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p-Tolylsulfinyl Amides: Reagents for Facile Electrophilic Functionalization of Olefins

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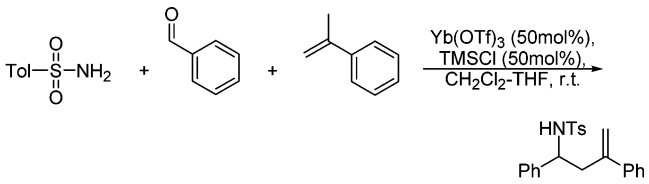
Abstract: A variety of olefins were found to react with sulfinyl amides in the presence of $POCl_3$ to give β-chlorosulfides and β-hydroxysulfides in good yields. In the absence of nucleophiles, *p*-tolylsulfinyl amides were found to react with olefins with the formation of allylsulfoxides.

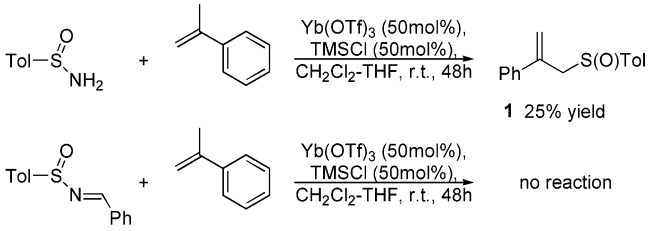
The general utility of sulfur-containing substituents in terms of subsequent elimination, reduction, and substitution makes them broadly applicable in organic synthesis.[1] The compounds containing S(IV) centers possess an additional feature of chirality at sulfur, which makes them targets for stereoselective synthesis. Several protocols with a sulfinyl group as a chiral auxiliary have been developed and utilized in the asymmetric synthesis of biologically active compounds.[2]

Considerable efforts have been devoted to oxidation of sulfides using catalytic amounts of metal complexes that give sulfoxides in good yields and with high enantiomeric excesses.[3] Sulfoxides can also be obtained by direct addition of the sulfinyl group to the double bond. For instance, phenylsulfinyl chloride is known to add to olefins with the formation of β-chlorosulfoxides.[4] Despite several literature precedents for this strategy, the chemistry remains underdeveloped mainly because of the low stability of arenesulfinyl chlorides. These compounds are air- and moisture-sensitive and are normally used directly upon preparation. Moreover, the reaction has fairly limited scope: only aromatic olefins react with arenesulfinyl chlorides. It has been postulated that the sulfinyl group reacts with olefins with the formation of a sulfoxonium cation, stabilized by resonance effects at sulfur.[1] Only a few examples of the electrophilic addition of sulfinyl chlorides to olefins under Lewis acid activation[5] are known. Electron-rich olefins such as silylated enols were found to react with phenylsulfinyl chloride in the presence of $SnCl_4$.[6] An intramolecular version of the sulfinyl chloride addition to the double bond was applied by Eli Lilly in the synthesis of Cefaclor−cephalosporin family of antibiotics.[7]

SCHEME 1



SCHEME 2



Sulfinyl amides are relatively stable compounds compared to the other sulfur(IV) derivatives. We were intrigued by the prospects of their application in olefin functionalization. There appear to be no reported examples of reactions between unsaturated hydrocarbons and sulfinyl amides. Our initial goal was to perform an asymmetric version of the multicomponent ene reaction between tolylsulfinyl amide, aldehyde, and α-methylstyrene, analogous to that reported for the tolylsulfonyl amide (Scheme 1).[8]

However, when tolylsulfonyl amide was replaced by *p*-tolylsulfinyl amide, no reaction was detected by TLC after 1 h. After 48 h, the only isolated product was allylsulfoxide **1** in a disappointing 25% yield. The aldehyde was not consumed in the reaction. In a control experiment, the premade *p*-tolylsulfinyl phenyl imine did not react under these conditions (Scheme 2), which indicated to us that the low yield of sulfoxide **1** was not the result of a background ene reaction.

The survey of reaction conditions is summarized in Table 1. The reaction does not take place without Yb(OTf)$_3$ (Table 1, entry 4). Although the role of TMSCl is presently unclear, its absence substantially increases the reaction time (Table 1, entry 5). The use of TMSOTf instead of TMSCl does not influence the yield of the process. Other Lewis acids such as TiF_4, $TiCl_4$, Ti(O*i*-Pr)$_4$, and $BF_3{\cdot}Et_2O$ were found to be inefficient in promoting the addition.

To investigate the plausible mechanism, enantiomerically pure *p*-tolylsulfinyl amide was synthesized from (*S*)-tolylsulfinyl menthyl ester according to the literature

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TABLE 1. Reaction Conditions for the Allylsulfoxide Formation

entry	NR_2	Lewis acid (equiv)	TMSX (equiv)	time (h)	yield (%)
1	$-NH_2$	$Yb(OTf)_3$ (0.5)	TMSCl (0.5)	48	25
2	$-NH_2$	$Yb(OTf)_3$ (0.1) or $Sc(OTf)_3$ (0.1)	TMSCl or TMSOTf (1 or 2.5)	48	10
3	$-NH_2$	$Yb(OTf)_3$ (0.1)	TMSCl (2.5)	48	34
4	$-CH_2(CH_2)_3CH_2-$		TMSCl (1)	12	0
5	$-CH_2(CH_2)_3CH_2-$	$Yb(OTf)_3$ (1)		12	<10

SCHEME 3

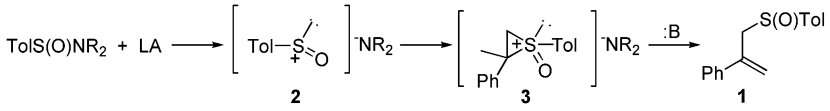
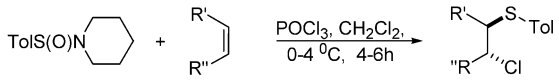
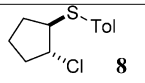
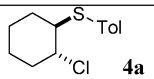
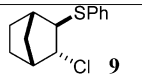
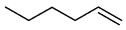
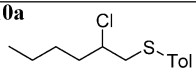
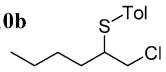
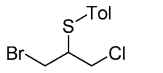
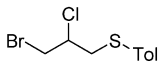


TABLE 2. Synthesis of *β*-Chlorosulfides from Olefins



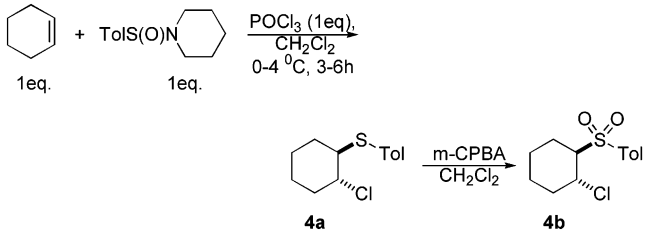
Entry	Olefin	Equivalents of Olefin	Product	Yield (%)
1		2	 **8**	95
2		2	 **4a**	85
3		5	 **9**	94
4		5	**10a**  **10b** 	71 (73:27)[a]
5		5	**11a**   **11b**	56 (86:14)[a]

[a] Ratios of **10a/10b** as well as **11a/11b** were determined by ^1H NMR.

procedure[9] and was submitted to the standard conditions. The product sulfoxide was found to be racemic. On the basis of this observation, the following mechanism can be formulated (Scheme 3). In the presence of a Lewis acid, *p*-tolylsulfinyl amide forms sulfinyl cation **2**, which reacts with the olefin to form an episulfonium salt **3**. The last step of the sequence is deprotonation with the amide anion liberated in situ during the reaction.

In the course of our further investigations into selective functionalization of olefins, we discovered that *p*-tolylsulfinyl piperidine reacts with olefins at 0−4 °C in the presence of $POCl_3$. Surprisingly, the product of the reaction with α-methylstyrene was found to be *β*-sulfide alcohol in 75% yield (Scheme 7).[10] This unexpected

SCHEME 4



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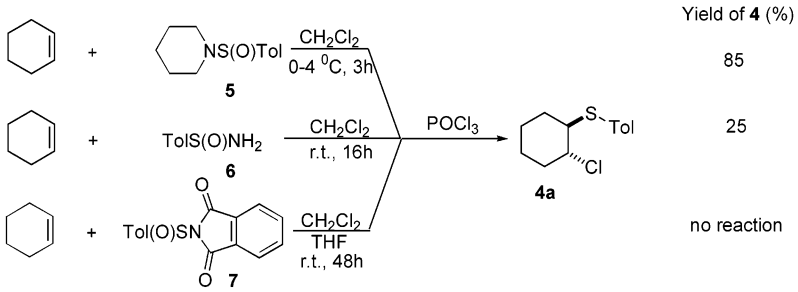
SCHEME 5



reduction of the sulfinyl functionality warranted investigation of the process in more detail.

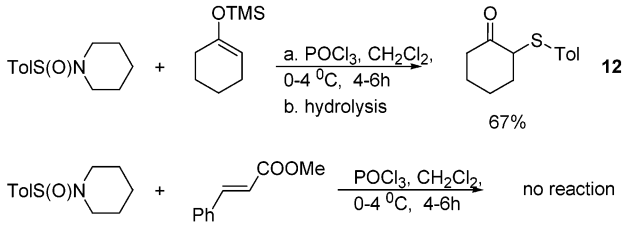
We established that *p*-tolylsulfinyl piperidine reacts with cyclohexene at 0−4 °C in the presence of $POCl_3$ as a Lewis acid and a source of chloride (Scheme 4). ^{1}H NMR spectrum of the reaction mixture after 3 h indicated 100% conversion of the sulfur reagent and corresponded to the formation of *trans*-1-chloro-2-*p*-tolylsulfenylcyclohexane **4a**. The trans configuration of **4a** was confirmed by converting it into sulfone **4b**, for which the value of the vicinal ^{1}H−^{1}H coupling constant is known.[11]

Alkyl-*β*-chlorosulfides can be obtained by addition of sulfinyl chlorides to the olefins. Better yields can be achieved by generating sulfinyl chloride in situ from symmetrical disulfides and Cl_2[12] or SO_2Cl_2.[13] Alternatively, alkyl-*β*-chlorosulfides can be prepared from DMSO and $SOCl_2$ or TMSCl.[14] Well-known difficulties in handling chlorine as well as sulfides and disulfides are among the notable disadvantages of these methods. In addition, in the case of sulfoxide-based reagents, copolymerization of the evolved SO_2 with olefins is known to occasionally take place.[15] This fact explains the limited scope of the olefins that participate in chlorosulfinylation.

To optimize the reaction conditions, other chlorine-containing Lewis acids were screened. Neither $ZnCl_2$ nor $SOCl_2$ induced any reaction, whereas the use of $AlCl_3$ and $TiCl_4$ caused decomposition of the sulfur reagent. The best additive, $POCl_3$, gave *β*-chlorosulfide **4a** in 85% isolated yield. Attempts to increase the yield by varying the amount of $POCl_3$ were not successful. The use of 0.5 equiv as well as the use of 3 equiv of $POCl_3$ reduced the yield. We first assumed that sulfinyl chloride formed in situ was responsible for the product formation. To investigate this possibility, sulfinyl chloride was synthesized and was reacted with cyclohexene at room temperature. The reaction mixture was monitored by ^{1}H NMR, and after 48 h, conversion of the sulfur reagent was found to be only 25%. Attempts to generate sulfinyl amide in situ by adding piperidine to the reaction mixture also yielded only traces of product and unreacted olefin.

The following sulfur reagents were synthesized and compared in their reaction with cyclohexene: tolyl sulfinyl piperidine (**5**), tolyl sulfinyl amide (**6**), and tolyl sulfinyl phthalimide (**7**). The results of the reactions with these reagents are summarized in Scheme 5. As the data indicate, the piperidine derivative is the amide of choice. It was found that 0−4 °C (ice−water mixture bath) was the optimal reaction temperature. Decreasing the temperature to −10 °C dramatically slowed the reaction rate. Increasing the temperature to 20 °C decreased the yield and purity of the product. Dichloromethane was found to be the best reaction medium. No reaction was observed using hexanes as a solvent. The conversion in acetonitrile was found to be only 45% after 12 h.

SCHEME 6



The best results were achieved using 1−1.2 equiv of $POCl_3$ and 2−5 equiv of olefin relative to the sulfinyl amide (0.33 M concentration of the amide reagent in anhydrous dichloromethane). These conditions were applied to a range of substrates (Table 2).

The reaction with cyclic olefins gave *β*-chlorosulfides in good yields. For instance, norbornene was converted into *endo*-3-chloro-*exo*-2-norbornyl-*p*-tolylthioether **9** (Table 2, entry 3). The relative stereochemistry of **9** was determined by ROESY and HSQC (see Supporting Information). In the case of unsymmetrical olefins, the reaction was also found to be regioselective, controlled by electronic rather than steric factors (Markovnikov addition). For instance, 1-hexene and allylbromide gave mixtures of regioisomers in 73:27 and 86:14 ratios, respectively (as determined by ^{1}H NMR).

Electron-rich olefins such as trimethylsilyl enol ether reacted under the reaction conditions with the formation of *β*-ketosulfide in 67% yield, whereas the olefins possessing electron-withdrawing groups (methyl ester of *trans*-cinnamic acid) did not react at all (Scheme 6). In the case of styrene and α-methylstyrene, *β*-chlorosulfides were easily hydrolyzed into the corresponding alcohols on the silica gel column. Otherwise, the hydroxylated products were obtained upon quenching the reaction mixture with saturated aqueous $NaHCO_3$ (Scheme 7).

To interpret the observed results, a mechanism that involves reduction of the sulfinyl group with $POCl_3$ can be proposed. Similar reduction of the sulfonyl group with

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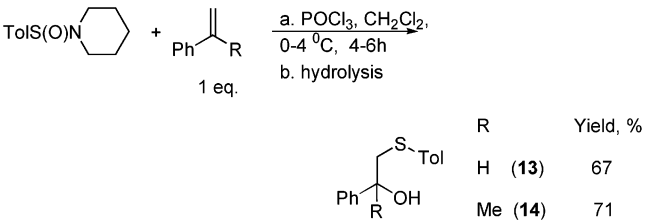
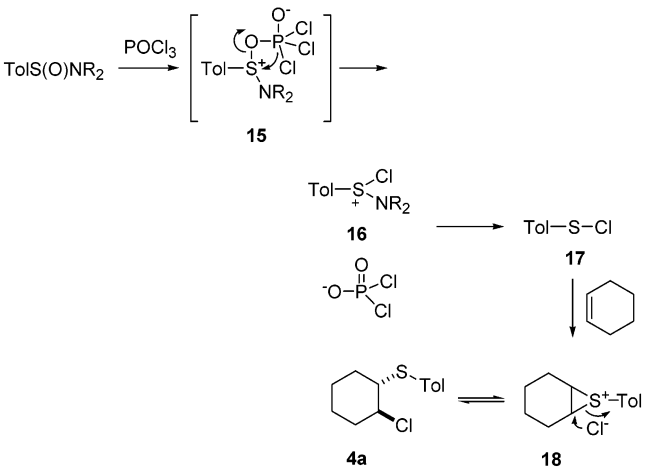
SCHEME 7



SCHEME 8



$TiCl_4$ was recently reported.[16] It is likely that $POCl_3$ coordinates to the oxygen of $TolS(O)NR_2$ (**15**) followed by attack of the chloride ion at the electrophilic sulfur center (Scheme 8). The oxygen atom is eliminated as part of the dichlorophosphate. Tolylsulfenyl chloride **17** is then attacked by the olefin with the formation of the episulfonium salt **18**. The episulfonium cation can be opened with the chloride nucleophile to give *trans*-*β*-chlorosulfide **4a**. The opening of this cationic intermediate with water results in *trans*-*β*-hydroxysulfide.

The new reactivity of sulfinyl amides was uncovered. It was found that tolylsulfinyl piperidine reacts with olefins in the presence of Lewis acids to give allylsulfoxides. It was also found that the sulfinyl group can be reduced in the presence of $POCl_3$ and valuable *β*-chlorosulfides and aryl-*β*-hydroxysulfides can be obtained upon reaction with olefins in good yields. The reaction was applied to a series of olefins and can be used as a new method for the preparation of alkyl-*β*-chlorosulfides and aryl-*β*-hydroxysulfides.

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Experimental Section

1-Methyl-4-[(2-phenyl-propenyl)sulfinyl]-benzene (1). A flame-dried Schlenk flask was charged with 4-methyl-benzenesulfinyl amide (1 mmol), dichloromethane (4 mL), $Yb(OTf)_3$/THF solution (62 mg of $Yb(OTf)_3$, 10 mol % in 1 mL of THF), and 650 μL (5 mmol) of α-methylstyrene under nitrogen. Then, 125 μL (1 mmol) of TMSCl was added to the reaction mixture dropwise at room temperature. After 12 h, no starting material was detected by TLC (hexane/EtOAc = 6/4; $R_f \approx 0.4$). The reaction mixture was concentrated and purified by column chromatography on silica gel (hexane/EtOAc = 6/4). A colorless oil was obtained (87 mg; 34%): ^{1}H NMR δ ($CDCl_3$) 2.38 (s, 3H), 3.96 (AX, dd, ^2J = 1.2 Hz, J = 17.2 Hz, 2H), 5.08 (d, ^2J = 0.8 Hz, 1H), 5.52 (d, ^2J = 0.8 Hz, 1H), 7.22−7.47 (m, 9H); ^{13}C NMR δ ($CDCl_3$) 21.8, 65.1, 119.8, 124.5, 126.1, 128.1, 128.6, 129.7, 137.6, 139.0, 140.3, 141.7;[17] EI MS, *m*/*e* (relative intensity) 78(31), 115(60), 139(13), 256(M^+); HRMS calcd for $C_{16}H_{16}OS$ (M^+) 256.0922, found 256.0921.

Procedure for *β*-Chlorosulfide Synthesis from Olefins. A flame-dried Schlenk flask was charged with 4-methyl-benzensulfinyl amide (1 mmol), olefin (1 or 2 mmol depending on the olefin; see Table 2 and Scheme 7), and dichloromethane (3 mL) under nitrogen. To the reaction mixture was then added 93 μL (1 mmol) of $POCl_3$ at 0−4 °C. The reaction mixture was stirred at 0−4 °C temperature for 3−6 h depending on the substrate. Completion of the reaction was determined by the disappearance of 4-methyl-benzenesulfinyl amide on TLC (hexane/EtOAc = 8/2). The reaction mixture was purified without concentration using flash chromatography on silica gel (pentane/ether = 8/2). In the case of aromatic olefins, *β*-chlorosulfoxides were easily hydrolyzed to the corresponding alcohols on the column (hexane/EtOAc = 8/2).

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of the compounds **1**, **4a**, **4b**, **8**, **9**, **10a**/**10b**, **11a**/**11b**, and **12**−**14** and procedures for the preparation of sulfinyl amides **5**−**7** and their ^{1}H and ^{13}C NMR. This material is available free of charge via the Internet at http://pubs.acs.org.

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