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Nucleophilic *Ortho* Allylation of Aryl and Heteroaryl Sulfoxides

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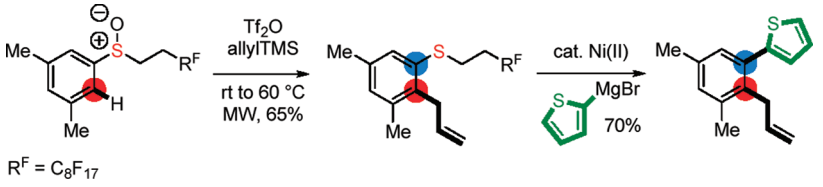
ABSTRACT



Aryl and heteroaryl sulfoxides undergo *ortho* allylation upon treatment with Tf_2O and allylsilanes. The method complements the use of sulfoxides to direct *ortho*-metalation and reaction with electrophiles as it allows allylic carbon nucleophiles to be added *ortho* to the directing group in a metal-free process. The versatile sulfide adducts can be selectively manipulated using various methods including Kumada–Corriu cross-coupling of the organosulfanyl group.

The selective formation of carbon–carbon bonds to aromatic and heteroaromatic rings is one of the most important synthetic objectives as an aromatic centerpiece forms the structural basis of many active pharmaceuticals, agrochemicals, and functional materials. New methods for the metalation of aromatics and heteroaromatics using stoichiometric metal reagents[1] and transition-metal-catalyzed activation of aromatic derivatives[2] have led to a step change in the way aromatic and heteroaromatic substrates are elaborated. These advancements have culminated in new metal-catalyzed methods for the formation of carbon–carbon bonds to unfunctionalized sites on aromatics and heteroaromatics where only a C–H is present.[3] The use of activating substituents that facilitate nucleophilic addition to aromatic systems is an underexploited approach. In recent years, the Pummerer reaction[4] of sulfoxides has been adapted to allow activation of aromatic rings. In particular, seminal reports from Kita,[5] Feldman,[6] and Padwa[7] have described the nucleophilic alkylation of some electron-rich heteroaryl sulfoxides and sulfilimides using Pummerer processes.

Inspired by the work of Kita,[5a,b] we here report the first general study of the nucleophilic *ortho* allylation of aryl and heteroaryl sulfoxides **1** (Scheme 1).[8] The method complements the use of sulfoxides to direct *ortho*-metalation, and quenching with electrophiles, as it allows allylic carbon *nucleophiles* to be added *ortho* to the directing group in a metal-free process with rearomatization. Selective manipulation of the C–S bond in the versatile

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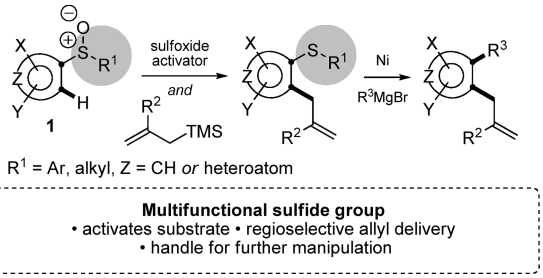
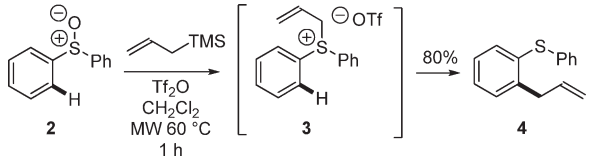
allylated sulfide adducts using Ni-catalyzed cross-coupling of the organosulfanyl group is also described.

Scheme 1. Nucleophilic *Ortho* Allylation of Aryl Sulfoxides



In the interrupted Pummerer reaction,[4] activated sulfoxides react with nucleophiles at sulfur, prior to more usual thionium ion formation. Drawing on the observations of Oshima and Yorimitsu,[9] we proposed that aryl sulfoxides would react with allylsilane nucleophiles to give sulfonium salts that would undergo *in situ* thio-Claisen rearrangement[10] to give products of regioselective aromatic substitution via an intermediate thionium ion. Optimization studies using diphenylsulfoxide illustrated the feasibility of the approach: treatment of diphenylsulfoxide **2** with Tf_2O[11] and allylTMS, under microwave heating at 60 °C, gave **4** in 80% yield after 1 h. No other regioisomeric products were obtained. Sulfonium intermediate **3** could be isolated from the reaction and characterized by ^1H NMR,[12] suggesting that an alternative mechanism involving direct allylation of the ring is not occurring (Scheme 2). Additional support for an interrupted Pummerer mechanism is presented in Scheme 4 (*vide infra*).

Scheme 2. Nucleophilic *Ortho* Allylation of Diphenylsulfoxide



To assess the generality of the process we have studied the nucleophilic *ortho* allylation of several arylsulfides, activated as their sulfoxides by *m*CPBA oxidation. Aryl sulfides were readily prepared by Cu[13] or Pd catalyzed-coupling[14] of thiols with aryl halides and heteroaryl sulfoxides were prepared by metalation and quenching with thiosulfonates or disulfides (followed by oxidation of the sulfide).

The reaction is general: neutral, electron-rich, and electron-deficient benzene rings are allylated under our simple reaction conditions using allylsilanes (Figure 1). Diphenylsulfoxide underwent nucleophilic *ortho* allylation using functionalized allylsilanes **5** and **6** to give **7a** and **7b**, respectively, in good yield. Unsymmetrical diarylsulfoxides bearing an electron-rich ring gave alkylation products **7c**–**g** in good yields and with high selectivity for the more electron-rich ring. Pleasingly, unsymmetrical diarylsulfoxides with considerable steric hindrance at sulfur underwent efficient allylation to give **7e** and **7f**. Aryl alkyl sulfoxides can also be used in the nucleophilic *ortho* allylation: aryl perfluoroalkyl sulfoxides ($R^F = C_8F_{17}$)[15] undergo efficient allylation to give **7h**–**m** and **7p** in good to excellent yields (Figure 1). The electronic properties of the perfluoroalkyl group facilitate aromatic substitution as *n*-decyl phenyl sulfoxide underwent allylation in 19% yield. The allylation is also compatible with substrates bearing halogen substituents although yields are lower (*vide infra*). Finally, naphthyl sulfoxides underwent efficient allylation to give **7h** and **7p** in excellent yields. The perfluoroalkyl group also allows fluorous solid phase extraction (FSPE)[16] to be used as a convenient alternative method for purification during the synthesis of sulfoxide substrates and the manipulation of sulfide products.

Although we have focused on additions to benzenes, the *ortho* nucleophilic allylation of medicinally relevant heterocycles is also possible (Figure 2). For substrates activated by a phenylsulfinyl group, Kita's conditions employing TFAA[17a] proved optimal. Interestingly, we found these conditions to be compatible with an indole bearing a free N–H, and **8e** was obtained in moderate yield.[17b] For a 2-thienyl perfluoroalkyl sulfoxide, the use our Tf_2O conditions with microwave heating gave excellent results, and **8c** and **8d** were obtained in high yield.

The presence of an electron-withdrawing bromine on the benzene ring leads to the formation of unallylated sulfide byproducts (Figure 1, preparation of **7n** and **7o**). This is also illustrated by comparing the efficient allylation of

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(11) Nf_2O is also an efficient activator in the allylation reactions.

(12) See Supporting Information for an assigned ^1H NMR of **3**.

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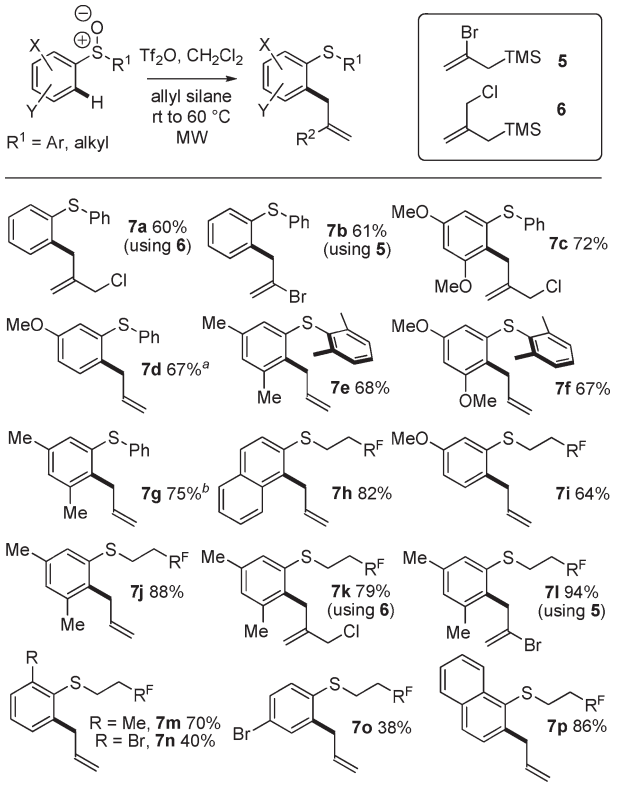
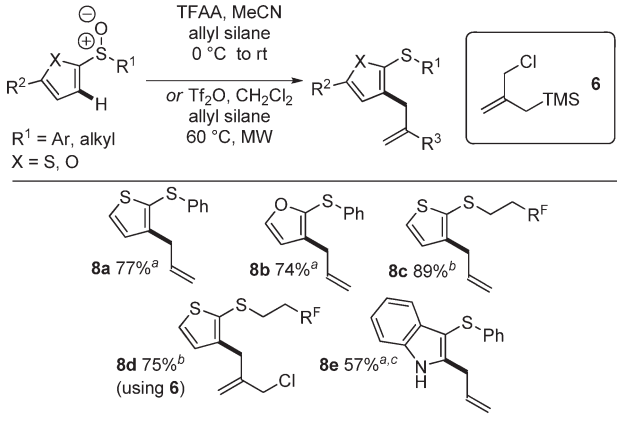
(17) (a) Kita observed the allylation of thiophene and furan sulfoxides using allyltributyltin. See ref 5b. (b) Kita has reported the allylation of the benzene ring in *N*-Ts 5-sulfoxy indoles using similar conditions. Interestingly, in Kita's work the indole bearing a free N–H did not undergo productive allylation. See ref 5a.



[a] major regioisomer, 5:1 mixture by ^{1}H NMR (allylation of electron-rich ring). [b] major regioisomer, 10:1 mixture by ^{1}H NMR (allylation of both rings).

Figure 1. Nucleophilic *ortho* allylation of aryl sulfoxides.

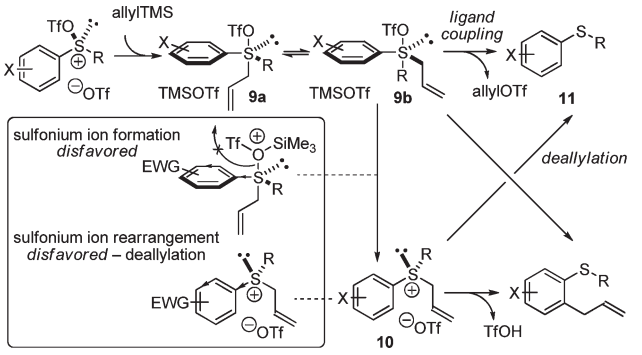


[a] TFAA conditions. [b] Tf_2O conditions in microwave. [c] CH_2Cl_2 as solvent.

Figure 2. Nucleophilic *ortho* allylation of heteroaryl sulfoxides.

an *ortho*-methyl sulfoxide (**7m** was obtained in 70% yield, Figure 1) with the less successful allylation of the corresponding *ortho*-trifluoromethyl sulfoxide (the sulfide was the major product and only a trace of allylated product was obtained). This can be explained by considering possible intermediates, sulfuranes **9**[18] and sulfonium salts **10**. Nucleophilic addition of allyl silanes to the trifluoromethanesulfonylated sulfoxide may give an equilibrium mixture of sulfuranes **9a** and **9b**. Allyl transfer from S to C in sulfurane **9a** is impeded by unfavorable orbital overlap. Although allyl transfer may be possible from sulfurane **9b**, ligand coupling (reductive elimination)[18] competes resulting in the formation of a mixture of allylated products and byproducts **11**. Electron-withdrawing substituents on the benzene ring may disfavor formation of sulfonium ion **10** and subsequent allyl transfer (Scheme 3). Alternatively,

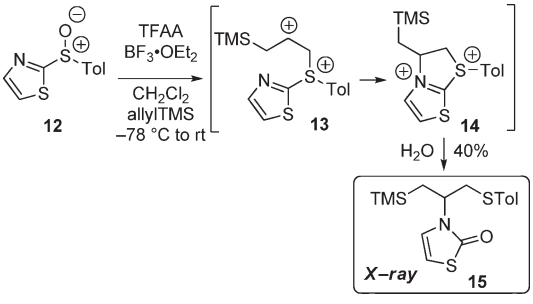
Scheme 3. Proposed Mechanism for the Nucleophilic *Ortho* Allylation of Aryl Sulfoxides



electron-withdrawing substituents on the benzene ring may alter the reactivity of sulfonium ion **10**, disfavoring rearrangement and promoting deallylation. Both hypotheses are supported by the observation that efficient allylation of sulfur is observed in the reactions of all substrates (^{1}H NMR), even those that ultimately result in mixtures of allylation products and sulfide byproducts **11**.

To gain additional evidence for the interrupted Pummerer mechanism, we prepared thiazole sulfoxide **12** containing an *ortho* heteroatom substituent capable of intercepting the carbocation intermediate resulting from allylsilane addition to sulfur. Pleasingly, exposure of thiazole sulfoxide **12** to our conditions for *ortho* allylation gave thiazolone **15** after interception of carbocation **13** and hydrolysis of salt **14** (Scheme 4).

Scheme 4. Interception of an Intermediate in the Interrupted Pummerer Reaction



(18) For a review of hypervalent organosulfur compounds, see: Furukawa, N.; Sato, S. *Top. Curr. Chem.* **1999**, *205*, 89.

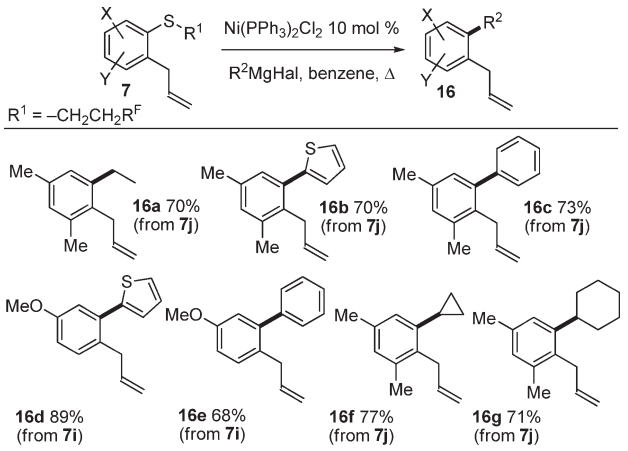


Figure 3. Coupling of *ortho* allyl arylsulfides with Grignard reagents under Ni catalysis.

The organylsulfanyl group in the products of nucleophilic *ortho* allylation provides further opportunities for bond formation and decoration of the aryl or heteroaryl template. In particular, aryl and heteroaryl sulfides are useful partners in a range of transition-metal-catalyzed cross-couplings.[19] For example, couplings with Grignard reagents,[20] organozinc reagents,[21a] arylboronic acids,[21b] and organotin reagents[21c,d] have been reported. Exploiting the conditions of Wenkert,[20a,b] *ortho* allyl aryl sulfides **7** have been been found to undergo efficient Kumada–Corriu coupling with a range of Grignard reagents under Ni catalysis to give adducts **16** (Figure 3). FSPE can be used to separate nonfluorous coupling products from fluorous disulfide, which can be recovered for reuse. Phenylsulfanyl adducts could also be used in Ni-catalyzed coupling reactions with Grignard reagents, but lower yields were observed presumably due to insertion of Ni into the less hindered ArS bond.[22]

In summary, aryl and heteroaryl sulfoxides undergo nucleophilic *ortho* allylation upon treatment with allyl silanes and Tf_2O under microwave heating. The straightforward method complements the use of sulfoxides to direct *ortho*-metalation, and quenching with electrophiles, as it allows allylic carbon nucleophiles to be added *ortho* to the directing group in a metal-free process with rearomatization. The allyl substituent introduced in the nucleophilic aromatic substitution is a versatile handle for further manipulation. The sulfide substituents in the products of allylation are precursors to arylmetals in Ni-catalyzed cross-couplings with Grignard reagents.

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Supporting Information Available. Experimental procedures, characterization data, and ^1H and ^{13}C spectra and X-ray crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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