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Modular Sulfondiimine Synthesis Using a Stable Sulfinylamine Reagent

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Supporting Information

ABSTRACT: Sulfondiimines—the double aza-analogues of sulfones—hold significant potential as leads in discovery chemistry, yet their application in this arena has been held back by the scarcity of appropriate synthetic routes. Existing methods employ sulfides as substrates, and rely on consecutive imination reactions using the hazardous reagent *O*-mesitylenesulfonyl hydroxylamine. Here we report a method for sulfondiimine synthesis that does not begin with a sulfide or a thiol, and instead employs two Grignard reagents and a bespoke sulfinylamine (R—N═S═O) reagent as starting materials. Lewis acid-mediated assembly of these three components provides efficient access to a series of sulfilimine intermediates. A novel rhodium-catalyzed imination of these electron-rich sulfilimines then delivers a varied range of sulfondiimines featuring orthogonal *N*-functionalization. Conditions for the selective manipulation of both *N*-atoms of the sulfondiimines are reported, allowing access to a broad range of mono- and difunctionalized products. The oxidation of the sulfilimine intermediates is also described, and provides a complementary route to sulfoximines.

Sulfur(VI)-derived functional groups feature prominently in bioactive molecules, with sulfonamides and sulfones in particular being incorporated into many marketed pharmaceuticals and agrochemicals.[1] The mono- and diaza analogues of these groups—sulfoximines, sulfondiimines and sulfonimidamides—are less prevalent; however, they too are emerging as useful functionalities in discovery chemistry (Figure 1a,b).[2] For example, the commercial insecticide Sulfoxaflor features a sulfoximine group,[3] as do several drug candidates that have been advanced to clinical trials.[4] Additionally, the pharmaceutical industry is starting to populate the patent literature with examples of sulfonimidamide-containing molecules.[5] Although sulfondiimines are the least represented member of this class, their attributes have also been recognized, with the result that they too are starting to feature in medicinal chemistry programs. Specific qualities associated with sulfondiimines include their heteroatom-rich nature, conferring both polarity and aqueous solubility, their three-dimensional topology, which is linked with the potential to "grow" the functional group along all 4-vertices from the central sulfur atom, and their potential to exist as single enantiomers.[2a]

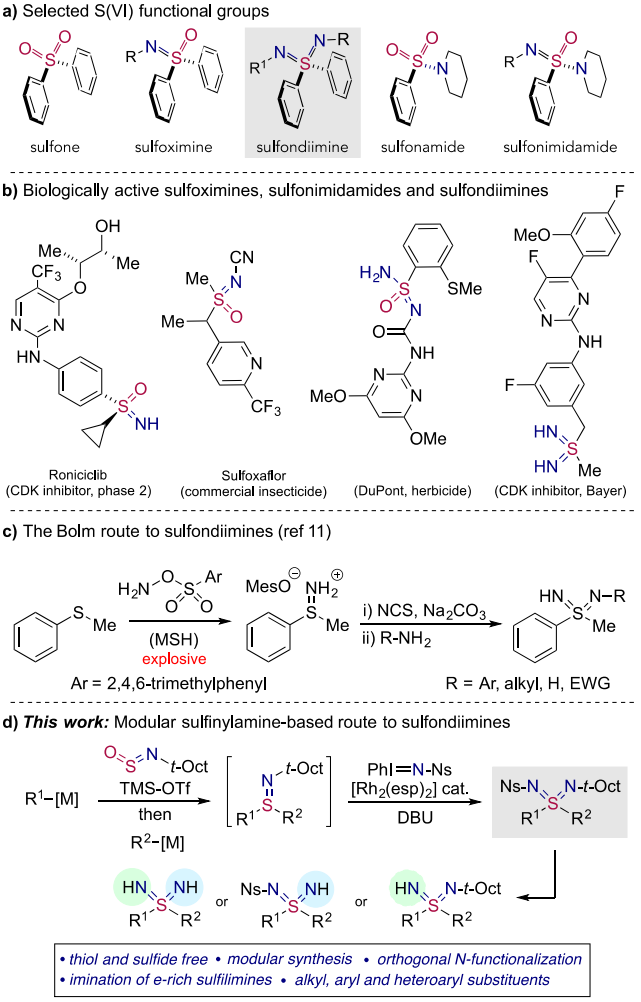

Figure 1. (a) Selected sulfur(VI) functional groups; (b) biologically relevant examples; (c) Bolm synthesis of sulfondiimines; (d) our modular synthesis of sulfondiimines.

The varying levels of uptake of these different aza-derivatives by the pharmaceutical and agrochemical industries can be broadly tracked to the advances achieved in the corresponding synthetic methods. For example, extensive studies from the Bolm laboratory,[6] as well as others,[7] have resulted in a variety

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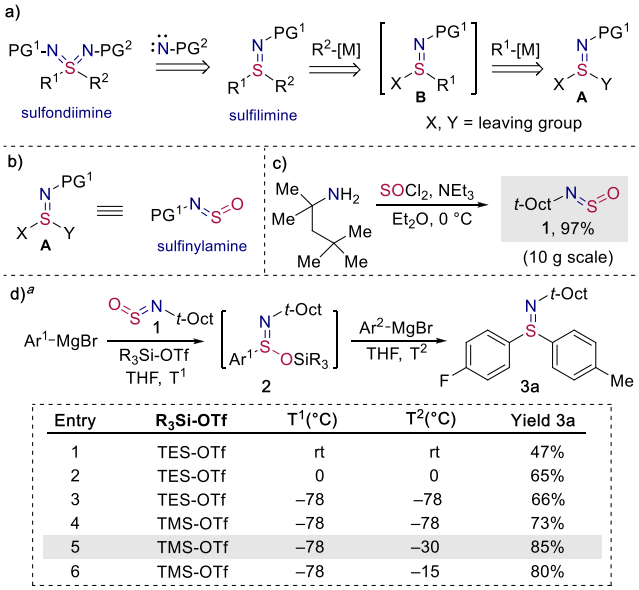
of methods for sulfoximine preparation, with most routes usually starting from the corresponding sulfides or sulfoxides. Reports targeting sulfonimidamides are considerably fewer,[8] although this has improved recently,[9] while the only method for sulfondiimine preparation that reports more than a handful of select examples is the 2012 account from Bolm.[10,11] The Bolm method employs sulfide substrates that are first converted to the corresponding N−H sulfilimine salts by treatment with *O*-mesitylenesulfonyl hydroxylamine (MSH), and then on to sulfondiimines by consecutive chlorination (*N*-chlorosuccinimide) and amine addition (Figure 1c). In this way, a broader range of sulfondiimines than had been previously accessible was obtained. Despite these advances, there remained several limitations; the sulfondiimines were obtained in generally modest yields, with the majority of examples featuring only an aryl group and a methyl group as the carbon-substituents at the sulfur center, with a single diaryl example being reported in poor yield. A single dialkyl-substituted example, derived from tetrahydrothiophene, was also reported. MSH is not an attractive reagent due to handling issues associated with its explosion risk. The use of sulfides, and therefore ultimately thiols, as substrates is a limitation due to their odorous nature and generally poorer commercial availability with respect to nonsulfur containing building blocks.

Motivated to deliver an enabling sulfondiimine synthesis capable of providing a broad range of substitution patterns, and to address the limitations of the existing methods, we embarked on the present study with the strategic decision to avoid the use of sulfides (and hence thiols) as starting materials. The resultant chemistry allows the modular assembly of sulfilimine intermediates from the combination of two Grignard reagents and a stable sulfinylamine reagent. Rhodium-catalyzed imination then provides a broad range of substituted sulfondiimines featuring orthogonal *N*-functionalization (Figure 1d).

To allow maximum flexibility for selective functionalization of the ultimate products, we targeted sulfondiimines with orthogonally functionalized *N*-atoms (Scheme 1a). Our immediate synthetic targets then became appropriately functionalized sulfilimines, although we were aware that the imination of *N*-functionalized sulfilimines to sulfondiimines had yet to be reported. In order to avoid the use of thiols, we envisioned an approach employing a central high-oxidation state sulfur linchpin to which functionalized carbon fragments could be sequentially attached (**A** → **B** → sulfilimine). A key simplifying element of our strategy, which avoids the need to prepare a sulfur fragment **A** with differentially reactive leaving groups, was to employ a sulfinylamine as the linchpin (Scheme 1b). The design of novel sulfinylamine **1**, derived from readily available *tert*-octylamine, was based on the requirements of (i) reagent stability balanced with reactivity, (ii) a deprotectable *N*-substituent, and (iii) an electron-rich *N*-substituent to enable sulfilimine imination. These criteria ruled out the use of the commercial sulfinylamine TrNSO,[9c,12] as well as known derivatives featuring electron-withdrawing *N*-substituents such as Ts or Cbz. Sulfinylamine **1** was conveniently prepared on multigram scale (Scheme 1c). The controlled consecutive addition of Grignard reagents to sulfinylamine **1** was achieved using Lewis acid activation (Scheme 1d). The optimal conditions involved addition of the initial Grignard reagent to sulfinylamine **1** and trimethylsilyl trifluoromethanesulfonate (TMS-OTf) at −78 °C for 1 min, before addition of the

Scheme 1. (a) Reaction Design; (b,c) Sulfinylamine Reagent 1; (d) Conditions for the Assembly of Sulfilimine 3a[a]



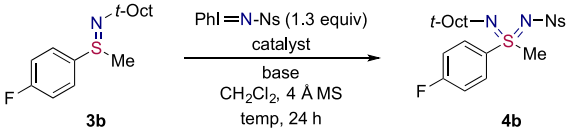
Entry	R_3Si-OTf	T^1(°C)	T^2(°C)	Yield 3a
1	TES-OTf	rt	rt	47%
2	TES-OTf	0	0	65%
3	TES-OTf	−78	−78	66%
4	TMS-OTf	−78	−78	73%
5	TMS-OTf	−78	−30	85%
6	TMS-OTf	−78	−15	80%

[a] Ar^1−MgBr (1.05 equiv), **1** (1.0 equiv), TMS-OTf (1.0 equiv), tetrahydrofuran (THF), −78 °C, 1 min, then Ar^2−MgBr (1.5 equiv), −30 °C, 10 min. Isolated yields.

second Grignard reagent at −30 °C. Under these conditions sulfilimine **3a** was obtained in an excellent 85% yield. Some flexibility for the temperature of the second addition was possible (entries 4−6, Scheme 1d).

With access to the desired sulfilimines achieved, we turned our attention to their conversion into the corresponding sulfondiimines. Although many reagent and catalyst combinations have been reported for the imination of sulfoxides[6,7,13] and sulfides,[6a,14] the only effective imination of sulfilimines involved a two-stage chlorination/amine addition sequence, and was only successful on N−H sulfilimine substrates.[10a,b,11] The direct imination of *N*-alkyl sulfilimines is unknown. We elected to develop a metal-catalyzed imination process using iminoiodinane reagents, and chose sulfilimine **3b** as our test substrate (Table 1). Exploratory reactions generating the

Table 1. Development of Conditions for the Preparation of Sulfondiimine 4b[a]



entry	catalyst	base	temp	yield of **4b**
1	$Rh_2(OAc)_4$ (5 mol %)	–	40 °C	13%
2	$Rh_2(OAc)_4$ (5 mol %)	Na_2CO_3	40 °C	40%
3	$Rh_2(esp)_2$ (5 mol %)	Na_2CO_3	40 °C	80%
4	$Rh_2(esp)_2$ (5 mol %)	DBU	40 °C	84%
5	$Rh_2(esp)_2$ (2.5 mol %)	DBU	40 °C	88%
6	$Rh_2(esp)_2$ (2.5 mol %)	DBU	22 °C	82%
7	$Rh_2(esp)_2$ (0.5 mol %)	DBU	40 °C	78%
8	$Fe(OTf)_2$ (10 mol %)	Na_2CO_3	40 °C	0%
9	$Cu(OTf)_2$ (10 mol %)	Na_2CO_3	40 °C	0%

[a] **3b** (1.0 equiv), PhI = N−Ns (1.3 equiv), CH_2Cl_2, 24 h. Isolated yields.

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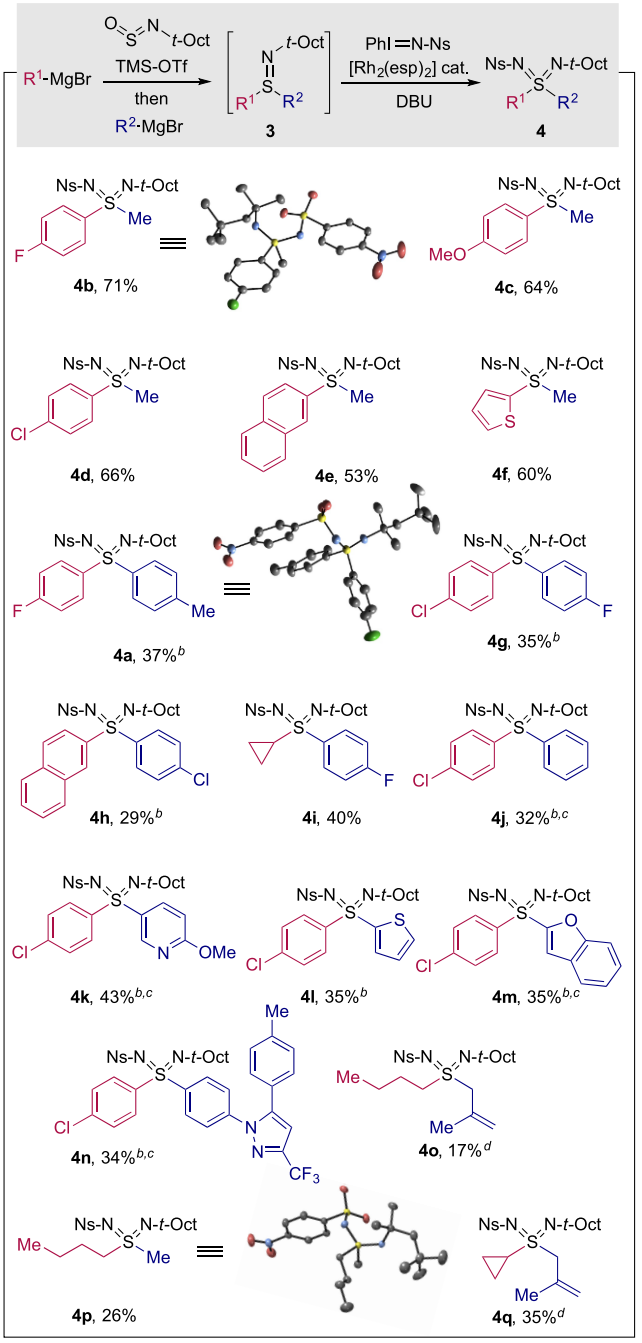
iminoiodinanes in situ from iodosobenzene diacetate and nosylamide soon established that the significant basicity of the sulfilimine substrate, combined with the acetic acid produced during iminoiodinane formation, was problematic, even with the addition of excess base. Accordingly, we switched to the use of the preformed iminoiodinane, and found that when using $Rh_2(OAc)_4$ as a catalyst a modest yield of sulfondiimine **4b** was obtained (entry 1). The addition of Na_2CO_3 and a move to $Rh_2(esp)_2$ as a catalyst[15] significantly improved the yield (entries 2 and 3). Optimal conditions involved the use of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and 2.5 mol % of catalyst at 40 °C (entries 4–7). The use of iron- or copper-based catalysts was not effective (entries 8 and 9).

Crucially, the optimized conditions for sulfilimine synthesis and for the imination of sulfilimines could be combined into a telescoped process to evaluate their application to sulfondiimine preparation (Table 2). In this way it was possible to avoid rigorous purification of the potentially sensitive sulfilimine intermediates, with an aqueous wash and extraction proving sufficient for most substrates. The more robust diarylsulfilimines were purified by flash chromatography. The sulfondiimine yields reported in Table 2 are for the two-stage procedure, with the initial Grignard reagent being the limiting component. A range of aryl Grignard reagents can be employed as the first organometallic reagent, followed by the addition of alkyl or aryl Grignard reagents, to provide sulfondiimines in respectable yields for this four-component two-stage assembly (**4a**–**4h**). These products are the first examples of orthogonally *N*-functionalized sulfondiimines prepared. The addition order can be reversed, with alkyl addition preceding aryl (**4i**). Organolithium reagents can also be used as nucleophiles (**4j**), providing greater flexibility in reagent choice, and allowing the introduction of a number of heteroaryl groups (**4k**–**4m**). The pyrazole-containing fragment incorporated into sulfondiimine **4n** corresponds to the aryl unit of the marketed COX-2 inhibitor Celecoxib. The moderate yields obtained for several of the diaryl examples are the consequence of a slow imination step, with unreacted sulfilimine remaining in most cases.[16]

Dialkyl-substituted sulfondiimines were the most challenging class of products to obtain, and the low yields achieved reflect the instability of the sulfilimine intermediates, which were not purified and undergo a degree of decomposition during the imination step. Despite these difficulties a number of straight-chain alkyl, and cyclo-alkyl examples were obtained in low-modest yields (**4o**–**4q**). Unlike the precursor sulfilimines, the corresponding dialkyl sulfondiimines display good stability. The reaction could be scaled, with sulfondiimine **4b** being obtained in 62% yield on a 10 mmol scale using only 0.5 mol % of the rhodium catalyst. The X-ray structures of sulfondiimines **4a**, **4b**, and **4p** shown in Table 2 provide a compelling graphical representation of the hindered environments around the fully substituted tetrahedral sulfur-centers in these molecules.

The ready preparation of a broad range of sulfilimines provided an opportunity to deliver a complementary route to sulfoximines, which would again avoid the use of thiols and sulfides as starting materials. As before, the optimal procedure involved a two-stage operation with the second stage now being sulfilimine oxidation, achieved using catalytic *tetra*-propylammonium perruthenate (TPAP) and *N*-methylmorpholine *N*-oxide (NMO).

Table 2. Preparation of Sulfondiimines 4[a]



[a]R^1–MgBr (1.0 equiv), **1** (1.05 equiv), TMS-OTf (1.0 equiv), THF, −78 °C, 1 min, then R^2–MgBr (1.5 equiv), −30 °C, 10 min. Aqueous workup. PhI = N–Ns (1.3 equiv), $[Rh_2(esp)_2]$ (2.5 mol %), CH_2Cl_2, 40 °C, 24 h. Isolated yields. [b]Total of 4.5 equiv of PhI = Ns used (1.5 × 3) and $[Rh_2(esp)_2]$ (5.0 mol %), 60 °C, 24 h. [c]Organolithium used as 2nd nucleophile. [d]Using 2-methyl-1-propenylmagnesium bromide as 2nd organometallic reagent.

The yields given for the individual examples are based on the initial Grignard reagent as the limiting substrate. Using this method a broad range of aryl–alkyl (**5a**–**c**) and aryl–aryl (**5d**–**5j**) substituted sulfoximines were obtained in high yields (Table 3). Included in the aryl–aryl examples are the three regioisomeric tolyl derivatives (**5g**–**5i**), demonstrating that sterically demanding *ortho*-substituents can be tolerated. Heteroaryl groups can also be installed efficiently using this

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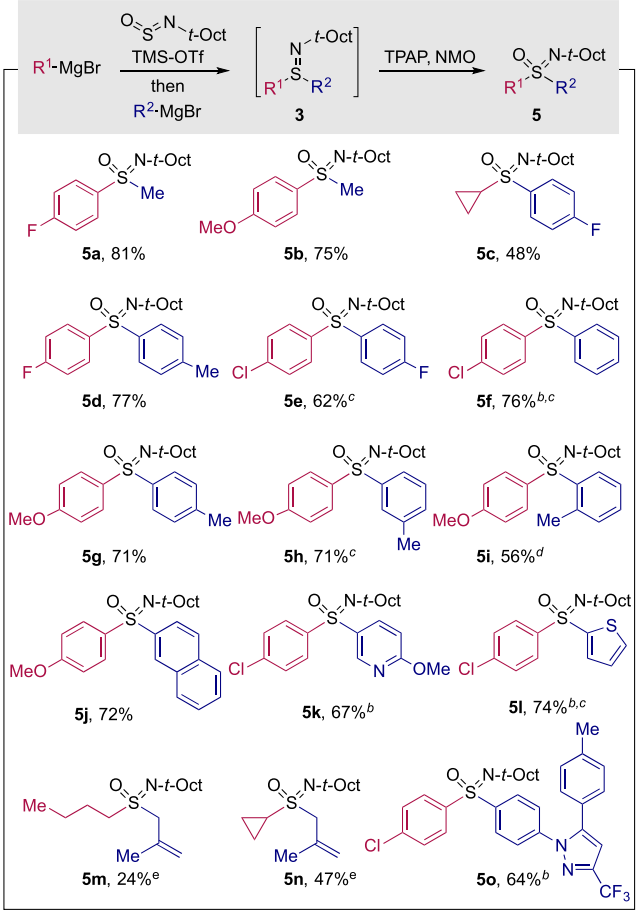
Table 3. Preparation of Sulfoximines 5[a]



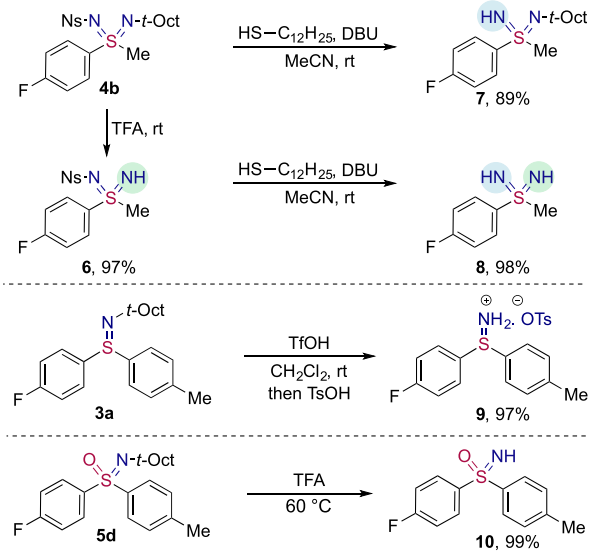
[a]R^1-MgBr (1.0 equiv), **1** (1.05 equiv), TMS-OTf (1.0 equiv), THF, −78 °C, 1 min, then R^2-MgBr (1.5 equiv), −30 °C, 10 min. Aqueous workup. TPAP (5 mol %), NMO (6.0 equiv), MeCN, 40 °C. Isolated yields. [b]Organolithium used as 2nd nucleophile. [c]50 °C for 2nd step. [d]TPAP (15 mol %). [e]Using 2-methyl-1-propenylmagnesium bromide as 2nd organometallic reagent.

approach (**5k,l**). As with the corresponding sulfondiimine examples, dialkyl sulfoximines were challenging to prepare, with sulfoximines **5m** and **5n** being representative. The final example in Table 3 includes the complex aryl unit of the COX-2 inhibitor Celecoxib (**5o**).

Returning to sulfondiimines, in addition to developing a synthesis capable of broad variation of the carbon-based groups attached at sulfur, we also wanted to allow maximum flexibility for *N*-functionalization. Our choice of *tert*-octyl and nosyl groups as *N*-substituents allowed orthogonal deprotection of these groups in high yields. For example, the *N*-*tert*-octyl group of sulfondiimine **4b** could be removed by simple treatment with TFA, providing N−H sulfondiimine **6** in high yield (Scheme 2). The *N*-nosyl group of **4b** was removed by treatment with dodecanethiol and DBU, providing N−H sulfondiimine **7** in 89% yield. The double N−H sulfondiimine **8** was available in excellent yield from Ns-derivative **6**. Additionally, the *t*-Oct group of sulfilimine **3a** was readily cleaved to provide the corresponding N−H derivative **9** in 97% yield. Similarly, N−H sulfoximine **10** was available efficiently from the corresponding N-*t*-Oct derivative.

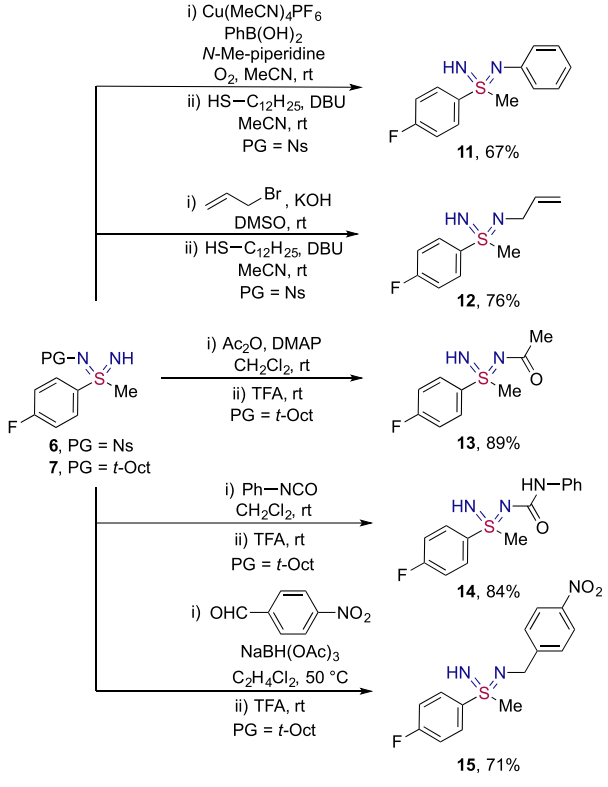
The ability to selectively unveil an N−H group in the presence of a second orthogonally protected *N*-atom allowed

Scheme 2. *N*-*tert*-Octyl and *N*-Nosyl Deprotection



for the preparation of a diverse range of *N*-derivatives. The complementary electronic character of the two *N*-protecting groups was key to achieving efficient reactions. For example, the electron-withdrawing ability of the nosyl group in sulfondiimine **6** allowed efficient *N*-arylation under Chan-Lam conditions,[17] as well as allylation using KOH and allyl bromide,[11] providing sulfondiimines **11** and **12**, respectively, following Ns cleavage (Scheme 3). Conversely, the electron-rich *N*-*tert*-octyl derivative **7** was converted to *N*-acyl derivative **13**, urea **14**, and *N*-benzyl derivative **15**, all after *N*-*tert*-octyl cleavage. Benzyl derivative **15** was obtained using a reductive

Scheme 3. *N*-Functionalization of Sulfondiimines 6 and 7



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amination procedure, a transformation reported here for the first time on a sulfondiimine.

In conclusion, we have developed a modular sulfondiimine synthesis from the combination of two organometallic reagents and a sulfinylamine linker, followed by a novel *S*-imination. The need to use malodorous and air-sensitive thiols is avoided. Alkyl, aryl, and heteroaryl *S*-substituents can all be introduced. The presence of orthogonal *N*-substituents allows the use of a diverse range of *N*-functionalization reactions. Taken together, these features have allowed the preparation of the most diverse set of sulfondiimines yet reported. We anticipate that the scope and flexibility of the developed chemistry will lead to further applications of sulfondiimines in discovery chemistry.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.9b06831.

Experimental procedures and supporting characterization data and spectra (PDF)

Data for $C_{27}H_{32}FN_3O_4S_2$ (CIF)

Data for $C_{21}H_{28}FN_3O_4S_2$ (CIF)

Data for $C_{19}H_{33.00}N_3O_4S_2$ (CIF)

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Notes

The authors declare no competing financial interest.

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