Electrophilic Sulfur Reagent Design Enables Directed *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.

INTRODUCTION

Organosulfur compounds have diverse functions and find applications as pharmaceuticals[1] and functional materials.[2] Organosulfides, in particular, can also be readily converted into other functional groups, making them versatile building blocks in synthesis.[3] While reliable approaches for catalytic two-component C–S bond formation[4] via cross-coupling reactions[5] and C–H functionalization[6] have emerged during the past two decades, multicomponent C–S bond-forming reactions remain less explored.[7] 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[8], Denmark[9] and others[10], the most well-established method for 1,2-carbosulfenylation of alkenes involves formation of a thiiranium ion intermediate[11] through electrophilic sulfenyl transfer and subsequent nucleophilic ring opening, with *anti*-stereoselectivity arising from the S$_N$2 nature of the ring-opening step and regioselectivity dictated by alkene substitution pattern (scheme 1A). 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[8a], acetylides[8b], and organozinc reagents[10d], 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 (scheme 1B). 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.[9g, 12]
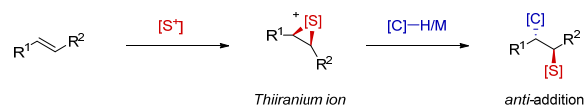
Recently, nickel-catalyzed redox-neutral 1,2-functionalization of unactivated alkenes[13] has emerged as a powerful method for joining together a nucleophile, an electrophile, and an alkene in a selective fashion.[14] Depending on the identity of the coupling partners, two closely related yet distinct mechanisms can operate (scheme 1C). A Ni(0)/Ni(II) cycle occurs by an oxidative-addition-first pathway, where the electrophile is incorporated distal to the directing group.[15] Meanwhile, a Ni(I)/Ni(III) cycle involving a transmetalation-first mechanism typically manifests in reversed regioselectivity.[16] 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[15c], 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.
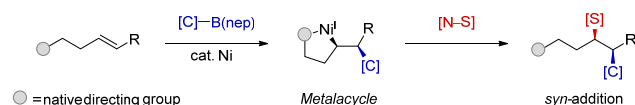
Herein we report a nickel-catalyzed *syn*-selective 1,2-carbosulfenylation reaction[17] of simple unactivated alkenes[18]. Critical to the success of this reaction is the identification of *N*-sulfenyl-*N*-alkyl sulfonamides as N–S electrophiles (scheme 1D). Taking inspiration from various electrophiles in the literature that contain nitrogen-based leaving groups for fluorination[19], trifluoromethylthiolation[20], cyanation[21], and acylation[22], 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.

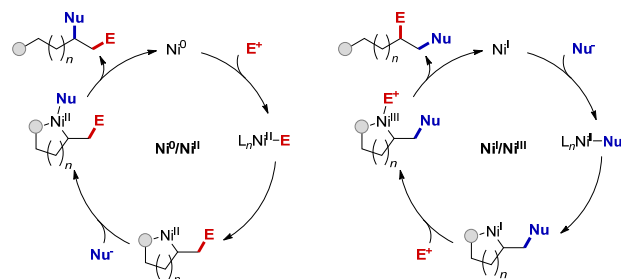## Scheme 1. Background and Synopsis of Current Work

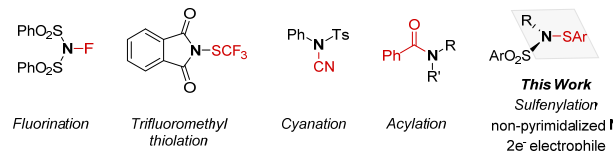**A.** Thiiranium-ion-mediated anti-selective 1,2-carbosulfenylation.

$R^1 \diagup \diagdown R^2$ → [S+] → Thiiranium ion → [C]—H/M → anti-addition

Thiiranium ion

anti-addition

B. *This work*: *syn*-selective 1,2-carbosulfenylation of unactivated alkenes.

⬤ = native directing group

[C]—B(nep), cat. Ni → Metalacycle → [N–S] → *syn*-addition

Metalacycle

syn-addition

C. Nickel-catalyzed redox-neutral alkene 1,2-difunctionalization.

Ni⁰/Ni^II

Ni^I/Ni^III

D. Carbon- and heteroatom electrophiles containing nitrogen leaving groups.

PhO₂S–N(–F)–SO₂Ph

Fluorination

N–SCF₃ (phthalimide)

Trifluoromethyl thiolation

Ph–N(Ts)–CN

Cyanation

Ph–C(O)–N(R)(R')

Acylation

ArO₂S–N(R)–SAr

This Work
Sulfenylation
non-pyrimidalized **N**
2e⁻ electrophile

RESULTS AND DISCUSSION

Reaction discovery. To begin the investigation, we focused on the model reaction of alkenyl sulfonamide **1**[23] with *p*-tolylboronic acid neopentyl glycol ester (**2a**) and various N–S electrophiles (scheme 2A). 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**)[7a]; 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 N$_{LG}$**5**–N$_{LG}$**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**)[24] 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**).[25]
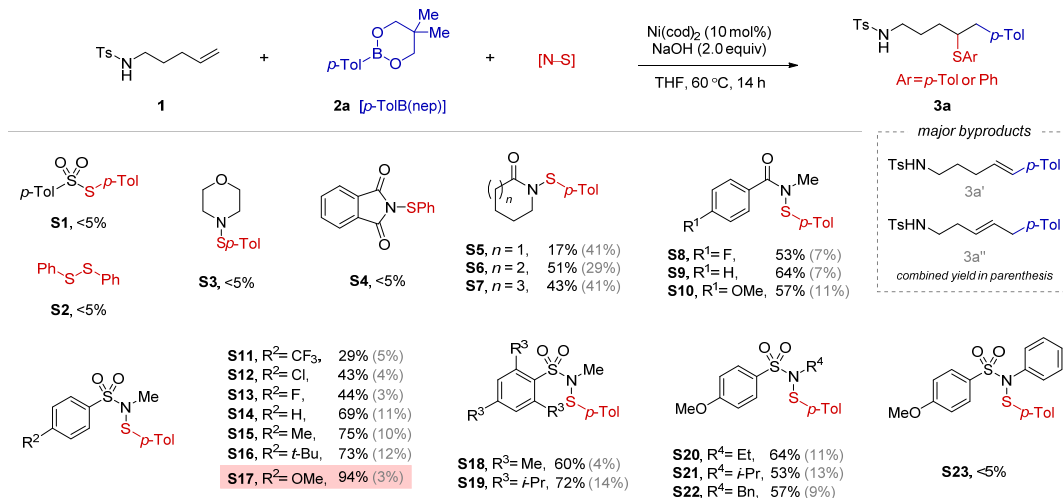
We performed computational parameterization of the tested reagents to understand the origins of the high product yield with **S17** (scheme 2B). As N−S reagents were expected to be involved mainly during the oxidative addition step, LUMO energy and bond dissociation energy (BDE)[26] were computed and 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,[25] 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)[24]. 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[9, 12], was too stable to react (BDE = 79.2 kcal/mol).

X-ray crystallographic analysis (scheme 2C) of representative N–S electrophiles revealed a non-pyramidalized N-atom[27] 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.
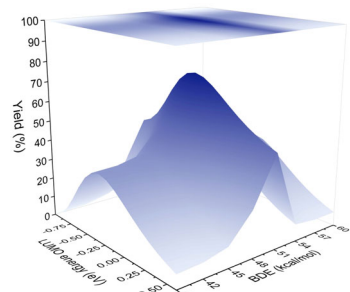
Substrate scope. Having identified an optimal class of N–S electrophiles, we examined the scope and limitations of the method (Table 1). Regarding the electrophile scope, arylsulfenyl moieties with electron-neutral or -withdrawing substituents (**3aa**–**3ag**) could be efficiently introduced with the 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. In preliminary experiments, we found that an alkylsulfenyl group could also be introduced onto two representative alkenyl sulfonamide substrates, though yields were low in these cases (**3al**–**3am**).

Scheme 2. Discovery of nickel-catalyzed 1,2-carbosulfenylation of unactivated alkenes
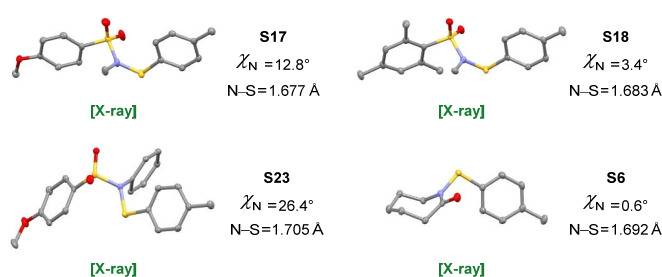
A. Optimization of reaction conditions[a]

Ni(cod)$_2$ (10 mol%)
NaOH (2.0 equiv)
THF, 60 °C, 14 h

Ar = *p*-Tol or Ph

major byproducts

S1, <5%

S2, <5%

S3, <5%

S4, <5%

S5, *n* = 1, 17% (41%)
S6, *n* = 2, 51% (29%)
S7, *n* = 3, 43% (41%)

S8, R^1= F, 53% (7%)
S9, R^1= H, 64% (7%)
S10, R^1= OMe, 57% (11%)

3a'

3a''

combined yield in parenthesis

S11, R^2= CF$_3$, 29% (5%)
S12, R^2= Cl, 43% (4%)
S13, R^2= F, 44% (3%)
S14, R^2= H, 69% (11%)
S15, R^2= Me, 75% (10%)
S16, R^2= *t*-Bu, 73% (12%)
S17, R^2= OMe, 94% (3%)

S18, R^3= Me, 60% (4%)
S19, R^3= *i*-Pr, 72% (14%)

S20, R^4= Et, 64% (11%)
S21, R^4= *i*-Pr, 53% (13%)
S22, R^4= Bn, 57% (9%)

S23, <5%

B. DFT parameterization[b]

C. X-ray structures of representative N–S reagents[c]

S17
χ_N = 12.8°
N–S = 1.677 Å
[X-ray]

S18
χ_N = 3.4°
N–S = 1.683 Å
[X-ray]

S23
χ_N = 26.4°
N–S = 1.705 Å
[X-ray]

S6
χ_N = 0.6°
N–S = 1.692 Å
[X-ray]

[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]Hydrogen atoms omitted for clarity. Introduction of an electron-withdrawing group on the arylsulfenyl group (*p*-CF$_3$) with **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).

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**–**4h**), with the former giving slightly lower yield. Gratifyingly, benzenesulfonyl groups with different substituents at the *para*-position (**4a**–**4g**) and a methanesulfonyl group (**4h**) 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 **4f** and **4g** in 53% and 85% yield, respectively.[28] Moderate yield and diastereoselectivity were obtained with substrates containing α- or β-branching (**4i**–**4k**). With internal alkenes (**4l**–**4r**), *Z*-configured alkenes provided higher yield, as well as greater and opposite diastereoselectivity, compared with the corresponding *E*-isomers. With a skipped diene substrate, the reaction took place selectively at the γ,δ-position, due to the formation of a relatively stable 5-membered metallacycle (**4q**). With a 4-trifluoromethylbenzenesulfonyl directing group,[23] **4r** was obtained in 78% yield and >20:1 d.r. through a 6-membered metallacycle. A sulfonamide derived from *ortho*-allylaniline furnished **4s** in 59% yield with no chain-walking byproducts detected.

# Table 1. Electrophile, Nucleophile, and Alkenyl Sulfonamide Scope[a]

n = 1, 2

Ni(cod)$_2$ (10 mol%)
NaOH (2.0 equiv)
THF, 60°C, 16 h

Electrophile Scope

3aa, 92% [78%][b]

3ab, 68% (88%)[c]

3ac, 79%

3ad, X=Cl, 67%
3ae, X=Br, 79%

3af, 28%

3ag, 93%

3ah, 93%

3ai, X=Cl, 66%
3aj, X=Br, 58%

3ak, 79%

3al, R=OMe, 17% (*n*=2)[e]
3am, R=Me, 16% (*n*=1)[e]

Nucleophile Scope

3ba, R=H,	90%
3bb, R=*t*-Bu,	84%
3bc, R=OMe,	86%
3bd, R=F,	84%
3be, R=Cl,	77%
3bf, R=CF$_3$,	58%

3bg, 93%

3bh, 60%

3bi, 75%

3bj, R=OMe,	92%
3bk, R=OBn,	94%
3bl, R=*i*-Pr,	63%
3bm, R=CHO,	54%

3bn, 62%

3bo, 90%

3bp, 56%

3bq, 66%

3br, 59%

3bs, 75%

3bt, 88%

3bu, 45%

3bv, 31%

3bw, 29%

Limitations (<20% yield)[d]

N.D.

N.D.

N.D.

17% (^{1}H NMR)

20% (^{1}H NMR)

Alkene Scope

= PG

= Ts

= Cs

= Ms

4a, Ar=*p*-Tol, 79% (*n*=1)
4b, Ar=PMP, 72% (*n*=1)

4c, Ar=*p*-Tol, 64% (*n*=1)

4d, Ar=PMP, 52% (*n*=1)
4e, Ar=*p*-Tol, 78% (*n*=2)

4f, Ar=*p*-Tol, 53% (*n*=1)
4g, Ar=*p*-Tol, 85% (*n*=2)

4h, Ar=*p*-Tol, 69% (*n*=1)

4i, 42%, 4:1 d.r. (*n*=0)
4j, 83%, 3:1 d.r. (*n*=1)

4k, 69%, 6:1 d.r.

4l, 38% yield, 8:1 d.r. (from *E*)

4m, 80%, 20:1 d.r. (from *Z*)
4m', 27%, 1:7 d.r. (from *E*)

4n, 88% yield, >20:1 d.r. (from *Z*)

4o, 78%, 13:1 d.r. (from *Z*)
4o', 53%, 1:8 d.r. (from *E*)

4p, 74% yield, >20:1 d.r. (from *Z*)

4q, 61% yield, 11:1 d.r. (from *E*)

4r, 78% yield, >20:1 d.r. (from *Z*)

4s, 59%

[a]Reactions performed on 0.1 mmol scale. Percentages represent isolated yields. [b]Yield in brackets was obtained from an experiment performed on 1.0 mmol scale. [c]Yield in parentheses was obtained with **S34** (featuring **N$_{LG}$11** as leaving group, see SI for details). [d]Percentage yields represent ^{1}H NMR yields with benzyl 4-fluorobenzoate as internal standard. N.D.=not detected. [e]Yield obtained with **S35** (see SI for details).

We next investigated alkenes containing other synthetically useful native functional groups (Table 2). 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.[16d] 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 1.1:1 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[29], 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.

Table 2. Alkene Scope[a]
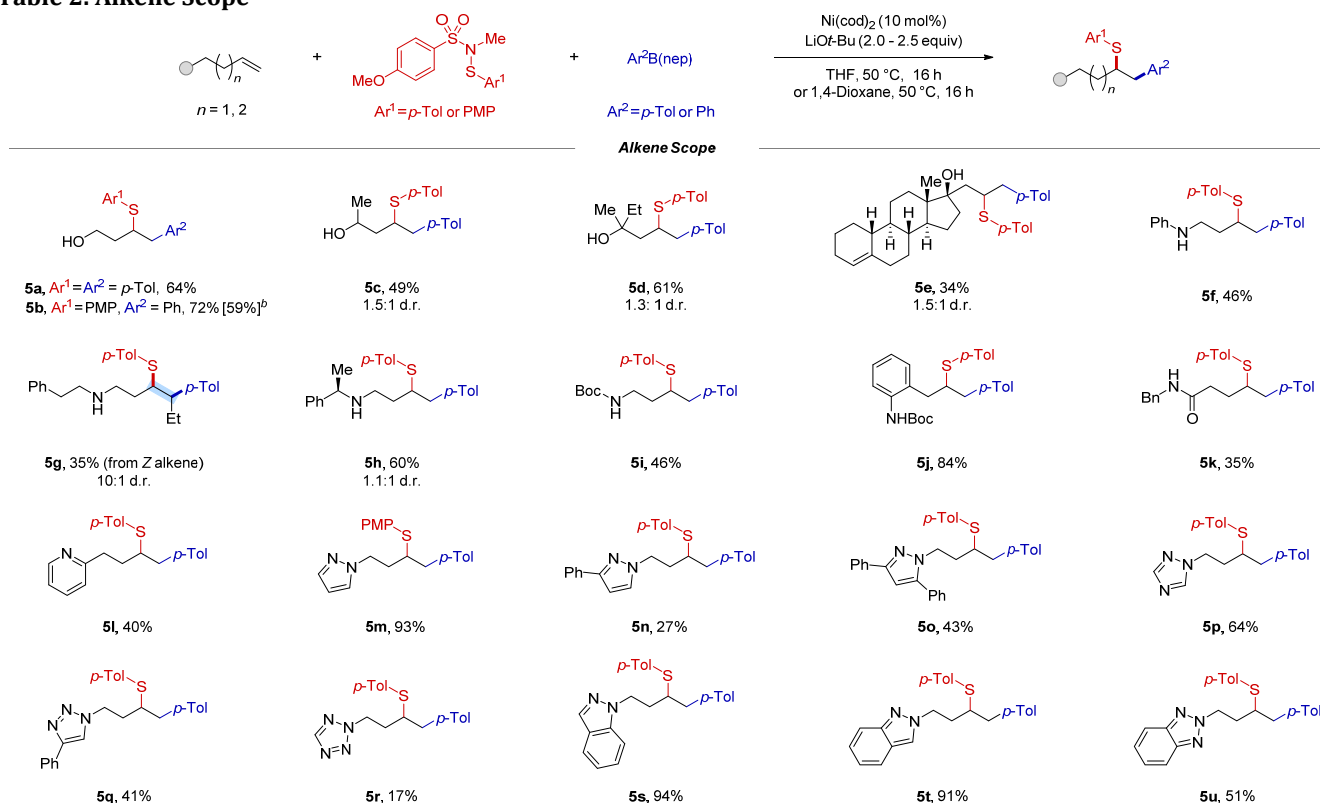
[a]Reactions performed on 0.1 mmol scale. Percentages represent isolated yields. Diastereomeric ratios were determined by ^{1}H NMR analysis of the isolated products.
[b]Results in brackets was obtained on 4.0 mmol scale.

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 scheme 3A (80% yield, entry 1a).[30] 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 (scheme 3B). From a –NH(Cs) product , N-alkylation and - arylation followed by mild deprotecting furnished **6a** and **6b**.[28]

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.[31] 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.[32] Finally, a thianthrene-based radical precursor **6g** was prepared over 3 steps in 72% overall yield.

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 (scheme 3C). Similarly, substrates without a suitable directing group such as 1-phenylbutene and 1-dodecene were unreactive (see SI for detail). No desired product was formed from styrenyl
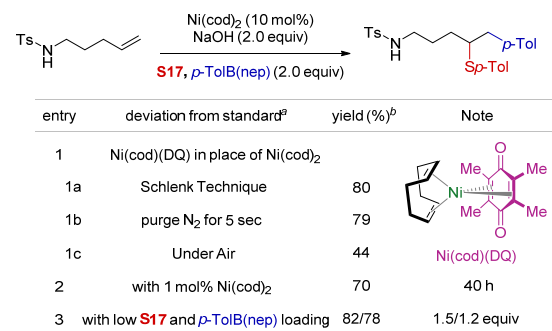
sulfonamide (**7b**), which rules out a stepwise oxidative Heck/hydrosulfenylation pathway. The relative stereochemistry of **4o'** (major) was determined by single-crystal X-ray diffraction of an oxidized derivative, indicating a *syn*-addition mechanism. Kinetic studies were performed using the conversion of **1** to **3bd** as the model reaction applying the method of initial rates (scheme 3D, 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 be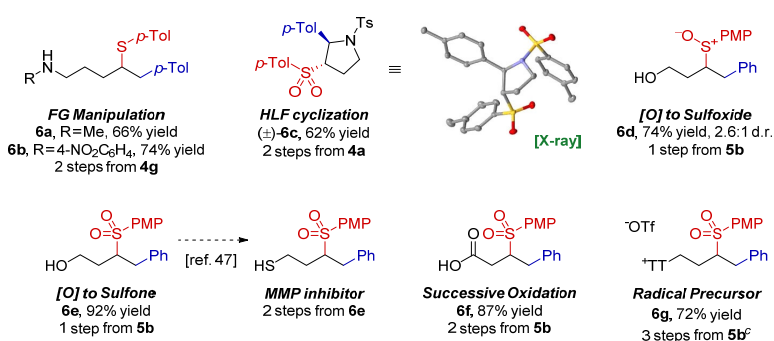havior at high [**1**]. The other two components, [ArB(nep)] and [NaOH], were zero-order. Collectively, the data are consistent with the Ni^I/Ni^{III} cycle shown in scheme 3E, involving a sequence of transmetalation, migratory insertion, N–S oxidative addition, and C–S reductive elimination.[16, 33] 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.
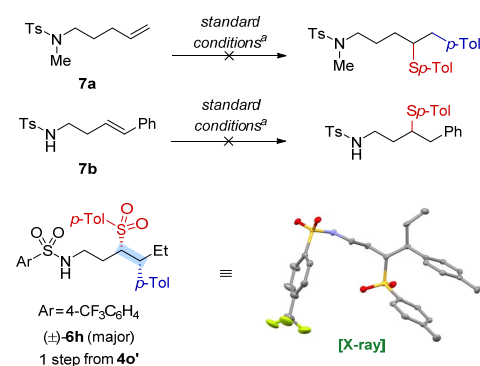
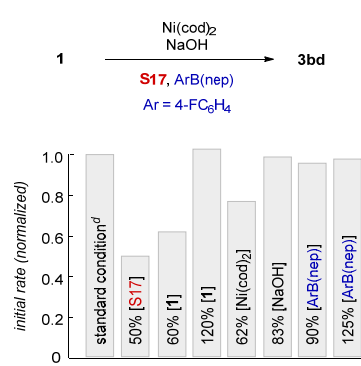## Scheme 3. Synthetic Versatility and Mechanistic Studies
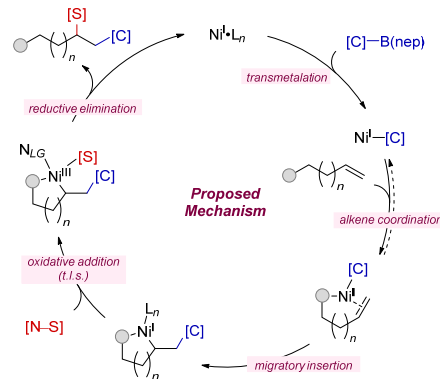
A. Stress tests

entry	deviation from standard[a]	yield (%)[b]	Note
1	Ni(cod)(DQ) in place of Ni(cod)$_2$		
1a	Schlenk Technique	80	
1b	purge N$_2$ for 5 sec	79	
1c	Under Air	44	
2	with 1 mol% Ni(cod)$_2$	70	40 h
3	with low **S17** and *p*-TolB(nep) loading	82/78	1.5/1.2 equiv

B. Product derivatization

FG Manipulation
6a, R=Me, 66% yield
6b, R=4-NO$_2$C$_6$H$_4$, 74% yield
2 steps from **4g**

HLF cyclization
(±)-**6c**, 62% yield
2 steps from **4a**

[X-ray]

[O] to Sulfoxide
6d, 74% yield, 2.6:1 d.r.
1 step from **5b**

[O] to Sulfone
6e, 92% yield
1 step from **5b**

[ref. 47]

MMP inhibitor
2 steps from **6e**

Successive Oxidation
6f, 87% yield
2 steps from **5b**

Radical Precursor
6g, 72% yield
3 steps from **5b**[c]

C. Mechanistic experiments

7a

standard conditions[a] ✗

7b

standard conditions[a] ✗

Ar = 4-CF$_3$C$_6$H$_4$
(±)-**6h** (major)
1 step from **4o'**

[X-ray]

D. Kinetic experiments

1 → **3bd**
Ni(cod)$_2$
NaOH
S17, ArB(nep)
Ar = 4-FC$_6$H$_4$

E. Proposed mechanism

Proposed Mechanism

[S] / [C]
reductive elimination

Ni^I•L$_n$

[C]—B(nep)
transmetalation

Ni^I—[C]

alkene coordination

N$_{LG}$–Ni^{III} [S] [C]
oxidative addition (t.l.s.)
[N–S]

[C]
Ni^I

migratory insertion

[a]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. [b]All percentages represent ^{1}H NMR yields with benzyl 4-fluorobenzoate as internal standard. [c]TT = thianthrene. [d]Standard conditions: Ni(cod)$_2$/**1**/**S17**/4-FC$_6$H$_4$B(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 conditions as 1.0 within each set of experiments. For details see supporting information.

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.

ASSOCIATED CONTENT

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Notes
The authors declare no competing financial interest.

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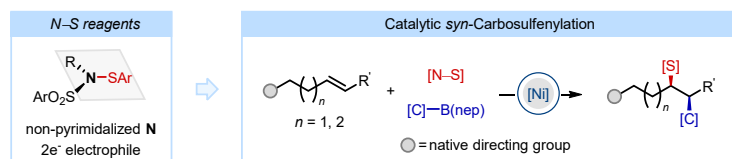
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N–S reagents

non-pyrimidalized **N**
2e⁻ electrophile

Catalytic *syn*-Carbosulfenylation

n = 1, 2

[N–S]

[C]—B(nep)

[Ni]

[S]

[C]

= native directing group

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