Title: Electrophilic Sulfur Reagent Design Enables Catalytic *syn*-Carbosulfenylation of Unactivated Alkenes

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Abstract: A multi-component approach to structurally complex organosulfur products is described via the nickel-catalyzed 1,2-carbosulfenylation of unactivated alkenes with organoboron nucleophiles and tailored organosulfur electrophiles. Key to the development of this transformation is the identification of a modular *N*-alkyl-*N*-(arylsulfenyl)arenesulfonamide family of sulfur electrophiles. Tuning the electronic and steric properties of the leaving group in these reagents controls pathway selectivity, favoring three-component coupling and suppressing side reactions, as examined via computational studies. The unique *syn*-stereoselectivity differs from traditional electrophilic sulfenyl transfer processes involving a thiiranium ion intermediate and arises from the directed arylnickel(I) migratory insertion mechanism, as elucidated through reaction kinetics and control experiments. Reactivity and regioselectivity are facilitated by a collection of monodentate, weakly coordinating native directing groups, including sulfonamides, alcohols, amines, amides, and azaheterocycles.

Main Text: Organosulfur compounds have diverse functions and find applications as pharmaceuticals[1-2] and functional materials.[3] Organosulfides, in particular, can also be readily converted into other functional groups, making them versatile building blocks in synthesis.[4] While reliable approaches for catalytic two-component C−S bond formation[5-6] via cross-coupling reactions[7] and C−H functionalization[8] have emerged during the past two decades, multicomponent C–S bond-forming reactions remain less explored.[9-10] In this context, reactions that merge an alkene, a sulfur-based reaction partner, and a carbogenic group combine C–C skeletal formation and C–S installation into a single operation, representing an attractive means of generating complex, stereochemically dense organosulfur products from simple chemical inputs. Pioneered by Trost[11-12], Denmark[13] and others[14], the most well-established method for 1,2-carbosulfenylation of alkenes involves formation of a thiiranium ion intermediate[15] through electrophilic sulfenyl transfer and subsequent nucleophilic ring opening, with *anti*-stereoselectivity arising from the S_N2 nature of the ring-opening step and regioselectivity dictated by alkene substitution pattern. While enabling in its own right, existing methodology for three-component *anti*-1,2-carbosulfenylation of alkenes is limited to a small collection of carbon-nucleophiles, namely cyanide[11], acetylides[12], and organozinc reagents[14], and in the latter case, the transformation is only compatible with styrene substrates. Complementing this existing methodology with a *syn*-stereoselective counterpart that proceeds via a distinct mechanistic pathway would be highly enabling. By bypassing thiiranium ion formation, we envisioned that it would not only be possible to achieve the opposite stereochemical outcome but also to expand the alkene scope to include nucleophilic functional groups that are prone to intramolecular cyclization in established thiiranium chemistry.[16]

Recently, nickel-catalyzed redox-neutral 1,2-functionalization of unactivated alkenes[17-18] has emerged as a powerful method for joining together a nucleophile, an electrophile, and an alkene in a selective fashion.[19] Depending on the identity of the coupling partners, two closely related yet distinct mechanisms can operate. A Ni(0)/Ni(II) cycle occurs by an oxidative-addition-first pathway, where the electrophile is incorporated distal to the directing group.[20-23] Meanwhile, a Ni(I)/Ni(III) cycle involving a transmetalation-first mechanism typically manifests in reversed regioselectivity.[24-28] In both cases, *syn*-selectivity is dictated by inner-sphere migratory insertion. With these considerations in mind and informed

by our previous experience in developing nickel-catalyzed 1,2-difunctionalization of alkenes directed by native functional groups[22], we reasoned that it would be possible to develop a *syn*-selective 1,2-carbosulfenyation by employing sulfur-based electrophiles within this mode of catalysis. While attractive in principle, the envisioned three-component coupling would require surmounting several challenges, including premature sulfenyl transfer to the alkene or carbon nucleophile, competitive β-hydride elimination from the alkylnickel intermediate, and the potential inhibition from the sulfur-containing products or leaving group generated upon sulfenyl transfer.

Herein we report a nickel-catalyzed *syn*-selective 1,2-carbosulfenylation reaction[29-31] of simple unactivated alkenes[32]. Critical to the success of this reaction is the identification of *N*-sulfenyl-*N*-alkyl sulfonamides as N–S electrophiles. Taking inspiration from various electrophiles in the literature that contain nitrogen-based leaving groups for fluorination[33-34], trifluoromethylthiolation[35], cyanation[36], and acylation[37], this design takes advantages of the sterically and electronically tunable nature of the sulfonamide leaving group (N_{LG}), which can be readily modified along each of its two vectors to control pathway selectivity and thereby maximize the yield of desired three-component coupling.

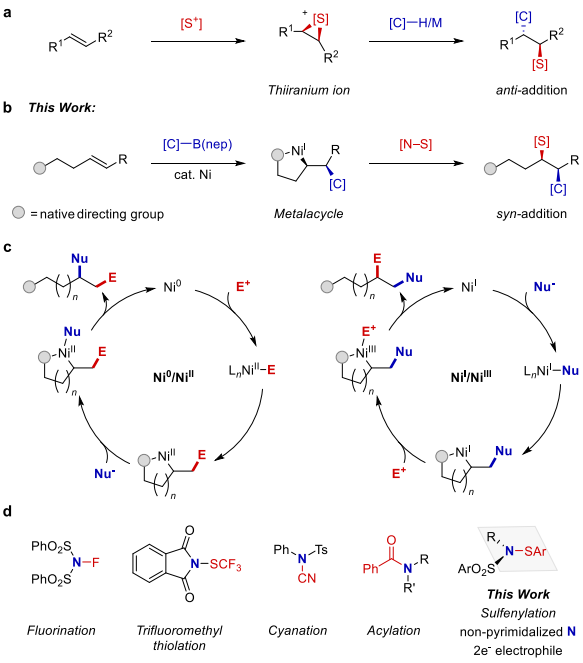

Fig. 1. Background and Synopsis of Current Work. a, Thiiranium-ion-mediated *anti*-selective 1,2-carbosulfenylation. **b,** This work: *syn*-selective 1,2-carbosulfenylation of unactivated alkenes with native directing groups. **c**, Nickel-catalyzed redox-neutral alkene 1,2-difunctionalization. **d**, Survey of carbon- and heteroatom electrophiles containing nitrogen leaving groups.

Results and Discussion:

Reaction discovery. To begin the investigation, we focused on the model reaction of alkenyl sulfonamide **1**[38] with *p*-tolylboronic acid neopentyl glycol ester (**2a**) and various N−S electrophiles. In effort to find a suitable sulfenyl electrophile with the proper reactivity profile—appropriately tempered to not transfer the sulfenyl group to the alkene or arylnickel(I) intermediate yet sufficiently reactive to engage the alkylnickel(I) intermediate with a rate faster than that of β-hydride elimination—we first attempted established sulfenyl electrophiles from the literature (**S1**−**S7**). Modest success was found with *N*-sulfenyl lactams (17–51% yield, **S5**−**S7**)[9]; however, desired three-component coupling was accompanied by formation of nearly equimolar quantities of oxidative Heck byproducts, indicating similar rates of intramolecular β-hydride elimination and intermolecular N–S oxidative addition. Extensive screening of the reaction conditions did not improve yields or product selectivity with leaving groups $\mathbf{N}_{LG}\mathbf{5}$−$\mathbf{N}_{LG}\mathbf{7}$. In contrast, with an *N*-Me benzamide as leaving group, better yields (53–64%) and product selectivities (7–11% combined byproducts) were observed (**S8**−**S10**). We then examined **S11**−**S23** with *N*-substituted arylsulfonamides as leaving groups, taking advantage of the easily tunable nature of this scaffold, which allows numerous modifications to be quickly assayed. Although electron-withdrawing groups (as in **S11**−**S13**)[39] proved deleterious for the reaction, improved yields (69–94%) were observed with **S14**−**S17**. When a *para*-methoxy group was used (**S17**), the desired product was obtained in 94% yield and with <5% oxidative Heck byproducts. Steric modification to either the arylsulfonyl or *N*-alkyl vectors revealed no further improvement (**S18**−**S22**). Interestingly, when the *N*-alkyl group was changed to a *N*-phenyl group, no desired product was observed (**S23**).[40]

We performed computational parameterization of the tested reagents to understand the origins of the high product yield with **S17**. As N−S reagents were expected to be involved mainly during the oxidative addition step, LUMO energy and bond dissociation energy (BDE)[41] were computed and plotted against percentage yields. The former value relates to kinetics and thermodynamics of organonickel coordination to the N−S reagent, while the latter reflects the subsequent oxidative addition process. By visualizing the data using a 3D-plot, we were pleased to find the maximum yield is obtained when both parameters are within certain threshold (50 to 52 kcal/mol for BDE and −0.6 to −0.1 eV for LUMO energy). Within this data set, analysis of several poor-performing electrophiles is informative. Reagents **S11**−**S13** possess BDEs near the optimal range but have low LUMO energy (mean of −0.9 eV), reflecting the presence of the electron-withdrawing groups. On the other hand, **S23**, which contains the same leaving group as a previously reported radical fluorinating agent,[40] has a LUMO energy within the typical range of high-yielding variants but features a BDE of 39.6 kcal/mol—as low as the well accepted SOMO-phile **S1** (39.8 kcal/mol)[39]. In this case, single-electron transfer (SET) may take place to generate off-cycle species (i.e., a stable nitrogen centered radical and a sulfur radical). This also agrees with our hypothesis that **S17** functions as a $2e^-$ covalent electrophile. The moderate yields obtained with **S5**−**S10** could reflect the slightly higher than optimal BDE of 52.7 kcal/mol, with the sulfur possessing diminished electrophilicity due to the weaker electron-withdrawing effect of the *N*-alkylamide versus *N*-alkylsulfonamide leaving group. Interestingly, **S4**, which has been applied in Lewis-base-catalyzed sulfenyl transfer reactions involving thiiranium intermediates[13, 16], was too stable to react (BDE = 79.2 kcal/mol).

X-ray crystallographic analysis of representative N–S electrophiles revealed a non-pyramidalized N-atom[42] stemming from delocalization of the lone pair electron from nitrogen to the S=O π^* orbitals (**S17**, **S18**). Meanwhile, in the case of **S23**, a more pyramidalized nitrogen and longer N−S bond indicates diminished delocalization and thus a weaker N−S bond. **S6** on the other hand, features an approximately trigonal planar structure which is responsible for its higher BDE (55.3 kcal/mol) and lower reactivity.

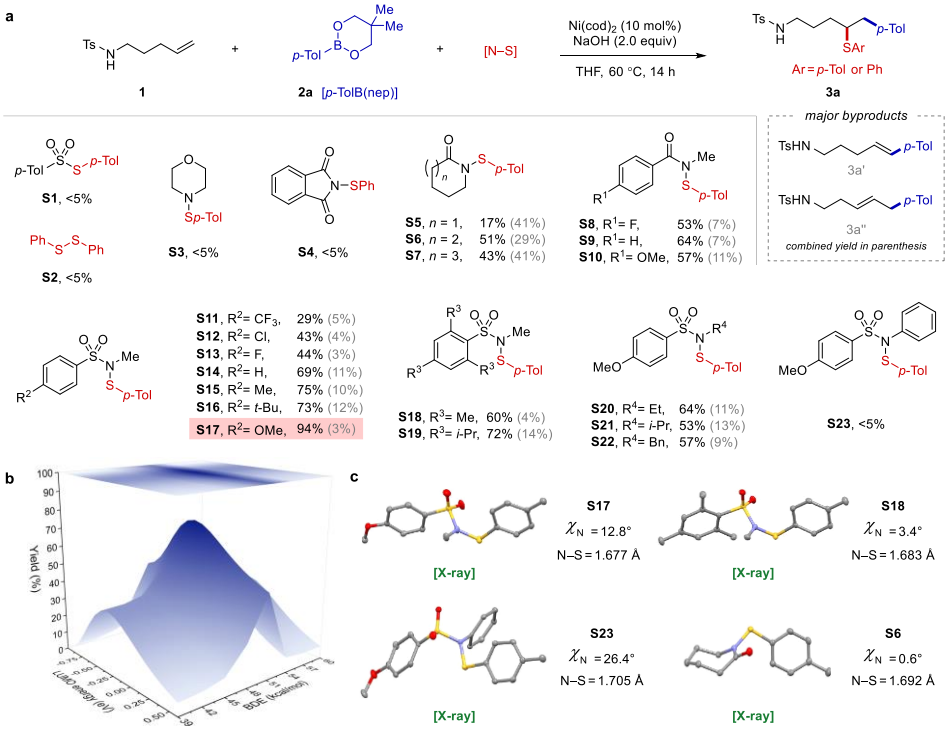

Fig. 2. Discovery of nickel-catalyzed 1,2-carbosulfenylation of unactivated alkenes. a, Optimization of reaction conditions. $Ni(cod)_2$/**1**/**2a**/[N−S]/NaOH = 0.01/0.1/0.2/0.2/0.2 (mmol), Reaction was run in THF (0.05 M) at 60 °C. All percentages represent ^{1}H NMR yields with benzyl 4-fluorobenzoate as internal standard. **b**, Surface of Yield/LUMO energy/BDE plot generated by 3D mathematical fitting. For detailed 2D Yield/LUMO energy and Yield/BDE plots with computed data points, see supporting information. Gas phase LUMO energy calculated at M05-2X/6-311+G(d,p) level of theory. Solution phase BDE calculated at SMD(acetonitrile)//M05-2X/6-311+G(d,p), SMD(acetonitrile)//M05-2X/6-31+G(d) level of theory. **c**, X-ray structures of representative N−S reagents. **S17** (CCDC 2114518), **S18** (CCDC 2110121), **S23** (CCDC 2117151), and **S6** (CCDC 2110122); hydrogen atoms omitted for clarity. Introduction of an electron-withdrawing group on the arylsulfenyl group (*p*-CF_3) with $\mathbf{N_{LG}17}$ led to a more pyramidalized nitrogen (χ_N = 32.17856) and longer N−S bond (1.69376 Å); See supporting information for crystal structure of **S28** (CCDC 2110120).

Substrate scope. Having identified an optimal class of N–S electrophiles, we examined the scope and limitations of the method. Regarding the electrophile scope, arylsulfenyl moieties with electron-neutral or -withdrawing substituents (**3aa**–**3ag**) could be efficiently introduced with the optimal leaving group (**N$_{LG}$17**). On the other hand, the highly electron-donating *p*-methoxy case (**3ab**) benefited from using a less electron-rich leaving group (**N$_{LG}$15**), indicating that it is possible to further fine-tune the leaving group to match the electronic properties of the arylsulfenyl moiety as needed (see SI for comparative data). Sterically bulky arylsulfenyl groups did not significantly inhibit the reaction (**3ah**–**3ak**), and halo-substituted arylsulfenyl coupling partners were tolerated (**3ac**–**3ae**, **3ai**–**3aj**), offering the opportunity for further derivatization by cross-coupling.

Next, we surveyed different organoboron nucleophiles. Arylboron coupling partners substituted at the *para*- or *meta*- positions with electron-donating or -withdrawing groups were generally well tolerated, with the former slightly higher-yielding in general (**3ba**–**3bo**). Potentially inhibitory or reactive groups, such as –NHBoc, –CHO, and –CN, were all compatible (**3bg**–**3bi**, **3bm**–**3bn**). Furthermore, with an *ortho*-methyl substituent, **3bp** was obtained in 56% yield. Bicyclic coupling partners also proved suitable, giving **3bq**–**3bt** in moderate to good yield. Six-membered heteroaryl nucleophiles, including quinoline, pyridine, and purine moiety, could be installed though a substituent at the 2-position was required to attenuate the coordinating ability of the basic N(sp^2) atom (**3bu**–**3bw**). On the other hand, unmasked pyridine and purine as well as electron-rich five-membered heterocycles were incompatible in this reaction. Alkenyl–B(nep) reactants constitute another limitation, as only 20% of the corresponding product was observed in the case of a representative styrenyl coupling partner.

A series of substituted alkenyl sulfonamides were evaluated. Sulfonamides derived from both homoallyl and bishomoallyl amines were tolerated (**4a**–**4m**), with the former giving slightly lower yield. Gratifyingly, benzenesulfonyl groups with different substituents at the *para*-position (**4a**–**4f**) and a methanesulfonyl group (**4g**) all furnished the corresponding products in moderate to good yield. 4-Cyanobenzenesulfonamide (Cs) can serve the dual role of directing group and amine activating group (see

below) and gave **4e** and **4f** in 53% and 85% yield, respectively.[43] Moderate yield and diastereoselectivity were obtained with substrates containing α- or β-branching (**4h**–**4j**). With internal alkenes, *Z*-configured alkenes provided higher yield, as well as greater and opposite diastereoselectivity, compared with the corresponding *E*-isomers (**4k**–**4l'**). A sulfonamide derived from *ortho*-allylaniline furnished **4m** in 59% yield with no chain-walking byproducts detected.

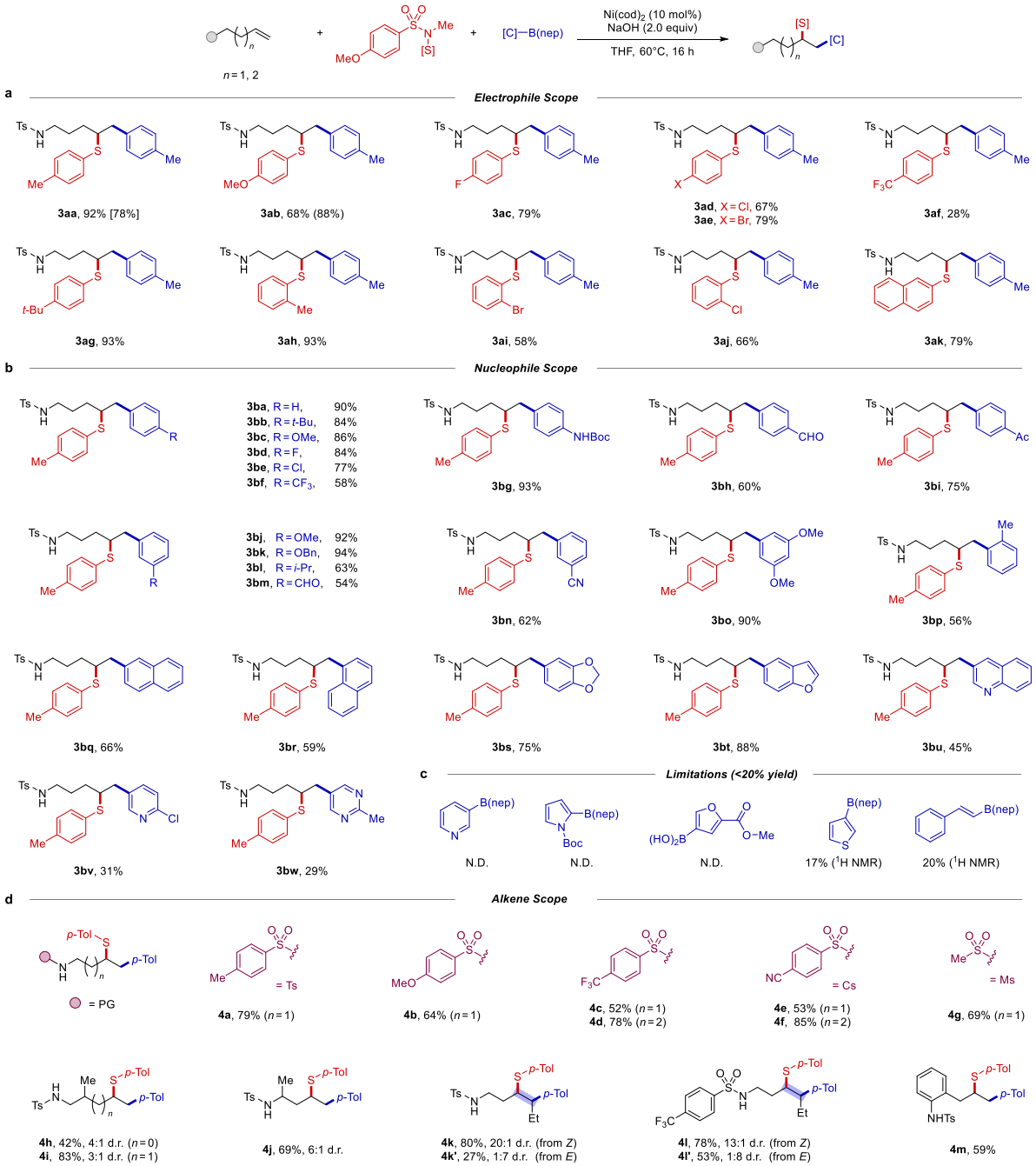

Fig. 3. Electrophile, nucleophile, and alkenyl sulfonamide scope. Reactions performed on 0.1 mmol scale. Percentages represent isolated yields. **a**, Electrophile scope. For **3aa**, the yield in brackets was obtained from an experiment performed on 1.0 mmol scale. For **3ab**, the yield in parentheses was obtained with **S34** (featuring $\mathbf{N_{LG}11}$ as leaving group, see SI for details). **b**, Nucleophile scope. **c**, Limitations. Percentage yields represent ^{1}H NMR yields with benzyl 4-fluorobenzoate as internal standard. N.D.=not detected. **d**, Alkene scope.

We next investigated alkenes containing other synthetically useful native functional groups. This seemingly straightforward extension is complicated by the fact that minor changes to the directing group structure have a significant impact on coordination strength and metallacycle stability. To our delight, after brief optimization of base and solvent (see SI for details), a diverse collection of native directing groups was found to facilitate this transformation. Starting from homoallyl alcohol, **5a** and **5b** were obtained in 64% and 72% yield, respectively.[27] A large-scale experiment on 4 mmol scale furnished **5b** in 59% yield. Substituents at the α-position with respect to the hydroxyl group furnished **5c** and **5d** in 49% and 61% yields, respectively, with negligible diastereoselectivity. Late-stage functionalization of allylestrenol, a progestin medication, furnished the corresponding product in 34% yield with 1.5:1 diastereoselectivity (**5e**). Free alkenyl amines bearing a basic N(sp^3) atom are traditionally challenging substrates owing to their ability to sequester the catalyst off-cycle. Gratifyingly, **5f**–**5j** were obtained in moderate to good yield. With a chiral benzyl amine directing auxiliary, **5h** was obtained in 60% yield and 2:1 diastereoselectivity. In addition, an alkene bearing an amide group proved compatible, giving **5k** in 35% yield. Motivated by our previous success in developing a 1,2-allylmethylation reaction of alkenes directed by diverse azaheterocycles[44], we attempted these useful substrate families and were pleased to find that pyridine (**5l**), pyrazoles (**5m**–**5o**), triazoles (**5p**–**5q**), tetrazole (**5r**), indazoles (**5s**–**5t**), and benzotriazole (**5u**) were all compatible directing groups.

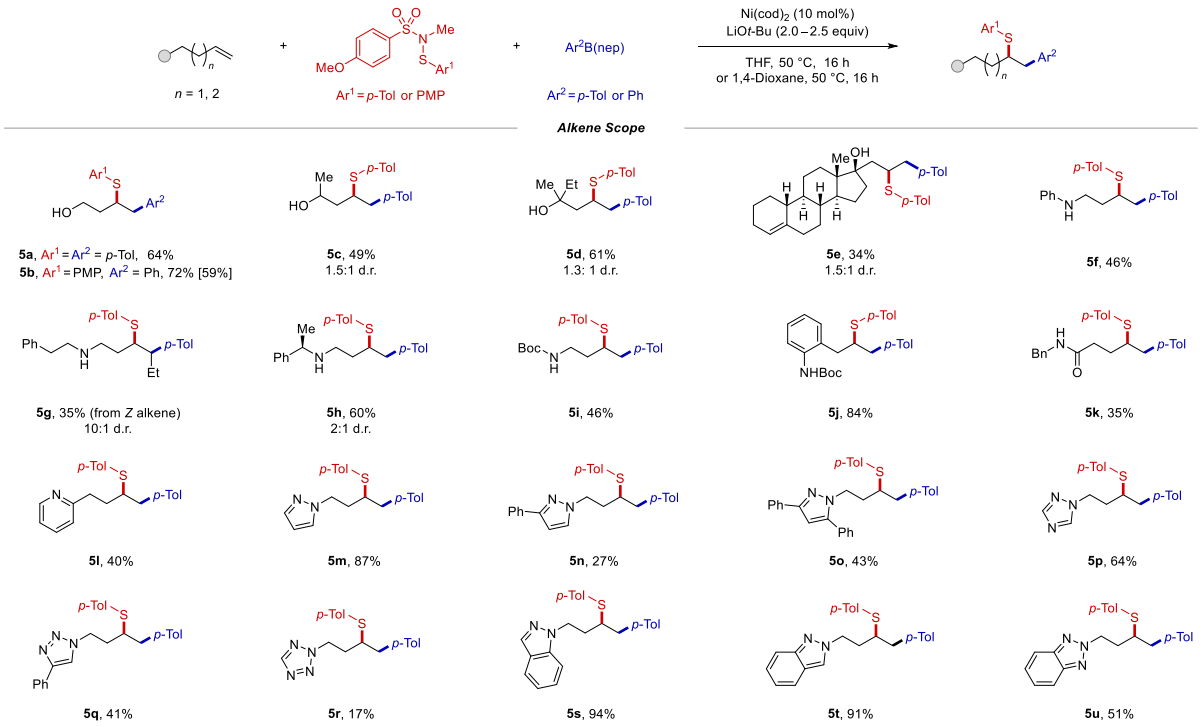

Fig. 4. Alkene Scope. Reactions performed on 0.1 mmol scale. Percentages represent isolated yields. Diastereomeric ratios were determined by ^{1}H NMR analysis of the isolated products. For **5b**, the yield in brackets was obtained from an experiment performed on 4.0 mmol scale.

Synthetic versatility. The N−S reagents used in this study can readily be prepared on decagram scale using modular and operationally convenient chemistry. If desired, the sulfonamide leaving group can be recovered in nearly quantitative yield and recycled (see SI for detail). The reaction can be performed outside of the glovebox using the air-stable precatalyst Ni(cod)(DQ) under Schlenk technique, as demonstrated using the model reaction in Fig. 5a (80% yield, entry 1a).[45] A series of stress tests showed that this protocol is fairly robust. Simply purging with nitrogen over the solvent surface was sufficient (entry 1b), and even running the reaction under air gave 44% yield (entry 1c). When 1 mol% catalyst loading was used with extended reaction time of 40 h, 70% yield was obtained (entry 2). Reducing the electrophile and nucleophile loading led to lower yet synthetically useful yields (entry 3). A series of product derivatizations were performed to showcase the synthetic utility of the method (Fig. 5b). From a –NH(Cs) product , *N*-alkylation

and -arylation followed by mild deprotecting furnished **6a** and **6b**.[43] This sequence allows straightforward incorporation of groups that are problematic in the nickel-catalyzed 1,2-carbosulfenylation (e.g., nitroarenes). Hofmann−Löffler−Freytag (HLF) cyclization furnished 1,2-disubstituted pyrrolidine **6c** in 62% overall yield over 2 steps.[46] Controlled oxidation of the thioether to the sulfoxide or sulfone and successive oxidation to the sulfonyl carboxylic acid using different oxidants furnished **6d**−**6f** in excellent yields[9], with **6e** representing a key intermediate in the synthesis of matrix metalloproteinases (MMP) inhibitor.[47] Finally, a thianthrene-based radical precursor **6g** was prepared over 3 steps in 72% overall yield.

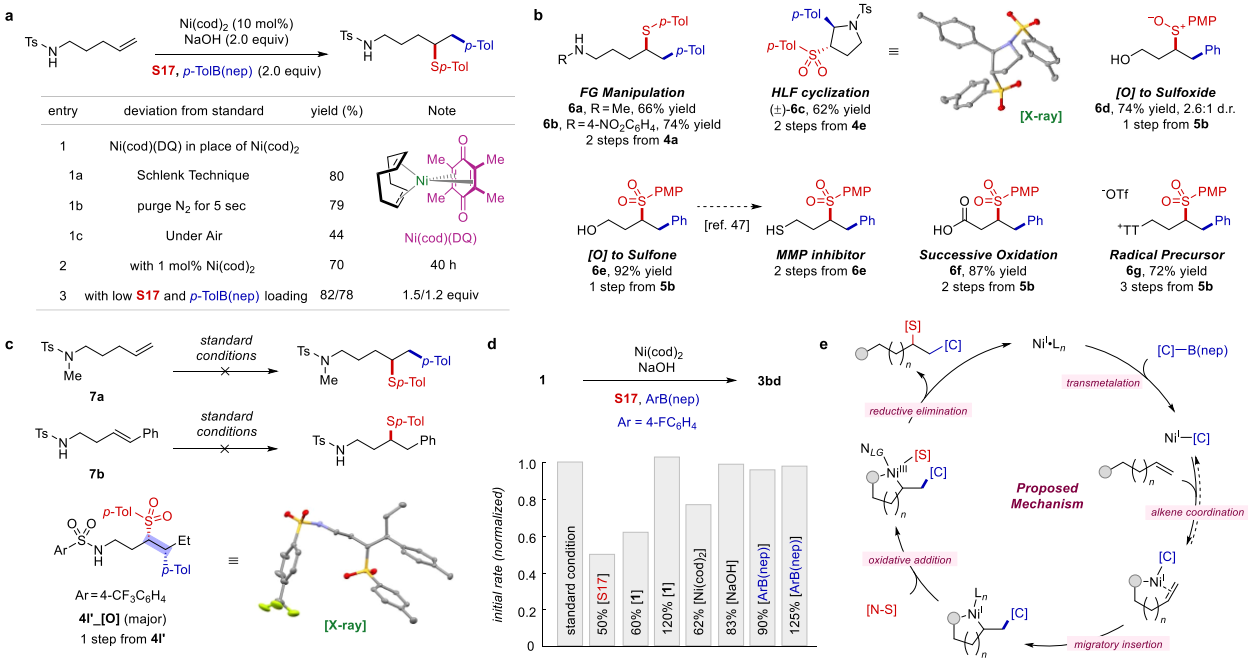

Fig. 5. Synthetic Versatility and Mechanistic Studies. a, Practicality analysis. Standard conditions: $Ni(cod)_2$/**1**/**S17**/**2a**/NaOH = 0.01/0.1/0.2/0.2/0.2 (mmol). Reaction was run in THF (0.05 M) at 60 °C. All percentages represent ^1H NMR yields with benzyl 4-fluorobenzoate as internal standard. **b**, Product diversification. For **6g**, TT = thianthrene. **c**, Mechanistic experiments. **d**, Reaction kinetics. Standard conditions: $Ni(cod)_2$/**1**/**S17**/4-FC_6H_4B(nep)/NaOH = 0.015/0.15/0.27/0.3/0.3 (mmol). Reaction was run in THF (0.05 M) at 35 °C. Normalized initial rate was calculated by defining initial rate of the standard condition as 1.0 within each set of experiments. For details see supporting information. **e**, Proposed mechanism.

Mechanistic studies. A control experiment with *N*-methyl alkenyl sulfonamide (**7a**) under standard conditions did not lead to product formation, suggesting that the sulfonamide group coordinates through nitrogen (Fig. 5c). Similarly, no desired product was formed from styrenyl sulfonamide (**7b)**, which rules out a stepwise oxidative Heck/hydrosulfenylation pathway. The relative stereochemistry of **4l'** (major) was determined by single-crystal X-ray diffraction of an oxidized derivative, indicating a *syn*-addition mechanism. Kinetic studies were performed using the conversion of **1** to **3bd** as the model reaction applying the method of initial rates (Fig. 5d, see SI for detail). The reaction was positive order in [$Ni(cod)_2$] and [**S17**]. Saturation kinetics were observed in [**1**], as it showed positive order at low [**1**] and zero-order behavior at high [**1**]. The other two components, [ArB(nep)] and [NaOH], were zero-order. Collectively, the data are consistent with the Ni^{I}/Ni^{III} cycle shown in Fig. 5e, involving a sequence of transmetalation, migratory insertion, N–S oxidative addition, and C–S reductive elimination. The kinetic data indicate that the turnover-limiting step at standard or elevated alkene concentration is N–S oxidative addition, whereas at low alkene concentration, an earlier step becomes turnover-limiting, namely alkene coordination or irreversible migratory insertion following reversible alkene binding.

Conclusion:

In conclusion, a novel family of N−S reagents with *N*-alkylsulfonamide leaving groups was developed to enable 1,2-carbosulfenylation of unactivated alkenes under nickel catalysis. The synthetic versatility of the method stems from the broad scope of compatible alkenes bearing different native directing groups. The identification of N–S reagents based upon modular components allows for fine tuning of the electronic and steric properties, which ultimately affect stability, reactivity, and catalytic performance. DFT calculations indicate that optimal yield is achieved when parameters such as BDE and LUMO energy fall within a narrow range of values. This finding is expected to guide the development of other heteroatom-based electrophiles for use in multicomponent catalytic couplings.

Data availability

The authors declare that the data supporting the findings of this study are available within the article and Supplementary Information files or from the corresponding author upon reasonable request. The

experimental procedures, computational results, and characterization of all new compounds are provided in the Supplementary Information.

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Author contributions

Z.-Q.L. and K.M.E. conceived this work. Z.-Q.L. and Y.C. optimized the reaction and evaluated the scope. Z.-Q.L., Y.C., and T.K. carried out synthesis of alkene starting materials. Z.-Q.L. and Y.C. carried out computational work. Z.-Q.L. performed mechanistic experiments. Z.-Q.L. and K.M.E. wrote the manuscript with input from all other authors.

Competing Interests: The authors declare no competing financial and non-financial interest.

Method: Outside of the glovebox, to an oven-dried 2-dram (8-mL) reaction tube equipped with a magnetic stir bar were added the appropriate alkene (0.1 mmol), N–S reagent (0.2 mmol), and arylboronic acid neopentyl glycol ester (0.2 mmol). The vial was then introduced into an argon-filled glovebox antechamber. Once transferred inside the glovebox, NaOH (8.0 mg, 0.2 mmol, for alkenyl sulfonamides) or LiO*t*-Bu (16.0 mg or 20.0 mg, 0.2 mmol or 0.25 mmol, for alkenes discussed in Fig. 4), and $Ni(cod)_2$ (2.8 mg, 10 mol%) were added to the vial, followed by THF (2.0 mL) or 1,4-Dioxane (2.0 mL). The vial was sealed with a screw-top septum cap, removed from

the glovebox, and left to stir at 60 °C (for alkenyl sulfonamides) or 50 °C (for alkenes discussed in Fig. 4) for 16 h. After this time, the reaction was diluted with saturated $NaHCO_3$ solution (10 mL). The aqueous solution was then extracted with ethyl acetate (3 × 2 mL). The combined organic layers were dried by passage through a pad of silica gel with ethyl acetate as eluent. The filtrate was concentrated and purified by preparative thin-layer chromatography (PTLC) to furnish the desired product.

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