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Regioselective Cobalt-Catalyzed Addition of Sulfides to Unactivated Alkenes

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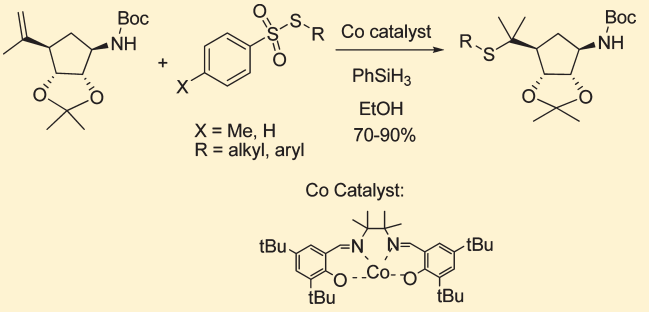
Supporting Information

ABSTRACT: A novel method to synthesize tertiary alkyl/aryl sulfides in a mild and regioselective manner from unactivated alkenes using cobalt catalysis is described. The methodology is compatible with sensitive functionalities and is successful with several different types of alkenes and sulfides.



Sulfur is found in many biologically relevant compounds, and therefore, it is commonly used in medicinal chemistry programs in the form of sulfonamides, sulfones, sulfoxides, or sulfides.[1] Recently, our medicinal chemistry efforts were directed toward the synthesis of tertiary alkyl/aryl sulfones of type **1** and sulfides of type **2** (Figure 1).

Since the scaffold contained sensitive functionalities as well as numerous chiral centers, a mild method of introducing sulfur into the molecule without interfering with any sensitive functional groups was required. Literature searches of tertiary alkyl sulfides uncovered some examples of the synthesis of these types of functionalities, although many of the chemistries involved were performed on scaffolds with no heteroatoms and required harsh conditions such as strong acids and high temperatures.[2] In 2006, Dunach and co-workers discovered a mild method of synthesizing tertiary sulfides from unactivated alkenes and thiols using indium(III) trifluoromethanesulfonate as a Lewis acid.[3] Unfortunately, this method failed to provide the product **2** when it was attempted on alkene **3**, most likely due to the acid instability of **3** (Figure 2).

To overcome the aforementioned drawbacks, we needed to discover a novel, mild method of synthesizing tertiary alkyl sulfides. It was apparent that the most efficient method to add sulfur to our molecule would be via a Markovnikov addition of a sulfur reagent across the alkene **3**, much like the Lewis acid mediated processes described earlier. Since alkene **3** was not activated by any neighboring groups, the type of sulfur reagent as well as the method of activating the alkene to addition was critical to the success of the hydrothiolation reaction. Recent work by Carreira and co-workers has demonstrated that many different types of functional groups (i.e., azides, nitriles, Cl) can be added to unactivated olefins with complete Markovnikov selectivity using cobalt catalysis (Figure 3).[4] This work inspired us to develop this reaction with sulfur reagents which to the best of our knowledge had not been previously demonstrated in the literature.

Since our system **3** contained sensitive functionalities, it was important to establish that it was compatible with the conditions used in the cobalt-catalyzed reaction. Therefore, we chose Carreira's hydroazidation as a test reaction and found that it provided a good yield of the tertiary azide **7** when used with the cobalt catalyst **5** (Scheme 1).[5] Many mechanistic studies performed by the Carreira group have suggested the formation of a cobalt−hydride complex from the reaction of the cobalt catalyst with phenylsilane.[6] This complex undergoes regioselective olefin hydrocobaltation, positioning the cobalt on the most substituted carbon, followed by the interception of the organocobalt or derived radical by the tosylazide which leads to the regioselectivity found in the reaction.

Since the substrate **3** seemed amenable to this type of reaction, the next goal was to find an appropriate sulfur reagent that could effect the addition to the alkene bond. We envisioned that the reaction would use a mechanism very similar to that seen in the hydroazidation reaction and would therefore provide similar regioselectivity. In order to understand the sulfur reactivity required for the reaction, our first attempts involved the use of commercially available thiophenol **8** or diphenyl disulfide **9**. Unfortunately, both of these reactions provided exclusively the reduced alkene **10** (Figure 4).

The failure of the diphenyl disulfide reaction, in particular, suggested that the sulfur reagent needed to be even more reactive in order to compete with the reduction process. According to the mechanism of the hydroazidation reaction proposed by Carriera in the aforementioned papers, tosyl azide worked well in the reaction not only because the tosyl is a good leaving group but

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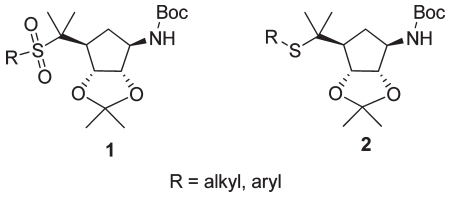


Figure 1. Tertiary sulfone and sulfide targets.

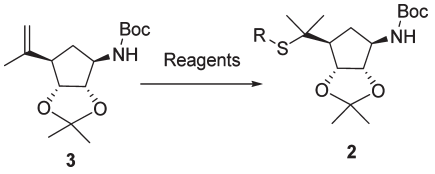


Figure 2. Proposed hydrothiolation reaction of compound **3**.

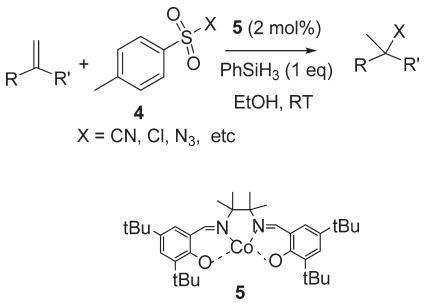


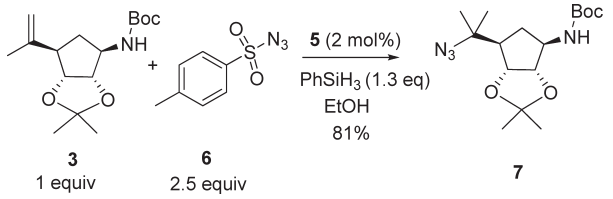
Figure 3. Carreira reaction to functionalize unactivated alkenes.

also because the tosyl activated the nitrogen of the azide toward nucleophilic attack. Since tosyl sulfides are known to react with carbon nucleophiles to provide alkyl sulfides, they were promising substrates to test the hydrothiolation reaction hypothesis.[7] Yokoyama and co-workers recently developed an efficient method of synthesizing tosyl sulfides from the corresponding dialkyl/aryl sulfides and toluenesulfinic acid sodium salt in the presence of iodine.[8] Using this methodology, several tosyl sulfides (**12**−**16**) were synthesized in reasonable yields with the exception of the *tert*-butyl sulfide **14** ,which provided a low yield possibly due to sterics (Table 1).

With these tosyl sulfides in hand, we embarked on the cobalt-catalyzed hydrothiolation reaction. When 3 equiv of tosyl sulfide **12** was combined with compound **3** in the presence of 2 mol % of cobalt catalyst **5** and 1.3 equiv of phenylsilane, an excellent yield (90%) of the desired sulfide product **17** was obtained (Figure 5).

As seen in Table 2, the reaction worked well with many of the other tosyl sulfides to provide both tertiary alkyl and aryl sulfides (**18**−**22**). The only tosyl sulfide that did not provide the desired product **19** was the highly hindered *tert*-butyl sulfide **14** (only biproduct **10** was isolated). The reaction also provided a good yield of the desired product **20** using the commercially available *S*-phenyl benzenethiosulfonate. The electronics of the tosyl sulfides did not seem to have a great impact on the reaction as seen with the yields of entries **21** and **22**. It is important to note that 3 equiv of the tosyl sulfide was found to be optimal in order to ensure complete conversion of the valuable intermediate **3** to the sulfide products. When less than this amount was used in the

Scheme 1. Hydroazidation of 3



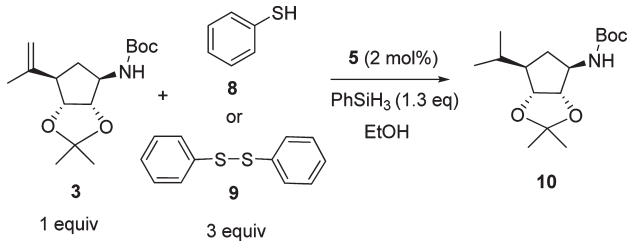
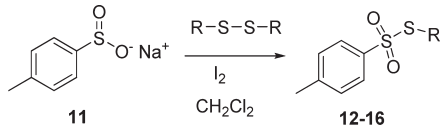


Figure 4. Attempted hydrothiolation with readily available sulfur reagents.

Table 1. Synthesis of Tosyl Sulfides 12−16



entry	R	yield (%)
12	Me	68
13	Et	62
14	*t*-Bu	8
15	3-F-phenyl	85
16	4-OMe-phenyl	86

reaction, compound **10** was occasionally seen as a side product (10−40%).

In order to further test the scope of the reaction, we attempted the hydrothiolation reaction on other substituted alkenes with varying electronics as well as sensitive functionalities. As can be seen from Table 3, the aliphatic alkenes **24** and **25** provide good yields of the desired product with the ester of **25** being unaffected by the reaction conditions. The reaction also worked well on styrene-based alkene **26** though the yield dropped slightly for indene analogue **27** possibly due to polymerization of the indene starting material. The reaction also provided a good yield and complete regioselectivity when performed on a trisubstituted alkene as shown by example **28**.

The sulfides created by this reaction could be useful in the synthesis of sulfones. As shown in Figure 6, a representative oxidation of the sulfide **17** with *m*-CPBA provided an excellent yield of the desired sulfone **29**. It is reasonable to assume that the sulfoxides could also be isolated via this protocol by using only 1 equiv of *m*-CPBA, but this reaction was not attempted.

This paper has described a regioselective, novel methodology to create secondary or tertiary alkyl or aryl sulfides from unactivated alkene substrates with sensitive functionality. The reaction has proven to work well with both electron-deficient and

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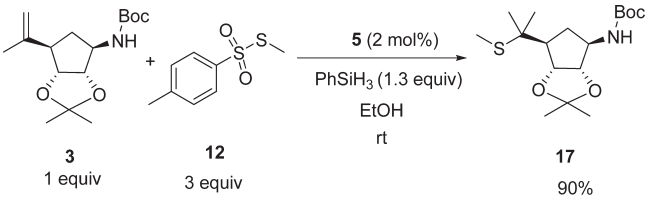
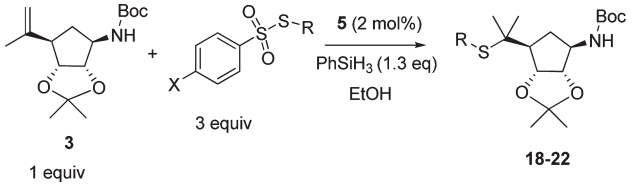


Figure 5. Successful hydrothiolation reaction with **12**.

Table 2. Examination of Various Tosyl Sulfides in the Hydrothiolation Reaction



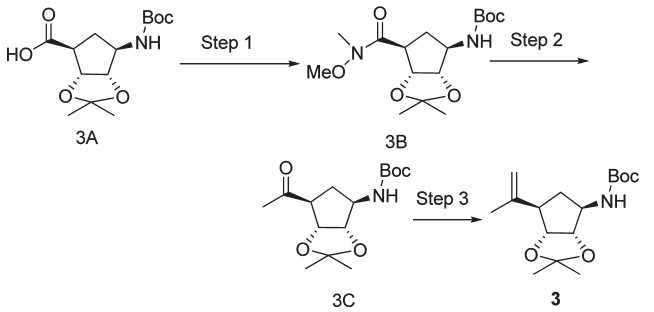
entry	R	X	yield (%)
18	Et	Me	70
19	t-Bu	Me	0
20	phenyl	H	97
21	4-F-phenyl	Me	98
22	4-OMe-phenyl	Me	79

electron-rich sulfur electrophiles as well as different types of substituted alkenes. This methodology provides access to compounds with high levels of complexity in a mild manner and could be useful in medicinal chemistry programs.

EXPERIMENTAL SECTION

General Details. Dry solvents were purchased and used without further purification. Other solvents or reagents were used as obtained except when otherwise noted. Analytical thin layer chromatography (TLC) was performed on precoated silica gel plates and was accomplished with UV light or by staining with basic $KMnO_4$ solution, methanolic sulfuric acid, or Vaughn's reagent. Column chromatography was performed silica gel 60 (particle size 0.040−0.055 mm, 230−400 mesh) or using an automated chromatographic system. NMR specra were recorded in $CDCl_3$ or DMSO-d_6 in 400 MHz (^{1}H NMR), and 100 MHz (^{13}C NMR). Low- and high-resolution mass spectra were obtained using electron spray or FAB ionization methods.

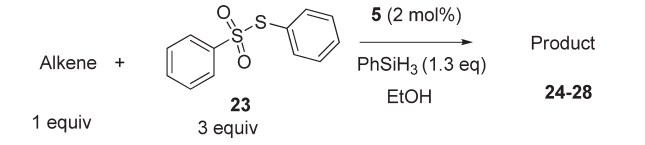
***tert*-Butyl (3a*S*,4*R*,6*R*,6a*R*)-2,2-dimethyl-6-(prop-1-en-2-yl)tetrahydro-3a*H*-cyclopenta[*d*][1,3]dioxol-4-ylcarbamate (3).**

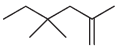
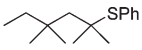
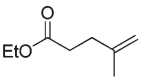
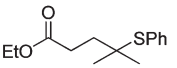
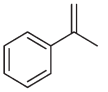
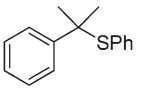
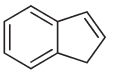
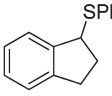
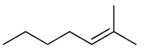
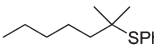


Step 1. Compound **3A** (15.0 g, 50 mmol), 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (11.4 g, 60 mmol), 95% 1-hydroxybenzotriazole (9.5 g, 70 mmol), and *N*,*O*-dimethylhydroxylamine hydrochloride (7.27 g, 75 mmol) were suspended in methylene chloride (250 mL) and treated with triethylamine (21 mL, 150 mmol). The reaction was stirred overnight at room temperature and then quenched with water. The organic layer was washed with saturated sodium bicarbonate, water, and brine, dried over sodium sulfate, and concentrated. Column chromatography (1:1 hexanes/ethyl acetate) provided compound **3B** as a thick colorless oil (13.5 g, 78%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.15 (m, 1H), 4.7 (m, 1H), 4.45 (m, 1H), 4.15 (m, 1H), 3.7 (s, 3H), 3.4 (m, 1H), 3.2 (s, 3H), 2.5 (m, 1H), 1.8 (m, 1H), 1.45 (s, 3H), 1.4 (s, 9H), 1.25 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 175.9, 155.3, 110.8, 87.2, 84.0, 78.9, 61.6, 56.6, 47.7, 32.3, 32.1, 28.5, 26.7, 24.4; HRMS (ESI) calcd for $C_{16}H_{29}N_2O_6$ ($[M + H]^+$) 345.2020, found 345.2025.

Step 2. Compound **3B** (2.3 g, 6.66 mmol) was dissolved in THF (50 mL) and cooled in an ice bath. A solution of 3 M methylmagnesium bromide in diethyl ether (13.3 mL, 40 mmol) was added dropwise, and after 30 min, the reaction was allowed to warm to room temperature and stirred for another 1 h. The reaction was then quenched with saturated ammonium chloride solution and extracted with ethyl acetate twice. The combined organic layers were dried over sodium sulfate and concentrated. Column chromatography (3:1 hexanes/ethyl acetate) provided compound **3C** as a white solid(1.8 g, 90%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.2 (bs, 1H), 4.75 (m, 1H), 4.4 (m, 1H), 4.1 (m, 1H), 3.15 (m, 1H), 2.35 (m, 1H), 2.25 (s, 3H), 1.85 (m, 1H), 1.45 (s, 3H), 1.4 (s, 9H), 1.25 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 210.5, 155.5,

Table 3. Examination of Various Alkenes in the Hydrothiolation Reaction



Entry	Alkene	Product	Yield [%]
24			95
25			86
26			78
27			51
28			90

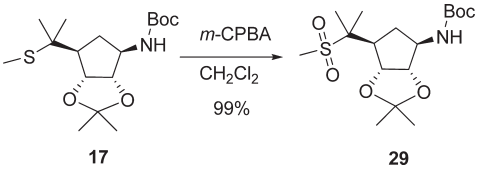


Figure 6. Oxidation of sulfide **17** to sulfone **29**.

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111.3, 86.4, 82.0, 58.8, 56.8, 30.9, 29.3, 28.4, 26.7, 24.4; HRMS (ESI) calcd for $C_{15}H_{26}NO_5$ ([M + H]$^+$) 300.1805, found 300.1808.

Step 3. Triphenylphosphonium bromide (29.2 g, 84 mmol) was suspended in THF (300 mL). A 0.5 M solution of potassium hexamethyldisilazide (160 mL) was added slowly, and the yellow solution was stirred for 30 min at room temperature and then cooled on an ice bath. Compound **3C** (10.0 g, 33.3 mmol) was dissolved in THF (100 mL) and added dropwise to the stirring solution over a 15 min period. The reaction was stirred for 1 h on the ice bath and then warmed to room temperature and stirred for another 2 h. The reaction was then quenched with saturated ammonium chloride solution and extracted with ethyl acetate twice. The combined organic layers were dried over sodium sulfate and concentrated. Column chromatography (4:1 hexanes/ethyl acetate) provided compound **3** as a white solid (7.1 g, 72%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.7 (s, 1H), 4.6 (s, 1H), 4.35 (t, J = 6.25 Hz, 1H), 4.28−4.2 (m, 1H), 3.82−3.74 (m, 1H), 2.45−2.38 (m, 1H), 2.2−2.1 (m, 1H), 1.6 (s, 3H), 1.52−1.42 (m, 1H), 1.35 (s, 3H), 1.3 (s, 9H), 1.1 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 155.5, 145.4, 112.6, 110.2, 85.6, 82.9, 79.5, 57.0, 50.6, 35.3, 28.3, 27.3, 24.9, 21.7; HRMS (ESI) calcd for $C_{16}H_{28}NO_4$ ([M + H]$^+$) 298.2013, found 298.2015.

***tert*-Butyl (3a*S*,4*R*,6*R*,6a*R*)-6-(2-azidopropan-2-yl)-2,2-dimethyltetrahydro-3a*H*-cyclopenta[*d*][1,3]dioxol-4-ylcarbamate (7).** Compound **5** (18 mg, 0.03 mmol) was dissolved in ethanol (2 mL) and then treated sequentially with compound **3** (300 mg, 1 mmol) dissolved in ethanol (8 mL), tosyl azide (497 mg, 2.5 mmol), and phenylsilane (0.16 mL, 1.3 mmol). The reaction was allowed to stir at room temperature for 1.5 h and was quenched with brine and extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate and concentrated. Column chromatography (4:1 hexanes/ethyl acetate) provided compound **7** as a colorless oil (275 mg, 81%): ^{1}H NMR (CD_3OD, 400 MHz) δ 4.45 (t, ^3J = 6.8 Hz, 1H), 4.25 (t, ^3J = 6.2 Hz, 1H), 3.8 (m, 1H), 2.1 (m, 1H), 2.0 (m, 1H), 1.46 (s, 3H), 1.44 (s, 9H), 1.36 (s, 3H), 1.3 (s, 3H), 1.27 (s, 3H); ^{13}C NMR (CD_3OD, 100 MHz) δ 156.5, 112.9, 84.6, 79.6, 78.7, 61.4, 56.2, 52.9, 32.6, 27.2, 26.4, 23.9, 23.7, 23.6; HRMS (ESI) calcd for $C_{16}H_{29}N_4O_4$ ([M + H]$^+$) 341.2183, found 341.2182.

***tert*-Butyl (3a*S*,4*R*,6*R*,6a*R*)-6-isopropyl-2,2-dimethyltetrahydro-3a*H*-cyclopenta[*d*][1,3]dioxol-4-ylcarbamate (10).** Compound **5** (18 mg, 0.03 mmol) was dissolved in ethanol (2 mL) and then treated sequentially with compound **3** (300 mg, 1 mmol) dissolved in ethanol (8 mL), diphenyl disulfide (535 mg, 2.5 mmol), and phenylsilane (0.16 mL, 1.3 mmol). The reaction was allowed to stir at room temperature for 1.5 h, quenched with brine and, extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate and concentrated. Column chromatography (4:1 hexanes/ethyl acetate) provided compound **7** as a white solid (254 mg, 85%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.75 (bs, 1H), 4.3−4.2 (m, 2H), 3.8 (m, 1H), 2.25 (m, 1H), 1.65 (m, 1H), 1.5−1.45 (m, 1H), 1.45 (s, 3H), 1.4 (s, 9H), 1.3−1.2 (m, 1H), 1.25 (s, 3H), 0.96 (d, ^{3}J = 6.4 Hz, 3H), 0.85 (d, ^{3}J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 155.5, 113.0, 85.0, 80.1, 79.5, 56.9, 53.8, 46.3, 33.7, 28.3, 27.9, 27.6, 27.3, 25.3, 21.7, 14.4; HRMS (ESI) calcd for $C_{16}H_{30}NO_4$ ([M + H]$^+$) 300.2169, found 300.2170.

General Procedure A (Synthesis of Tosyl Sulfides). *S-Methyl 4-Methylbenzenesulfonothioate (**12**).* Sodium 4-methylbenzenesulfinate (compound **11**) (10.0 g, 56 mmol), dimethyl disulfide (1.59 g, 17 mmol), and iodine (8.06 g, 32 mmol) were dissolved in methylene chloride (200 mL) and the mixture stirred for 5 h. The reaction was quenched with 10% aqueous sodium thiosulfate and extracted with methylene chloride. The organic layer was dried over sodium sulfate and concentrated. Column chromatography (20:1 hexanes/ethyl acetate) provided compound **12** as a yellow solid (4.39 g, 68%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.8 (d, ^3J = 8.5 Hz, 2H), 7.34 (d, ^3J = 8.3 Hz, 2H), 2.48 (s, 3H), 2.44 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 144.8, 129.9, 127.1, 21.6, 18.1; HRMS (ESI) calcd for $C_8H_{11}O_2S_2$ ([M + H]$^+$) 203.0195, found 203.0194.

*S-Ethyl 4-Methylbenzenesulfonothioate (**13**).* Compound **13** (4.26 g, 62%) was obtained as a colorless oil using the general procedure A: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.8 (d, ^3J = 8.6 Hz, 2H), 7.35 (d, ^3J = 8.2 Hz, 2H), 3.0−2.95 (m, 2H), 2.42 (s, 3H), 1.25 (t, ^3J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 144.6, 141.9, 129.9, 126.9, 30.5, 21.8, 14.1; HRMS (ESI) calcd for $C_9H_{13}O_2S_2$ ([M + H]$^+$) 217.0351, found 217.0352.

*S-tert-Butyl 4-Methylbenzenesulfonothioate (**14**).* Compound **14** (624 mg, 8%) was obtained as a colorless oil using the general procedure A: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.8 (d, ^3J = 8.3 Hz, 2H), 7.32 (d, ^3J = 8.2 Hz, 2H), 2.42 (s, 3H), 1.42 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 144.3, 143.9, 129.6, 127.0, 55.0, 30.9, 21.7; HRMS (ESI) calcd for $C_{11}H_{17}O_2S_2$ ([M + H]$^+$) 245.0665, found 245.0664.

*S-3-Fluorophenyl 4-Methylbenzenesulfonothioate (**15**).* Compound **15** (7.67 g, 85%) was obtained as a white solid using the general procedure A: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.46 (m, 2H), 7.4−7.3 (m 1H), 7.25−7.20 (m, 2H), 7.2−7.14 (m, 2H), 7.1−7.05 (m, 1H), 2.42 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.5, 161.0, 145.1, 140.1, 132.29, 132.25, 130.6, 129.5, 127.5, 123.0, 118.7, 118.5, 21.6; HRMS (ESI) calcd for $C_{13}H_{12}FO_2S_2$ ([M + H]$^+$) 283.0257, found 283.0255.

*S-4-Methoxyphenyl 4-Methylbenzenesulfonothioate (**16**).* Compound **16** (10.5 g, 86%) was obtained as a white solid using the general procedure A (reaction was performed in 1.3× scale): ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.4 (m, 4H), 7.2 (m, 2H), 6.95 (m, 2H), 3.79 (s, 3H), 2.4 (s, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 162.6, 145.4, 140.0, 138.4, 130.2, 127.6, 118.1, 115.7, 56.0, 21.5; HRMS (ESI) calcd for $C_{14}H_{15}O_3S_2$ ([M + H]$^+$) 295.0457, found 295.0455.

General Procedure B for Hydrosulfuration Reactions. *tert-Butyl (3aS,4R,6S,6aR)-2,2-Dimethyl-6-(2-(methylthio)propan-2-yl)-tetrahydro-3aH-cyclopenta[d][1,3]dioxol-4-ylcarbamate (**17**).* Compound **5** (18 mg, 0.03 mmol) was dissolved in ethanol (2 mL) and then treated sequentially with compound **3** (300 mg, 1 mmol) dissolved in ethanol (8 mL), compound **12** (3 mmol), and phenylsilane (0.16 mL, 1.3 mmol). The reaction was allowed to stir at room temperature for 1.5 h, quenched with brine, and extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate and concentrated. Column chromatography (4:1 hexanes/ethyl acetate) provided compound **17** (310 mg, 90%) as a thick colorless oil:^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.8 (bs, 1H, NH), 4.5 (t, J = 6.25 Hz, 1H), 4.2 (t, J = 7.03 Hz 1H), 3.8 (m, 1H), 2.25 (m, 1H), 2.1 (m, 1H), 2.0 (s, 3H), 1.6−1.5 (m, 1H), 1.45 (s, 3H), 1.38 (s, 9H), 1.21 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 155.4, 113.0, 84.8, 80.0, 79.2, 57.0, 53.0, 44.8, 33.6, 28.4, 27.6, 26.7, 26.4, 25.2, 10.8; HRMS (ESI) calcd for $C_{17}H_{32}NO_4S$ ([M + H]$^+$) 346.2047, found 346.2048.

*tert-Butyl (3aS,4R,6S,6aR)-6-(2-(ethylthio)propan-2-yl)-2,2-dimethyltetrahydro-3aH-cyclopenta[d][1,3]dioxol-4-ylcarbamate (**18**).* Compound **18** (251 mg, 70%) was obtained as a colorless oil using the general procedure B: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.7 (bs, 1H, NH), 4.52 (dd, J = 7.03, 5.47 Hz, 1H), 4.23 (t, J = 6.25 Hz, 1H), 3.85 (m, 1H), 2.6−2.5 (m, 2H), 2.32 (m, 1H), 2.12 (m, 1H), 1.59 (m, 1H), 1.5 (s, 3H), 1.42 (s, 9H), 1.32 (s, 3H), 1.3 (s, 3H), 1.28 (s, 3H), 1.22(t, ^3J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 155.5, 113.3, 85.1, 80.2, 79.4, 56.9, 53.9, 46.2, 33.8, 28.2, 27.9, 27.5, 27.3, 25.3, 21.8, 14.4; HRMS (ESI) calcd for $C_{18}H_{34}NO_4S$ ([M + H]$^+$) 360.2203, found 360.2204.

*tert-Butyl (3aS,4R,6S,6aR)-2,2-Dimethyl-6-(2-(phenylthio)propan-2-yl)tetrahydro-3aH-cyclopenta[d][1,3]dioxol-4-ylcarbamate (**20**).* Compound **20** (394 mg, 97%) was obtained as a thick colorless oil using the general procedure B: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.55−7.52 (m, 2H), 7.4−7.25 (m, 3H), 4.7 (bs, 1H, NH), 4.6 (dd, J = 7.8, 6.26 Hz, 1H), 4.25 (dd, J = 7.82, 6.25 Hz, 1H), 3.85 (m, 1H), 2.4 (m, 1H), 2.2 (m, 1H), 1.7 (m, 1H), 1.5 (s, 3H), 1.42 (s, 9H), 1.3 (s, 3H), 1.2 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 155.5, 138.0, 131.5, 129.0, 128.5, 113.0,

84.8, 80.3, 79.8, 57.0, 53.4, 50.1, 34.0, 28.5, 28.0, 27.7, 27.5, 25.4; HRMS (ESI) calcd for $C_{22}H_{34}NO_4S$ ($[M + H]^+$) 408.2203, found 408.2203.

*tert-Butyl (3aS,4R,6S,6aR)-6-(2-(3-Fluorophenylthio)propan-2-yl)-2,2-dimethyltetrahydro-3aH-cyclopenta[d][1,3]dioxol-4-ylcarbamate (**21**).* Compound **21** (417 mg, 98%) was obtained as a thick colorless oil using the general procedure B: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.35−7.25 (m, 3H), 7.05 (m, 1H), 4.7 (bs, 1H, NH), 4.6 (dd, J = 7.8, 5.5 Hz, 1H), 4.28 (dd, J = 7.03, 6.25 Hz, 1H), 3.81 (m, 1H), 2.35 (m, 1H), 2.19 (m, 1H), 1.62 (m, 1H), 1.5 (s, 3H), 1.42 (s, 9H), 1.3 (s, 3 H), 1.22 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.5, 160.5, 133.6, 129.8, 129.6, 124.6, 124.4, 116.2, 116.0, 113.2, 84.8, 80.0, 79.5, 57.0, 53.0, 50.5, 33.4, 28.2, 27.4, 25.2; HRMS (ESI) calcd for $C_{22}H_{33}FNO_4S$ ($[M + H]^+$) 426.2109, found 426.2108.

*tert-Butyl (3aS,4R,6S,6aR)-6-(2-(4-Methoxyphenylthio)propan-2-yl)-2,2-dimethyltetrahydro-3aH-cyclopenta[d][1,3]dioxol-4-ylcarbamate (**22**).* Compound **22** was obtained as a white solid using the general procedure B: ^{1}H NMR (CD_3OD, 400 MHz) δ 7.45 (m, 2H), 6.9 (m, 2H), 4.55 (dd, J = 7.82, 5.47 Hz, 1H), 4.28 (t, 1H), 3.8 (s, 3H), 2.20 (m, 1H), 2.1 (m, 1H), 1.65 (m, 1H), 1.45 (m, 12H), 1.28 (s, 3H), 1.2 (s, 3H), 1.18 (s, 3H); ^{13}C NMR (CD_3OD, 100 MHz) δ 161.1, 157.0, 139.4, 122.4, 114.4, 114.2, 113.1, 84.9, 80.3, 79.1, 56.9, 54.8. 53.1, 49.3, 33.7, 27.8, 27.6, 27.2, 26.9, 26.1, 24.5; HRMS (ESI) calcd for $C_{23}H_{36}NO_5S$ ($[M + H]^+$) 438.2309, found 438.2311.

General Procedure C for Hydrosulfuration Reactions. *Phenyl-(2,4,4-trimethylhexan-2-yl)sulfane (**24**).* Compound **5** (7 mg, 0.012 mmol) was dissolved in ethanol (1 mL) and then treated sequentially with 2,4,4-trimethylhex-1-ene (72 mg, 0.57 mmol) dissolved in ethanol (1 mL), *S*-phenyl benzenesulfonothioate (350 mg, 1.42 mmol), and phenylsilane (0.091 mL, 0.74 mmol). The reaction was allowed to stir at room temperature for 1.5 h, quenched with brine, and extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate and concentrated. Column chromatography (hexanes) provided compound **24** (128 mg, 95%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.6−7.5 (m, 2H), 7.4−7.2 (m, 3H), 1.7 (s, 2H), 1.4−1.25 (m, 8 H), 1.0 (s, 6H), 0.8 (t, J = 7.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 137.8, 129.0, 128.6, 128.3, 52.5, 51.0, 37.0, 35.2, 30.4, 28.5, 8.5; HRMS (ESI) sample run in the presence of acetic acid therefore calcd for $C_{15}H_{25}OS$ ($[M + H]^+$) 253.1621, found 253.1616.

*Ethyl 4-Methyl-4-(phenylthio)pentanoate (**25**).* Compound **25** (123 mg, 86%) was obtained as a lightly yellow colored oil using the general procedure C: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.5 (m, 2H), 7.4−7.3 (m, 3H), 4.15 (q, J = 7 Hz, 2H), 2.6 (t, J = 7.82 Hz, 2H), 1.8 (t, J = 7.81 Hz, 2H), 1.26 (t, J = 7.03 Hz, 3H), 1.23 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.9, 137.9, 131.8, 129.5, 128.5, 60.0, 48.5, 37.0, 30.5, 28.4, 14.0; HRMS (ESI) calcd for $C_{14}H_{21}O_2S$ ($[M + H]^+$) 253.1257, found 253.1256.

*Phenyl(2-phenylpropan-2-yl)sulfane (**26**).* Compound **26** (101 mg, 78%) was obtained as a lightly yellow colored oil using the general procedure C: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.5 (m, 3H), 7.35−7.15 (m, 6H), 7.1 (m, 1H), 1.3 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 146.7, 137.0, 129.1, 128.6, 127.5, 127.1, 126.5, 125.5, 43.8, 25.3; HRMS (ESI) calcd for $C_{15}H_{15}S$ ($[M + H]^+$) 227.0889, found 227.0887.

*(2,3-Dihydro-1H-inden-1-yl)(phenyl)sulfane (**27**).* Compound **27** (66 mg, 51%) was obtained as a lightly yellow colored oil using the general procedure C: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.4 (m, 2H), 7.35−7.18 (m, 7H), 4.8 (m, 1H), 3.0 (m, 1H), 2.85 (m, 1H), 2.55 (m, 1H), 2.22 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 143.8, 142.8, 131.4, 128.9, 127.8, 126.5, 125.0, 124.8, 51.8, 33.6, 30.8; HRMS (ESI) calcd for $C_{15}H_{15}S$ ($[M + H]^+$) 227.0889, found 227.0888.

*(2-Methylheptan-2-yl)(phenyl)sulfane (**28**).* Compound **28** (114 mg, 90%) was obtained as a lightly yellow colored oil using the general procedure C: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.52 (m, 2H), 7.35 (m, 3H), 1.5−1.45 (m, 4H), 1.4−1.25 (m, 4H), 1.24 (s, 6H), 0.92 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 137.5, 132.4, 128.5, 128.3, 49.4, 42.4, 32.3, 28.7, 24.5, 22.7, 14.2.

*tert-Butyl (3aS,4R,6S,6aR)-2,2-Dimethyl-6-(2-(methylsulfonyl)propan-2-yl)tetrahydro-3aH-cyclopenta[d][1,3]dioxol-4-ylcarbamate (**29**).* Compound **17** (160 mg, 0.465 mmol) was dissolved in methylene chloride (8 mL) and treated with 77% *m*-CPBA (259 mg, 1.16 mmol). After being stirred at room temperature for 2 h, the reaction mixture was washed with 1 M potassium carbonate solution, dried over sodium sulfate, and concentrated. Column chromatography (2:1 ethyl acetate/hexanes) provided compound **29** (173 mg, 99%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.95 (bs, 1H, NH), 4.5 (m, 1H), 4.35 (m, 1H), 3.8 (m, 1H), 2.8 (s, 3H), 2.4 (m, 2H), 1.65 (m, 1H), 1.45 (s, 3H), 1.4 (s, 3H), 1.38 (s, 9H), 1.33 (s, 3H), 1.23 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 113.5, 84.0, 79.6, 79.4, 62.6, 56.5, 48.0, 35.5, 34.0, 28.3, 27.5, 25.2, 21.0, 18.5; HRMS (ESI) calcd for $C_{17}H_{32}NO_6S$ ($[M + H]^+$) 378.1945, found 378.1945.

■ ASSOCIATED CONTENT

Supporting Information. ^{1}H NMR and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ REFERENCES

(1) (a) Gleason, J. G. *Org. Compd. Sulphur, Selenium, Tellurium* **1975**, *3*, 190–218. (b) Parry, R. J. *Tetrahedron* **1983**, *39* (8), 1215–1238. (c) Prinsep, M. R. *Stud. Nat. Prod. Chem.* **2003**, *28*, 617–751.

(2) (a) Naya, K.; Okayama, T.; Fujiwara, M.; Nakata, M.; Ohtsuka, T.; Kurio, S. *Bull. Chem. Soc. Jpn.* **1990**, *63* (8), 2239–2245. (b) Ipatieff, V. N.; Pines, H.; Friedman, B. S. *J. Am. Chem. Soc.* **1938**, *60*, 2731–2734.

(3) (a) Weiwer, M.; Chaminade, X.; Bayon, J. C.; Dunach, E. *Eur. J. Org. Chem.* **2007**, *15*, 2464–2469. (b) Weiwer, M.; Coulombel, L.; Dunach, E. *Chem. Commum.* **2006**, *3*, 332–335.

(4) (a) Gaspar, B.; Carreira, E. M. *Ange. Chem. Int. Ed.* **2008**, *47*, 5758–5760. (b) Gaspar, B.; Waser, J.; Carreira, E. M. *Synthesis* **2007**, *24*, 3839–3845. (c) Gaspar, B.; Carreira, E. M. *Ange. Chem. Int. Ed.* **2007**, *46*, 4519–4522. (d) Waser, J; Nambu, H.; Carreira, E. M. *J. Am. Chem. Soc.* **2005**, *127*, 8294–8295.

(5) Synthesis of the catalyst can be found in: Morris, G. A.; Zhou, H.; Stern, C. L.; Nguyen, S. T. *Inorg. Chem.* **2001**, *40*, 322–3227.

(6) Mechanistic elucidation can be found in the following: Waser, J.; Gaspar, B.; Nambu, H.; Carriera, E. M. *J. Am. Chem. Soc.* **2006**, *128*, 11693–11712.

(7) (a) Kohei, O.; Shiro, T. *Tetrahedron.* **2009**, *65* (11), 2244–2253. (b) Piller, F. M.; Knochel, P. *Org. Lett.* **2009**, *11* (2), 445–448.

(8) Fujiki, K.; Tanifuji, N; Sasaki, Y.; Yokoyama, T. *Synthesis* **2002**, *3*, 343–348.