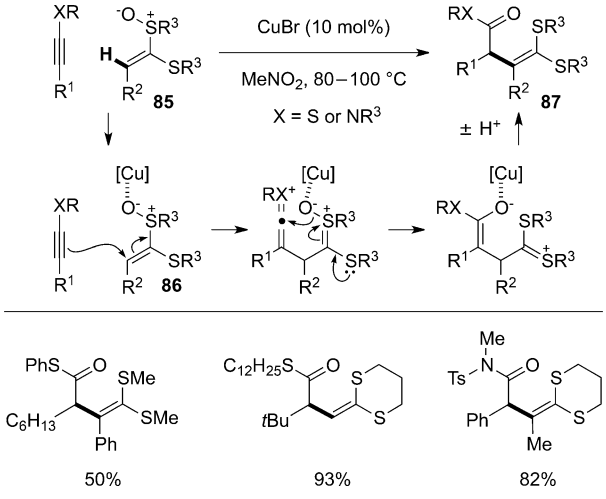
Scheme 32. Xu and Li's sulfoxide-mediated C–H/C–H allylic alkylation.



Scheme 33. Higuchi and Kawasaki's traceless-sulfoxide-directed C2α functionalization of indole derivatives.

Higuchi and Kawasaki reported an interesting C2α–H functionalization of indoles directed by DMSO (Scheme 33).[51] Once DMSO has been activated with TFAA, it reacts through the cationic sulfur center with the 3-position of the indole to form **82**. Tautomerization allows nucleophiles to attack in an S_N2' fashion at the C2α position of **83**. Various alkyl metal reagents as well as heteroatom-based nucleophiles were efficient coupling partners. As the sulfur moiety is not retained in the product **84**, the sulfoxide acts as a traceless directing group, which constitutes an ingenious approach to the activation of an unreactive C–H bond using a sulfoxide.

Matsubara, Yorimitsu, and Oshima showed that ketene dithioacetal monoxides **85** can also be coupled with alkynyl sulfides or ynamides under copper catalysis (Scheme 34).[52]



Scheme 34. Matsubara, Yorimitsu, and Oshima's sulfoxide-directed copper-catalyzed coupling of ketene dithioacetal monoxides with alkynyl sulfides and ynamides.

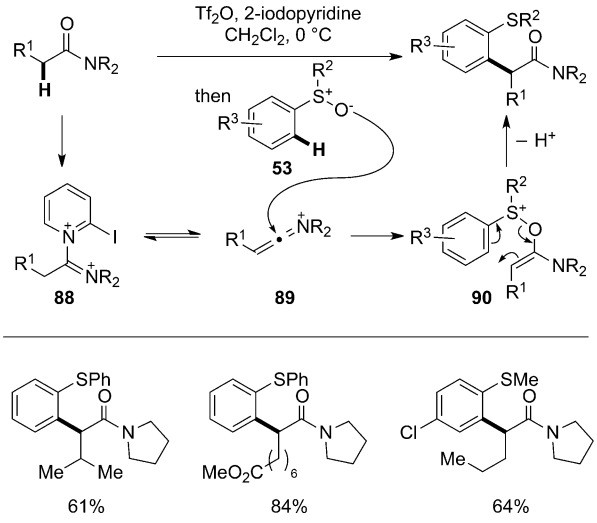
In this case, the copper catalyst activates the sulfoxide for a Pummerer-type reaction whereby the electron-rich alkyne reacts with the vinyl position of the activated sulfoxide **86**. Subsequent oxygen atom transfer and tautomerization result in γ,γ-disulfanyl-β,γ-unsaturated amides or thioesters **87**. This approach is different from the reactions described above in that a Lewis acid catalyst is used to activate the S–O bond prior to C–C bond formation. The mechanism was investigated computationally, and the results indicated that a stepwise mechanism was operational rather than a Diels–Alder cycloaddition type mechanism. The reaction is significant as it is the first metal-catalyzed Pummerer reaction where the sulfoxide is directly activated by the metal.

5.2. Reactions of Sulfoxides with Electrophilic Coupling Partners

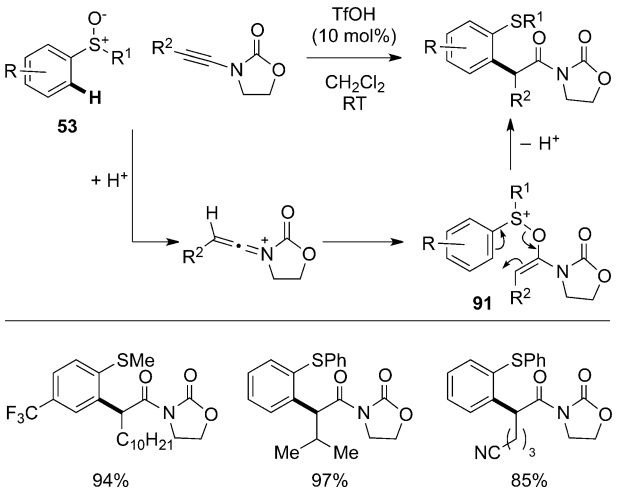
The preceding Section described how the electrophilicity of activated sulfoxides can be utilized to direct C–H bond functionalization. In this Section, the nucleophilicity of sulfoxides has been exploited, whereby sulfoxides react directly with electrophilic coupling partners to form sulfoxonium salts that subsequently enable C–H bond functionalization.

Maulide and co-workers showed that aryl sulfoxides **53** can undergo *ortho* C–H alkylation upon treatment with activated amides (Scheme 35).[53] The amides were activated with triflic anhydride in the presence of 2-iodopyridine and formed iminium dications **88** via iminium triflates. Either iminium dication **88** or keteniminium triflate **89** reacts with the nucleophilic sulfoxide oxygen atom to form sulfonium salt **90**, which can undergo a [3,3]-sigmatropic rearrangement. This C–H/C–H coupling reaction has a broad scope and even allows for the coupling of hindered amides and, impressively, the selective α-arylation of amides in the presence of esters and ketones.

In a mechanistically related reaction, Maulide and coworkers reported the *ortho* alkylation of aryl sulfoxides **53**



Scheme 35. Maulide's use of activated amides in the sulfoxide-directed *ortho* alkylation of arenes.



Scheme 36. Maulide's use of ynamides in the sulfoxide-directed *ortho* alkylation of arenes.

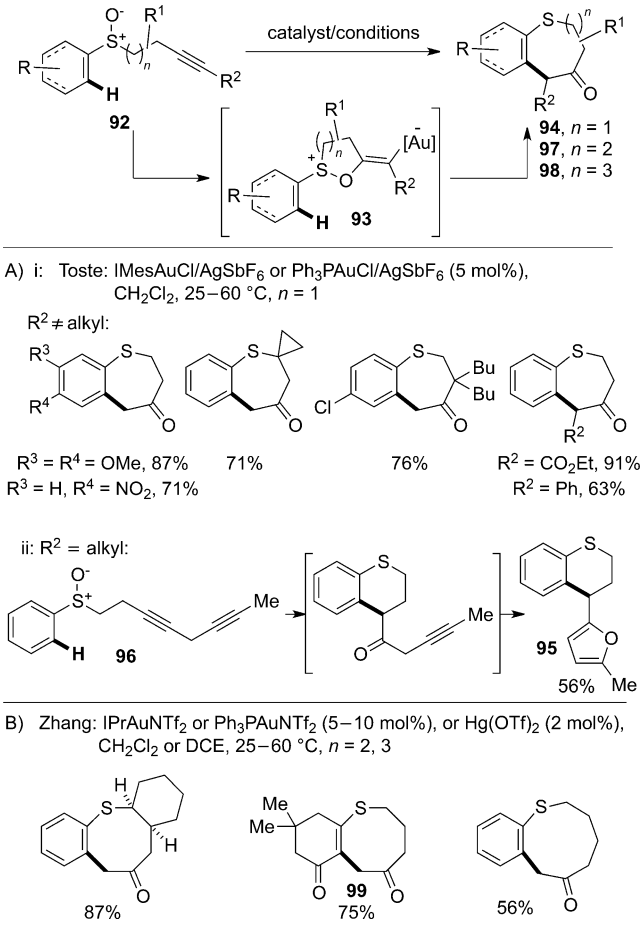
using ynamides mediated by a Brønsted acid catalyst to form α-arylated acyl oxazolidinones (Scheme 36).[54] The ynamide becomes susceptible to nucleophilic attack by the sulfoxide after protonation with triflic acid, and the resultant intermediate **91** then undergoes a [3,3]-sigmatropic rearrangement. Remarkably, the presence of enolizable functional groups was well tolerated.

6. Gold-Catalyzed Sulfoxide-Directed C–H Alkylation

Gold catalysis has become a powerful method for activating unsaturated C–C bonds for a variety of transformations.[55] Utilizing the oxygen nucleophilicity, gold can catalyze sulfoxide additions onto unsaturated C–C bonds under very mild conditions. The oxy-aurated intermediates undergo rearrangements to form new C–C bonds at the expense of C–H bonds, resulting in overall alkyne oxyarylation. Initial reports included intramolecular variants of the reaction to form sulfur-containing heterocycles, but recent advances have shown that the sulfoxide can efficiently direct intermolecular C–H coupling reactions of arenes and alkynes.

The Toste group first reported the use of gold in sulfoxide-directed C–H alkylation (Scheme 37 A).[56] Aryl sulfoxides linked to terminal, ester-, or aryl-substituted alkynyl moieties (**92**) via ethylene units were treated with a Au^I catalyst to effect a 5-*exo*-dig oxy-auration to form **93**, which, after further reaction, resulted in an oxy-arylation of the alkyne and formed tetrahydrobenzothiepines **94** (Scheme 37 A-i; see also Scheme 39 for a discussion of the mechanism). In contrast, when alkyl-substituted alkynes are used (R^2 = alkyl), the cyclization proceeds with different regioselectivity, and oxy-auration occurs in a 6-*endo*-dig fashion, giving thiochromans **95** (Scheme 37 A-ii). This regiodivergence was used in an interesting furan synthesis from 1,4-diyne **96**.

At around the same time, Zhang and Li reported a similar sulfoxide-directed C–H alkylation for the synthesis of tetrahydrobenzothiepines **94**, and later followed this up by

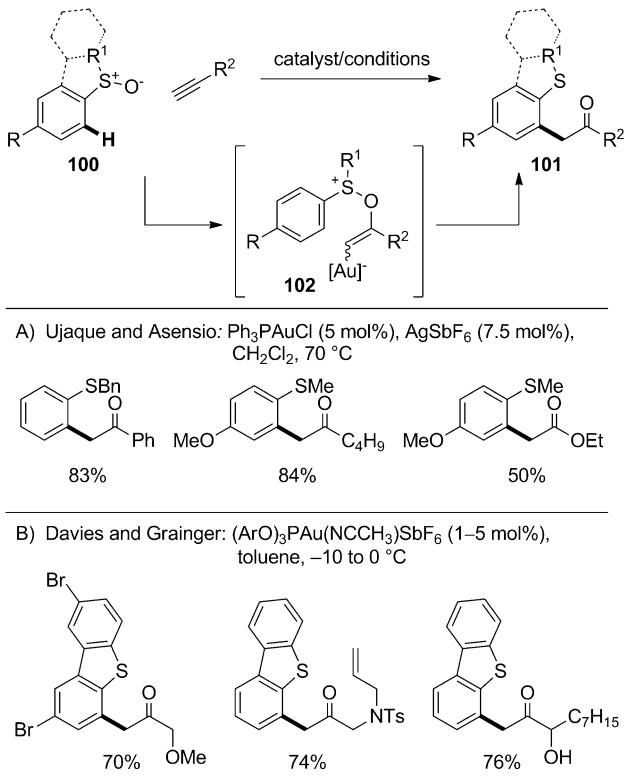


Scheme 37. Toste's (A) and Zhang's (B) sulfoxide-directed syntheses of sulfur heterocycles from homologous propargyl sulfoxides. IMes = 1,3-dimesitylimidazol-2-ylidene, IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene.

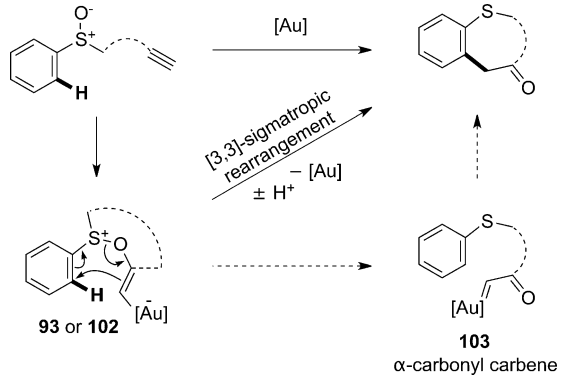
extending the scope to the formation of eight-membered tetrahydrobenzothiocines **97** and remarkably nine-membered hexahydrobenzothionines **98** (Scheme 37B).[57] Compounds **97** and **98** are formed by 6-*exo*-dig and 7-*exo*-dig oxy-auration reactions, respectively. Furthermore, non-aromatic sulfoxides served as efficient precursors to tetrahydrobenzothiocines **99**. A similar catalyst, $Hg(OTf)_2$ (2 mol%), was also effective in this transformation.

Ujaque, Asensio, and co-workers were the first to report an intermolecular version of this reaction; terminal alkynes and aryl sulfoxides **100** were coupled under gold catalysis to form α-arylated ketones and esters **101** via intermediate **102** (Scheme 38A).[58] Furthermore, Davies, Grainger, and Barrett expanded the scope to encompass dibenzothiophene *S*-oxides and a wide variety of alkynes to give functionalized dibenzothiophenes (Scheme 38B).[59,60]

The mechanism of the oxy-arylation of alkynes with sulfoxides is intriguing, and the reaction was originally proposed to occur through α-carbonyl gold carbenes (**103**; Scheme 39).[56] Initial oxy-auration of the alkyne yields a sulfide moiety and an α-carbonyl gold carbene. Intermediate **103** was proposed to undergo a Friedel–Crafts alkylation of the aryl sulfide. However, significant theoretical and



Scheme 38. Ujaque and Asensio's sulfoxide-directed coupling of arenes and alkynes (A), and Davies and Grainger's expansion to dibenzothiophene *S*-oxides (B). Ar = 2,4-di-*tert*-butylphenyl.



Scheme 39. Proposed mechanism for the sulfoxide-directed intra- or intermolecular gold-catalyzed *ortho* C–H alkylation of arenes using alkynes.

experimental evidence points towards a different mechanism.[57,58,60] The most compelling evidence came from the intermolecular reactions: Single regioisomers were observed in all cases even when an electronic bias should promote the formation of a different regioisomer during the Friedel–Crafts alkylation step, the gold carbene could not be trapped by other external nucleophiles, and cross-over experiments with other sulfides failed to give the crossed product. Furthermore, while studying the intramolecular reaction, Zhang and co-workers independently synthesized a prerequisite α-carbonyl gold carbene and found that it did not form the expected tetrahydrobenzothiepine. An alternative mech-

anism has been suggested, namely that a [3,3]-sigmatropic rearrangement occurs after the initial oxy-auration step.[43a,61] This is consistent with the exclusive *ortho* regioselectivity observed and was backed up by calculations. Moreover, the intermediate (**93**/**102**) that undergoes the [3,3]-sigmatropic rearrangement bears a striking resemblance to a common intermediate in many of the metal-free sulfoxide-directed C–H couplings described in the preceding Section.

7. Conclusion and Outlook

Sulfoxides have been shown to be efficient directors for the construction of new C–C bonds at the expense of C–H bonds, enabling the straightforward elaboration of simple molecules towards more complex systems. The directing effect can be achieved by coordination of an internal sulfoxide to a metal, the action of an external sulfoxide ligand, or through the capture of nucleophiles and electrophiles to give sulfonium salts.

Currently, sulfoxide-directed intermolecular coupling reactions through transition-metal-mediated C–H activation are limited to the activation of aryl C–H bonds and to the introduction of alkenyl substituents. The introduction of other carbon-based coupling partners and the activation of $C(sp^3)$–H bonds are areas in which significant progress is foreseen. The sulfoxide-derived sulfonium-based strategies are capable of introducing a variety of carbon substituents typically under metal-free conditions, but catalytic methods for S–O bond activation would constitute a significant advance. Although Brønsted acid, copper-, and gold-catalyzed processes have emerged, they are yet to be generalized. Furthermore, early developments in using sulfoxide-derived sulfonium salts as traceless directors are promising, but limited to a specific reaction, and we therefore expect developments in this regard. Finally, given that enantiomerically enriched sulfoxides are readily available,[62] it is surprising that so few of the catalytic or metal-free C–H bond functionalization reactions described above have utilized them, and we therefore anticipate their more widespread use in the near future for asymmetric C–H coupling.

Although there are still advances to be made in sulfoxide-mediated C–H functionalization, we have seen that this classical directing group has been taught some new tricks, contributing to the ever growing arsenal at the disposal of the synthetic chemist for the construction of C–C bonds at the expense of C–H bonds.

Acknowledgements

We thank the EPSRC (Established Career Fellowship to D.J.P.), The Leverhulme Trust (Fellowship to D.J.P.), and the School of Chemistry, University of Manchester.

How to cite: *Angew. Chem. Int. Ed.* **2016**, *55*, 9842–9860
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Received: February 12, 2016
Published online: July 13, 2016

