Addition of Bis-sulfinyl Anions to Ketones: Stereoselective Synthesis of Allylic Alcohols through Evans–Mislow Rearrangement Based Domino Reactions

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This paper is dedicated to our mentor, colleague, and friend Paul A. Wender on the occasion of his 60th birthday.

Abstract: Enantiopure cyclic allylic alcohols were obtained from cyclic ketones and bis-sulfoxides through a domino reaction mixing anionic and concerted elementary steps. Total transfer of chirality was achieved, presumably through cooperative effects of both sulfoxide units. Depending on the ring size, both sulfinyl groups could be converted, giving $C_2$-symmetric bis-allylic alcohols.

Key words: alkenation, carbanion, pericyclic reaction, sulfoxide, sulfur

The Evans–Mislow rearrangement is an extremely effective and rapid way to access allylic alcohols.\(^1\) Thanks to its pericyclic mechanism, very high control of the double bond geometry is possible and both carbon-to-carbon and sulfur-to-carbon chirality transfer are possible. Thus, the reaction has attracted considerable interest, notably for synthetic purposes. More complex domino reactions that use the Evans–Mislow rearrangement have been devised. The sulfoxide piperidine aldehyde condensation (SPAC) process is of particular interest (Scheme 1).\(^2\)

\[\text{ArSO}_2\text{EWG} + \text{RCHO} \rightarrow \text{RCH(OH)EWG} \]

Scheme 1

In this sequence, an easily accessible α-cyano, β-oxo, or α-methoxycarbonyl sulfoxide \(1\) can be transformed into a functionalized allylic alcohol \(4\) through a process featuring a Knoevenagel reaction, followed by base-triggered double bond migration, sigmatropic rearrangement, and final collapse of the sulfenate from \(3\). Moderate enantioergic excesses were obtained upon starting from enantiopure sulfoxides.\(^3\) The authors proposed that the stereochemical outcome arises from a diastereoselective protonation after the double bond migration. Nonetheless, the control of the allylic center was not optimal. Llera and co-workers introduced enantiopure bis-sulfoxides as partners for the SPAC reaction, but in this particular case the diastereoselectivity was poor.\(^4\) Following our interest in bis-sulfoxides,\(^5\) we wondered whether introducing strain into the Knoevenagel adducts would help the diastereoselectivity. We, thus, decided to focus on ketones instead of aldehydes in the hope that this would make Llera’s approach stereoselective;\(^4,6\) we report herein the results.

Bis-sulfoxide \(5\) was first reacted with cyclohexanone and piperidine, but to no avail (Table 1, entry 1). Thus, \(5\) was deprotonated at $-40^\circ C$ with butyllithium, then treated with cyclohexanone; when the reaction was allowed to warm to room temperature, two new products were obtained. The desired product \(6a\) was isolated in 30% yield together with \(7\), the product of the thiolation of \(5\), in 45% yield. This validated our approach, as the expected cascade was still taking place (Scheme 2).

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However, one half of the starting bis-sulfoxide was reacting as a thiophile, shifting the Evans–Mislow rearrangement toward the allylic alcohol at the expense of the overall yield. Despite this problem, the diastereoselectivity was high, since we did not observe any trace of a minor diastereomer, a noticeable improvement over previous work. This reaction suffered some reproducibility issues (approx. 5–10% variation in the yield of 6a). Upon working with an internal standard, we showed that this was not due to degradation of 6a during the purification step (Table 1, compare entries 2 and 3). Hence, our hypothesis was that the anion of 6a is not stable. To avoid this degradation, we decreased the reaction time. A quick screening of different thiophiles indicated that the lithium salt of thiophenol was optimal (Table 1, entries 4–6). Using these improved conditions, we could isolate a much higher yield of 6a (65%, one diastereomer), and no 7 (Table 1, entry 6).

With these conditions in hand, we endeavored to examine the scope of the reaction. Reaction with cyclopentanone was similar to that of cyclohexanone (Table 1, entry 8). Yet, allyl sulfoxide 8 (37%) was also obtained. 4-tert-Butylcyclohexanone not surprisingly delivered 6c, albeit the yields were slightly lower and the diastereoselectivity was not optimal (Table 1, entry 9). This is most certainly due to the anchoring tert-butyl group. Logically, further reduction of the ring size was detrimental (Table 1, entry 11); the reaction stopped after the initial addition of the

<table>
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<tr>
<th>Entry</th>
<th>Base</th>
<th>Ketone</th>
<th>Thiophile</th>
<th>Product</th>
<th>Yield (%)</th>
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<th>Yield (%) of 7</th>
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<td>–</td>
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<td>6b</td>
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*No reaction.

*b Crude yield (1,4-dimethoxybenzene as internal standard).

*c Allyl sulfoxide 8 (37%) was also obtained.

*d Degradation.

Table 1 Reaction of Bis-sulfoxides with Base and a Ketone
bis-sulfinyl anion to cyclobutanone giving 9; upon dehydration of 9, vinyl bis-sulfoxide 10 was isolated, albeit in low yield (31%), and it did not react further. This nonetheless provides an entry into hetero-substituted strained alkylidencyclobutanes. An increase in the ring size also resulted in efficiency loss (yield and selectivity) of the synthetic process (37% yield for cycloheptanone, 81:19 ds). The use of acyclic ketones, such as pentan-3-one, led only to degradation (Table 1, entry 12), while steric congestion on the cyclic ketone blocked the initial addition (Table 1, entry 10).

The absolute configuration of the newly created stereogenic center on 6a was established by chemical derivatization (Scheme 3). 2-[[[(R)-4-Tolylsulfinyl]methylene]cyclohexanol 6a was converted into 2-acetoxycyclohexanone 11, which was obtained enantiomerically pure. Optical rotation measurement ([\(\alpha\])\(_D^{25}\)) of 11 correlated to the S absolute configuration.\(^7\)

X-ray diffraction analysis of crystals grown from 6b indicated that the absolute configuration was identical to that of 6a (Figure 2). It also established the E configuration for the double bond.

The origin of the stereoselectivity is difficult to assess. We propose the following model: In both transition states A and B, the spectator sulfinyl group would lock the system by occupying the pseudoequatorial position and adopting a staggered conformation putting the sterically demanding tolyl group furthest away from the cyclic allylic methylene. Intermediate A would be favored because B would develop a nonbonding interaction between the tolyl group of the reacting sulfoxide and the cycloalkene ring (Scheme 4). In this regard, the two sulfinyl units would have a coordinated role reminiscent of a cog wheel.

As stated before, we observed that vinyl sulfoxide 6b slowly rearranged to allyl sulfoxide 8. This is in line with reported rates of double bond migration from an exocyclic position toward the inside position.\(^8\) It would eventually lead to a loss of the stereocchemical purity at the sulfur atom, however, the epimerization rate is relatively slow (half life of >1 d in THF at 30 °C) and this process can be halted at lower temperatures (no epimerization after more than two years in the freezer!). Configurationally stable allyl sulfoxides are rare, but not unprecedented.\(^9\) We decided to run a second Evans–Mislow rearrangement on diastereomERICally pure 8 (Scheme 5).
When submitted to triethyl phosphite in refluxing methanol, allyl sulfoxide 8 gave a bis-allyl alcohol that could not be separated from a minor impurity. The crude product was, thus, acylated to give diastereomeric diacetates 12 and 13 in 82% yield in a ratio of 94:6. The major product of the reaction 12 was optically active, thus it is the C2-symmetric isomer. Because the absolute configuration of the first stereogenic center has been shown to be S, we deduced the newly created center also to be S. This double Evans–Mislow could not be extended to the cyclohexylidene series; the migration of the exo-double bond to the intracyclic position could not be achieved. Nonetheless, the reaction in the cyclopentane series is very interesting since chiral bis-allylic alcohols can be obtained with good enantiomeric ratios and these can be further functionalized, via π-allyl palladium intermediates, for example.

The high diastereoselectivity achieved during the reaction can be attributed to the matching directing effects of the stereogenic sulfur and the already installed hydroxy group (Scheme 6). Indeed, a nonbonding interaction between the stereogenic sulfur and the already installed hydroxy group can be attributed to the matching directing effects of the intracyclic position could not be achieved. Nonetheless, the reaction in the cyclopentane series is very interesting since chiral bis-allylic alcohols can be obtained with good enantiomeric ratios and these can be further functionalized, via π-allyl palladium intermediates, for example.

To conclude, we have shown that enantiopure bis-sulfoxides are good starting materials for the preparation of chiral cyclic allylic alcohols from cyclic ketones. The key element that renders the process highly stereoselective is the increased steric hindrance on the carbonyl group. By playing on the cycle strain, one can direct the reaction towards either no allylic sigmatropy (cyclobutane case), single Evans–Mislow rearrangement (cyclohexane family), or double Evans–Mislow rearrangement (cyclopentane series). Work to exploit this reaction, as well as the full potential of bis-sulfoxides in synthesis is under way and will be reported in due course.

All reactions were performed under an argon or N2 atmosphere in anhyd solvents and dried flask. TLC was performed on Merck silica gel 60 F 254 and developed with either a UV lamp (λ = 254 nm) or p-anisaldehyde soln. Column chromatography was performed with silica gel Merck Gaduran SI (40–63 nm) and using Still’s method. Solvents were systematically distilled prior to use. IR spectra were recorded on a Perkin-Elmer 1420 or a Bruker Tensor 27 ATR diamond PIKE spectrophotometer. NMR spectra were recorded at r.t., either at 200 MHz (1H) or 50 MHz (13C) on an AC200 Bruker spectrometer, or at 400 MHz (1H) or 100 MHz (13C) on an ARX400 and an AVANCE 400 Bruker spectrometers. The reference for 1H NMR was residual solvent signal (δ 7.26 for CDCl3) and for 13C NMR it was the solvent central peak (δ 77.0 for CDCl3). Elemental analysis was performed by the Service Régional de Microanalyse de l’Université Pierre et Marie Curie or by ICN (CNRS, Gif-sur-Yvette, France). MS were performed by the Laboratoire Structure et Fonction de Molecules Bioactives (CNRS, UMR 7613, FR 2769, Paris, France). Melting points were obtained on a Reichert apparatus and are uncorrected. Chiral GC was run using a column CP-ChirasilDEX CB (25 m), FID and N2 as carrier gas.

Addition of Bis-sulfoxides to Ketones with Lithium Benzene-thiolate as Thiophile; General Procedure

Bis-sulfoxide 5 was heated overnight in vacuo at 80 °C prior to use. To a soln of 5 (1 equiv) and PhSH (3 equiv) in THF (6 mL/mmol of 5) at –40 °C was added 2.5 M BuLi in hexanes (4.1 equiv). After 1 h, the distilled ketone (3 equiv) was added dropwise. The mixture was then warmed to the relevant temperature (–20 °C for 6b, r.t. for 6a and 6c) until completion (for 6a and 6c, the reaction was stopped after 1 h; degradation was observed when the reaction time was increased), then quenched with aq sat. NH4Cl. The aqueous layer was extracted with CH2Cl2 and the combined organics were washed with brine and dried (MgSO4), filtered, and concentrated in vacuo. The crude product was purified by flash chromatography.

(5)-2-[(R)-4-Tolylsulfinyl]methylene)cyclohexanol (6a)

Following the general procedure from 5 (585 mg, 2.00 mmol) and cyclohexanone (0.62 mL, 3 equiv), chromatography (PE–EtOAc, 70:30 to 0:100) afforded 6a as a white solid; yield: 325 mg (65%); mp 156–158 °C. [α]D 20 = –144.0 (c 1.15, CHCl3).

IR (neat): 3283, 3053, 2983, 1645, 1597, 1081, 810, 790 cm–1.

1H NMR (400 MHz, CDCl3): δ = 1.44–1.59 (m, 3 H, CH2(CH3)2, 1.75–1.88 (m, 2 H, CH2CH3), 2.02–2.11 (m, 2 H, CH2CH3, CHIC3), 2.36 (s, 3 H, p-Tol), 3.24–3.28 (m, 1 H, CHIC3), 4.02–4.05 (m, 1 H, CHO), 6.34 (s, 1 H, =CH). 7.24 (d, J = 8.1 Hz, 2 H, arom), 7.42 (d, J = 8.1 Hz, 2 H, arom).

13C NMR (100 MHz, CDCl3): δ = 21.4 (p-Tol), 24.0 (CH3), 27.3 (CH2), 29.3 (CH3), 36.7 (CH2), 72.2 (CHOH), 124.8 (CH arom), 126.6 (c=CH), 129.9 (CH arom), 140.8 (C arom), 141.2 (C arom), 158.2 (c=CH).

(5)-2-[(R)-4-Tolylsulfinyl]methylene)cyclopentanol (6b)

Following the general procedure from 5 (1.75 g, 6.00 mmol) and cyclopentanone (1.59 mL, 3 equiv), chromatography (CH2Cl2–EtOAc, 75:25 to 10:90) and crystallization (CH2Cl2–EtOAc) afforded 6b as a white crystalline solid; yield: 873 mg (61%); mp 125–130 °C (dec). [α]D 20 = –142.5 (c 1.2, CH2Cl2).

IR (neat): 3283, 3053, 2983, 1645, 1597, 1081, 810, 790 cm–1.

1H NMR (400 MHz, CDCl3): δ = 1.62–1.69 (m, 2 H, CH2CH3), 1.91–1.95 (m, 1 H, CH2CH3), 2.05–2.10 (m, 1 H, CH2CH3), 2.40 (s, 3 H, p-Tol), 2.54–2.62 (m, 1 H, =C=CHH), 2.90–2.95 (m, 1 H, =C=CHH). 4.40 (br s, 1 H, CHO), 6.42 (br s, 1 H, =CH). 7.29 (d, J = 8.4 Hz, 2 H, arom), 7.49 (d, J = 8.4 Hz, 2 H, arom).
13C NMR (100 MHz, CDCl3): δ = 21.0 (=CCH2CH3), 21.6 (p-Tol), 28.5 (=CCH3), 34.3 (=CCHOHCH2), 75.8 (CHOH), 124.5 (CH arom), 127.9 (=CH), 130.3 (CH arom), 141.1 (C arom), 141.5 (C arom), 161.0 (=C).

(2S,4RS)-4-tert-Butyl-2-[(IR)-4-tolylsulfinyl]methylene)cyclohexanol (6c)

Following the general procedure from S (585 mg, 2.00 mmol) and 4-tert-butylcyclohexanone (925 mg, 3 equiv), in THF (doubled concentration, 3 mL/mmol of 5), chromatography (CH2Cl2–EtOAc, 80:20 to 10:90) delivered 6c as two diastereomers in order of elution: minor (42 mg, 7%) and major (215 mg, 35%).

Minor diastereomer

Colorless liquid.

IR (neat): 3000, 1600, 1490, 810 cm−1.

HRMS: m/z [M + Na]+ for C22H24O2S2: 391.1376; found: 391.1385.

Major diastereomer

White solid; mp 131–133 °C.

(5S)-2-[4-Tolylsulfinyl]methyl)cyclopent-2-enol (8)

Following the general procedure from S, bis-sulfinyl alcohol 9 was isolated as a white solid; yield: 60%; mp 128–130 °C.

HRMS: m/z [M + Na]+ for C22H22O2S3: 392.1408; found: 392.1415.

Bis(S)-4-Tolylsulfinyl)methyl 4-Tolyl Sulfide (7)

Following the general procedure, 7 was eluted as a byproduct (less polar fraction) as a white solid; mp 76–78 °C.

Preparation of (±)-2-(4-Tolylsulfinyl)cyclobutane (10)

To a soln of 9 (100 mg, 0.28 mmol, 1 equiv) in MeCN (2 mL) at r.t. were added N-cyclohexyl-N′-(2-[4-methylmorpholino]ethyl)carboxidimide p-toluenesulfonate salt (176 mg, 0.41 mmol, 1.5 equiv) and a catalytic amount of CuCl2 (0.1 equiv). The reaction was heated at 70 °C for 14 h. After cooling, the mixture was diluted with CH2Cl2 and filtered over a short pad of Celite and silica gel, and concentrated in vacuo to give bis-sulfoxide 10 as a white solid; yield: 31%; mp 112–114 °C.

HRMS: m/z [M + Na]+ for C19H18O2S2: 385.1209; found: 385.1212.
Ozone was added to a cold (–78 °C) soln of acetylated solved in pyridine (16 mL) and Ac2O (0.44 mL, 4 equiv) and DMAP mL, 5.82 mmol, 5 equiv) in MeOH (22 mL) was heated at reflux for r.t. for 2.5 h, then diluted with CH2Cl2 and washed with aq 1 M HCl (9 mg, 0.06 equiv) were added at 0 °C. The mixture was stirred at

IR (neat): 2940, 2840, 1730, 1625, 1445, 1370, 1240, 1080 cm–1.

To a soln of

were added at r.t. Ac2O (0.11 mL, 1.13 mmol, 2 equiv) and DMAP

1H NMR (400 MHz, CDCl3):

IR (neat): 2979, 1732, 1372, 1224, 1019 cm–1.

(6) Additions of the anion derived from Aggarwal’s cyclic bis-

The structure of 13 (minor diastereomer) was confirmed by GC-MS and by a characteristic 1H NMR signal (400 MHz, CDCl3): δ = 2.09 (s, 3, H, OAc).

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References


(6) Additions of the anion derived from Aggarwal’s cyclic bis-sulfoxide to not to sterically demanding ketones led to the corresponding bis-sulfanyl alcohols, without further reaction: Aggarwal, V. K.; Franklin, R.; Maddock, J.; Evans, G. R.; Thomas, A.;Mahon, M. F.; Molloy, K. C.; Rice, M. J. J. Org. Chem. 1995, 60, 2174.


