# Arenesulfinamides as New Reagents for the Synthesis of Allylic Sulfoxides

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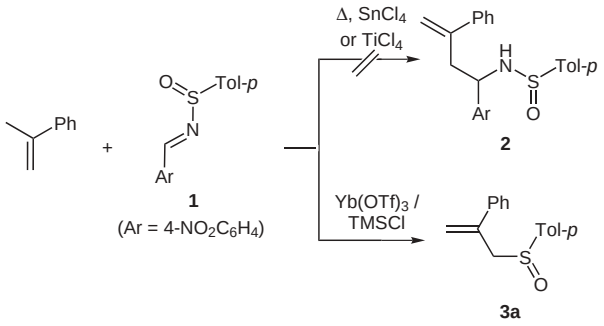
**Abstract:** Reaction of arenesulfinamides with alkenes bearing allylic hydrogens in the presence of $Yb(OTf)_3$/TMSCl led to the corresponding allylic sulfoxides in good yields.

**Key word:** alkenes, sulfinamides, lanthanides, regioselectivity, sulfoxides

A growing number of organosulfur compounds are widely used reagents in organic synthesis.[1] In particular, *N*-sulfinimines are versatile intermediates especially for the preparation of amine derivatives. They display unique reactivity and the presence of the chiral electron withdrawing sulfinyl group makes possible to control addition reactions to the C-N double bond in a highly diastereoselective manner. Besides, *N*-sulfinimines can be easily prepared in enantiopure form and are stable and isolable.[2] Browsing through the reported chemistry of this species we were drawn to the fact that the use of sulfinimines in imino ene reactions, one of the most attractive methodologies for the functionalization of olefins,[3] has not been exploited to date. The only work along these lines dates back one year, in which F. A. Davis and co-workers[4] reported the reaction of *N*-sulfinyl imino esters with allyl benzene. In this case they isolated an unexpected isothiazolidinecarboxylate. To explain the formation of this heterocycle the authors speculated on the possibility of an imino ene reaction followed by cyclization of the corresponding γ,δ-unsaturated α-amino ester intermediate, but the mechanism of this reaction remains unknown. For these reasons, we decided to investigate the behavior of sulfinimines **1** as iminoenophiles.

Unfortunately, the reaction of sulfinimine **1** with α-methyl styrene under thermal conditions or in the presence of the classical Lewis acids for catalyzing ene reactions ($SnCl_4$ and $TiCl_4$) led to complex mixtures of products where the imino ene adduct **2** was not detected (Scheme 1). Unexpectedly, when the reaction was accomplished in the presence of a mixture of $Yb(OTf)_3$ and TMSCl,[5] the allylic sulfoxide **3a** was isolated in 32% yield. The formation of **3a** was rationalized in terms of the reaction of the alkene with the sulfinamide **4a** (Equation 1), which could be formed in situ by hydrolysis of **1** under the reaction conditions. This hypothesis was independently proved by reacting **4a** and α-methyl styrene in the presence of the same catalytic system. The formation of the sulfoxide **3a** from




**Scheme 1** The treatment of α-methyl styrene with the sulfinimine **1** under Lewis acid catalysis led to the allylic sulfoxide **3a** as the only reaction product

**4a** and α-methyl styrene takes place by the attachment of the sulfoxide functionality to the less substituted carbon atom of the C-C double bond, with the removal of one hydrogen atom from the allylic position of the alkene, probably in an $NH_3$ molecule.

Aryl allyl sulfoxides such as **3a** are versatile and valuable building blocks in organic synthesis[6] which proved their remarkable synthetic utility in the syntheses of a variety of functionalized compounds[7] and natural products.[8] Hence, efficient and convenient methods for their preparation are still in demand and a challenging goal. A careful literature survey reveals that the main approach to allylic sulfoxides is the oxidation of allylic sulfides with electrophilic oxidants which features serious drawbacks as the lack of chemoselectivity.[9] Snider[10] and Moissenkov[11] have both reported synthetic methodologies for the preparation of allylic sulfoxides by reacting alkenes with sulfinyl chlorides in the presence of $EtAlCl_2$ and $ZnCl_2$, respectively. Nevertheless, these methodologies are rather less convenient due to the use of the highly moisture sensitive sulfinyl halides[12] as starting materials. On the contrary, arenesulfinamides **4** are very stable and isolable compounds.[13] Therefore, we focused our attention on the use of this new reaction as a potentially valuable process for the synthesis of aryl allyl sulfoxides.

To optimize the synthesis of **3a**, sulfinamide **4a** was reacted with α-methyl styrene under different reaction conditions (solvent, temperature and Lewis acid) (Equation 1, Table 1).

First, the reaction was conducted without Lewis acid at room temperature or under heating but the unchanged starting materials or a complex mixture of products were obtained respectively (Table 1; entries 1 and 2). Lewis acids such as $TiCl_4$, $SnCl_4$ or $ZnCl_2$ only led to complex

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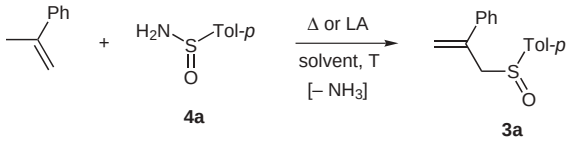
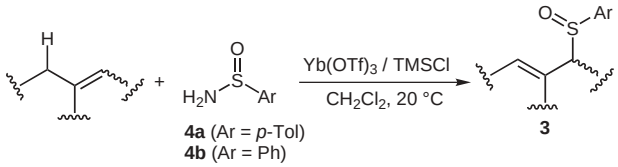



**Equation 1** The reaction of α-methyl styrene with the sulfinamide **4a** was tested under different reaction conditions




**Equation 2** The reaction of alkenes bearing allylic hydrogen atoms with the sulfinamides **4** yielded the corresponding sulfoxides **3** (see Table 2)

mixtures of products or to **3a** but in low yields (entries 3–5). The best results were obtained for the catalytic system $Yb(OTf)_3$/TMSCl, in particular, when the reaction was conducted in $CH_2Cl_2$ at room temperature and 0.5 equivalents and 1 equivalent of both reagents were used, respectively (entry 10). In this case, the sulfoxide **3a** was obtained in excellent yield (90%). Other stoichiometries, solvents or temperatures also provided **3a** although in significantly lower yields (entries 6–9). The presence of TMSCl turned to be essential as the yield of the final product dropped to 33% when the reaction was conducted without this additive (entry 11). Finally, TMSOTf was also a good Lewis acid (entry 12) although not so efficient as $Yb(OTf)_3$/TMSCl.

**Table 1** Reaction Conditions and Yields for **3a**

| Entry | Solvent | T (°C) | Lewis acid (equiv) | Yield **3a** (%)[a] |
|---|---|---|---|---|
| 1 | $CHCl_3$ | 20 | – | 0[b] |
| 2 | Toluene | Reflux | – | 0[c] |
| 3 | $CH_2Cl_2$ | 20 | $TiCl_4$ (1) | 0[c] |
| 4 | Toluene | Reflux | $SnCl_4$ (2) | 19 |
| 5 | $CH_2Cl_2$ | Reflux | $ZnCl_2$ (1) | 30 |
| 6 | Toluene | Reflux | $Yb(OTf)_3$ (1)/TMSCl (1) | 67 |
| 7 | Toluene | Reflux | $Yb(OTf)_3$ (0.5)/TMSCl (1) | 58 |
| 8 | Toluene | 20 | $Yb(OTf)_3$ (0.5)/TMSCl (1) | 81 |
| 9 | $CH_2Cl_2$ | 20 | $Yb(OTf)_3$ (0.1)/TMSCl (1) | 23 |
| **10** | **$CH_2Cl_2$** | **20** | **$Yb(OTf)_3$ (0.5)/TMSCl (1)** | **90** |
| 11 | Toluene | Reflux | $Yb(OTf)_3$ (1) | 33 |
| 12 | $CH_2Cl_2$ | 20 | TMSOTf (1) | 67 |

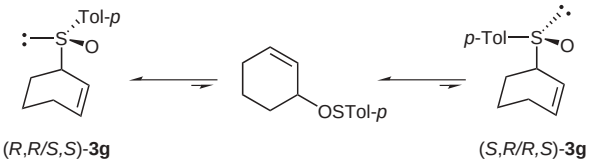
[a] After chromatography (%).
[b] No conversion.
[c] Complex mixture of products.

The generality of this procedure was tested by reacting a series of relatively simple alkenes bearing allylic protons with the two sulfinamides **4a** and **4b** under our standard reaction conditions (Equation 2).[14] The results are compiled in Table 2 (entries 1–7) and reveal that the reaction is quite versatile, proceeding in good yields with a variety of alkenes. As it is shown in Table 2 this process is highly regioselective since the sulfoxide functionality is always introduced at the less substituted carbon atom of the original alkene C-C double bond.

The *E*/*Z*-stereoselectivity was poor (Table 2; entries 4 and 5). Besides, when different types of allylic protons are available (entries 5 and 6) the reaction led to mixtures of regioisomeric allylic sulfoxides (**3e**–**3e′**, **3f**–**3f′**).

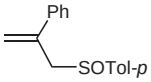
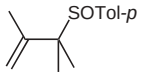
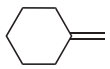
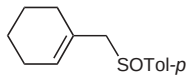
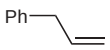
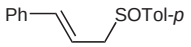
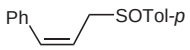
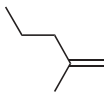
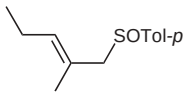
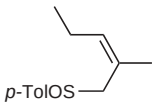
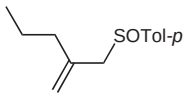
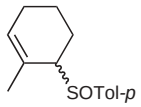
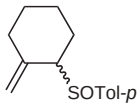
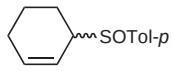
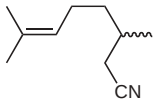
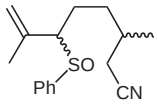
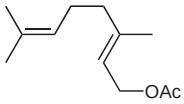
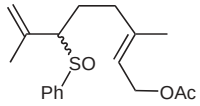
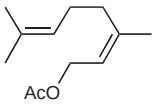
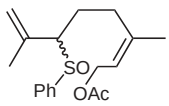
Nevertheless, highly site- and regioselective terminal functionalization of acyclic monoterpenes was carried out by using this new methodology (Table 2; entries 8–10). Thus, their treatment with sulfinamide **4b** under our standard conditions afforded the allylic sulfoxides **3h**–**j** in good yields. When more than one C-C double bond was present the more electron-rich terminal isopropylidene group was always preferably functionalized over the other olefinic portions (entries 9, 10). The potential usefulness of terminally functionalized olefins of this type has received much attention from the viewpoint of C-C bond formation with highly geometric and positional control.[15]

Taking into account the potential stereogenic nature of the sulfur atom in sulfoxides, poor diastereoselectivities were generally achieved in those cases where more than one diastereomer could be obtained (Table 2; entries 6–10) with the exception of **3g** (entry 7), for which a dr of 94:6 was measured and the *R*,*R*/*S*,*S*-diastereomer was the major component.[16] Although the formation of the two diastereomers are expected also in this case, they can interconvert through a [2,3]-sigmatropic sulfoxide/sulfenate rearrangement (Mislow–Braverman–Evans rearrangement; Scheme 2).[17] As it has been previously described this equilibrium is shifted towards the more stable *R*,*R*/*S*,*S*-diastereoisomer as the aryl group is away from the cyclohexene ring (‘*exo*’) in the transition state of the rearrangement leading to it.[16]




**Scheme 2** The interconversion equilibrium between the two diastereomers takes place through a sulfenate intermediate and it is shifted to the *R*,*R*/*S*,*S* one

**Table 2** Yields, Regio- and Diastereomeric Ratio of Allylic Sulfoxides **3**

| Entry | Alkene | Sulfinamide **4** | Allylic sulfoxide **3** | | | Yield of **3** (%)[a] |
|---|---|---|---|---|---|---|
| 1 |  | **4a** |  **3a** | | | 90 |
| 2 |  | **4a** |  **3b** | | | 79 |
| 3 |  | **4a** |  **3c** | | | 60 |
| 4 |  | **4a** |  (*E*)-**3d** |  (*Z*)-**3d** | | 18<br>(*E*)-**3d**:(*Z*)-**3d**<br>56:44 |
| 5 |  | **4a** |  (*E*)-**3e** |  (*Z*)-**3e** |  **3e′** | 93<br>(*E*)-**3e**:(*Z*)-**3e**:**3e′**<br>34:20:46 |
| 6 |  | **4a** |  **3f** |  **3f′** | | 79<br>**3f**:**3f′**<br>85:15<br>dr **3f**<br>68:32<br>dr **3f′**<br>73:27 |
| 7 |  | **4a** |  **3g** | | | 31<br>dr<br>94:6[b] |
| 8 |  | **4b** |  **3h** | | | 75<br>dr<br>25:25:25:25[c] |
| 9 |  | **4b** |  **3i** | | | 62<br>dr<br>59:41 |
| 10 |  | **4b** |  **3j** | | | 63<br>dr<br>59:41 |

[a] The regio- and diastereoisomeric ratios were calculated after chromatography by integration of characteristic signals in the corresponding $^1$H NMR spectra; error ±5% of the stated value.
[b] Configuration of the major diastereoisomer (*R*,*R*/*S*,*S*; see ref.[16]).
[c] The diastereomeric ratio was approximately determined due to the overlapping of all the signals.

The chemistry of sulfinamides has not been thoroughly investigated. However, it is well-known that they react with nucleophiles at the sulfur atom.[13] In this case, the electrophilicity of the sulfinamide is enhanced by activation through coordination with the catalytic system $Yb(OTf)_3$/TMSCl favoring the attack of the nucleophilic alkene. Although the mechanism of the reaction remains unknown, the regiochemistry of the reaction and the fact that the reaction with β-pinene gave a complex mixture of products suggests the intermediacy of a carbenium ion intermediate.

In summary, here we disclose the preparation of aryl allyl sulfoxides from alkenes and sulfinamides in the presence of the catalytic system $Yb(OTf)_3$/TMSCl. The main advantage of the present methodology compared to those

previously reported is the use of easily available and stable sulfinylating reagents, N-unsubstituted sulfinamides **4**, for which no applications in C-S bond forming reactions have been reported before.

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(14) **Typical Procedure for the Synthesis of Allylic Sulfoxides 3:** To a solution of *p*-toluenesulfinamide **1a** (0.15 g; 0.966 mmol) in dry $CH_2Cl_2$ (20 mL), $Yb(OTf)_3$ (0.30 g; 0.483 mmol), α-methyl styrene (0.34 g; 2.899 mmol) and TMSCl (0.11 g; 0.966 mmol) were sequentially added. After the addition, the reaction mixture was stirred at r.t. for 16 h. The inorganic salts were removed by filtration and the filtrate was collected. The solvent was evaporated to dryness and the residue purified by silica gel chromatography eluting with 1:3 to 1:1 EtOAc–hexanes. An analytically pure sample was obtained by recrystallization from $Et_2O$/*n*-pentane (white prisms). Yield (0.22 g, 90%); mp 63–65 °C. IR (neat): 1620, 1597, 1494, 1085, 1045, 810, 778, 701 $cm^{-1}$. $^1H$ NMR (200 MHz, $CDCl_3$): δ = 2.38 (s, 3 H, $CH_3$), 3.82 (d, 1 H, $^2J$ = 12.7 Hz, $CH_2SO$), 4.07 (d, 1 H, $^2J$ = 12.7 Hz, $CH_2SO$), 5.09 (s, 1 H, = $CH_2$), 5.53 (s, 1 H, = $CH_2$), 7.23–7.49 (m, 9 H, aromatics). $^{13}C$ {$^1H$} NMR (50 MHz, $CDCl_3$): δ = 21.3 (q), 64.7 (t), 119.7 (t), 124.3 (2 × d), 126.0 (2 × d), 128.0 (d), 128.4 (2 × d), 129.5 (2 × d), 137.5 (s), 138.9 (s), 140.2 (s), 141.6 (s). Anal. Calcd for $C_{16}H_{16}SO$: C, 74.96; H, 6.29; S, 12.51. Found: C, 74.72; H, 6.47; S, 12.20.

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