Asymmetric Michael Addition of Chiral Lithiated Sulfonates to Nitroalkenes: Diastereo- and Enantioselective Synthesis of α,β-Disubstituted γ-Nitro and β-Alkoxycarbonyl Methyl Sulfonates

Dieter Enders, Otto Mathias Berner, Nicola Vignola, Wacharee Harnying

Abstract: The diastereoselective Michael addition of lithiated enantiopure sulfonates to nitroalkenes is described. High asymmetric inductions were obtained by using 1,2,5,6-di-O-isopropylidene-α-D-allofuranose as a cheap and easily available chiral auxiliary. Racemization-free cleavage of the auxiliary led to α,β-disubstituted γ-nitro methyl sulfonates. A change of the cleavage conditions resulted in α,β-disubstituted β-alkoxycarbonyl sulfonates via the Meyer reaction (de ≥ 98%, ee ≥ 98%).

Key words: Michael additions, nitroalkenes, sulfonates, chiral auxiliaries, carbohydrates, Meyer reaction

Primary nitro compounds are known as very potent intermediates and consequently have been extensively used in organic synthesis. In recent years, a great variety of asymmetric Michael additions have been developed, including nitroalkenes as excellent acceptors, which are easily obtained via the Henry reaction and subsequent dehydration. In addition to being very reactive, the nitro group can be converted into a broad range of functionalities. The conversion to aldehydes by Nef reaction or the reduction to the amine can be viewed as the most useful transformations of primary nitro compounds. Also of importance is the Meyer reaction where primary nitro compounds are treated with hot concentrated mineral acids to give a carboxylic acid and hydroxylamine. Recently, an efficient procedure for the oxidation of primary nitro compounds to carboxylic acids was reported using sodium nitrite and acetic acid in DMSO.

Although several reports of enantioselective Michael additions to nitroalkenes do exist, no asymmetric 1,4-additions of metalated sulfonates bearing a chiral auxiliary have been described so far. Recently, we have developed an asymmetric synthesis of homotaurine Michael addition of lithiated chiral sulfonates to nitroalkenes. We now wish to report in detail on the 1,4-additions to nitroalkenes and describe the extension of this methodology to obtain a carboxylic acid moiety by making the appropriate changes to the cleavage conditions.

According to our first report on the diastereoselective α-alkylation of chiral lithiated sulfonates using 1,2,5,6-di-O-isopropylidene-α-D-allofuranose as a removable alcohol auxiliary, we have extended our methodology using aliphatic nitroalkenes as further electrophiles. The aim of our project was the asymmetric synthesis of functionalized sulfonic acid derivatives with the simultaneous generation of an additional stereogenic centre as well as introducing the versatile nitro group into the molecule creating bifunctional building blocks. The chiral substrates 1a and 1b (Figure 1) for the Michael additions were obtained by the reaction of the chiral auxiliary with benzylic sulfonyl chlorides, which are commercially available or prepared according to known procedures starting from the corresponding sodium sulfonates.

Figure 1

The enantiopure sulfonates 1a and 1b were metallated with exactly one equivalent of n-butyllithium in tetrhydrofuran and allowed to react with aliphatic nitroalkenes at −90 °C to −95 °C without any side reactions. The Michael adducts 2a–e were obtained in very good to excellent yields (84–99%) and high diastereoselectivities (ds 80–88%. Scheme 1, Table 1).

Deprotonation at −78 °C resulted in lower yields mainly caused by the attack of n-butyllithium on the sulfonate moiety. In all cases only three of the possible four diastereomers could be detected. In the case of 2a, for example, a ratio of 88:8:4 was obtained. In most cases purification via preparative HPLC or recrystallization provided the 1,4-ad-
with high diastereomeric purity. In the case of compound 2d, preparative HPLC purification resulted in a mixture of the two major diastereomers in a ratio of 84:16.

The absolute configuration of the newly formed stereogenic centers was determined to be \( R,R \) by X-ray crystal structure analysis in the case of product 2c and shows that the protons at the \( \alpha \)- and \( \beta \)-position of the major diastereomer are \( \text{anti} \) to each other (Figure 2).\(^{11}\)

By assuming a uniform reaction mechanism, all examples described should possess the same configuration. Further evidence is obtained for this assumption by the fact that the related electrophilic substitution under \( \alpha \)-alkylation shows the same relative topicity.\(^{12}\)

Originally, the removal of the chiral auxiliary to form the corresponding sulfonic acids was achieved by refluxing the Michael adducts in 98% EtOH containing a catalytic amount of Pd(OAc)\(_2\). To isolate the final products in a more accessible form, the sulfonic acids were directly converted with diazomethane to the corresponding \( \alpha,\beta \)-disubstituted \( \gamma \)-nitro methyl sulfonates (Scheme 2). In contrast to the non-functionalized alkylation products, special reaction conditions had to be investigated to obtain high yields. The reaction time had to be minimized in order to suppress a possible Meyer reaction, which may be caused by the liberated sulfonic acid converting the primary nitro group into a carboxylic acid (vide infra). The yields could be significantly increased if additional water was added to the reaction in order to slow the Meyer reaction. In analogy, it has been reported that additional water slows the related Nef-reaction.\(^{16}\) This reduction of the side reactions allowed an increase of reaction time, which resulted in higher yields. In general, the reaction mixture was refluxed until the solution became yellow (approximately 24 h) which was taken as an indication of side products. Thus, the \( \gamma \)-nitro methyl sulfonates, which are precursors of pharmacologically interesting homotaurine derivatives,\(^{17}\) were obtained in moderate to good yields and as virtually pure stereoisomers (Table 2).

![Scheme 1](image1)

**Scheme 1** Asymmetric Michael addition of sulfonates 1 to nitroalkenes to afford the 1,4-adducts (\( R,R \))-2

![Table 1](image2)

**Table 1** Asymmetric Michael Addition of Sulfonates 1 to Nitroalkenes to Afford the 1,4-Adducts (\( R,R \))-2

<table>
<thead>
<tr>
<th>Product R(^1) R(^2)</th>
<th>Yield (%)</th>
<th>dr(^a)</th>
<th>ds (%)</th>
<th>([\alpha]_D^{\text{c,c}}) (c, CHCl(_3))</th>
</tr>
</thead>
<tbody>
<tr>
<td>(( R,R ))-2a H Et</td>
<td>88</td>
<td>4:8:88(^b)</td>
<td>88 (( \geq 99))(^b)</td>
<td>+86.2 (0.98)</td>
</tr>
<tr>
<td>(( R,R ))-2b H n-Pr</td>
<td>90</td>
<td>5:9:86(^b)</td>
<td>86 (( \geq 99))(^b)</td>
<td>+81.2 (0.82)</td>
</tr>
<tr>
<td>(( R,R ))-2c H i-Pr</td>
<td>84</td>
<td>4:10:86(^d)</td>
<td>86 (( \geq 99))(^d)</td>
<td>+101.0 (1.15)</td>
</tr>
<tr>
<td>(( R,R ))-2d H Ph(( CH_3 ))(_2)</td>
<td>99</td>
<td>5:15:80(^e)</td>
<td>80 (84)(^e)</td>
<td>+75.0 (1.10)</td>
</tr>
<tr>
<td>(( R,R ))-2e t-Bu Et</td>
<td>91</td>
<td>87:10:3(^c)</td>
<td>87 (( \geq 98))(^c)</td>
<td>+80.7 (0.94)</td>
</tr>
</tbody>
</table>

\(^a\) In brackets after HPLC.
\(^b\) Determined by HPLC using a chiral stationary phase (Daicel AD, n-heptane–i-propanol, 95:5).
\(^c\) Determined by \( ^{13} \)C NMR.
\(^d\) In brackets after recrystallization.

![Figure 2](image3)

**Figure 2** X-ray crystal structure of 2c

![Scheme 2](image4)

**Scheme 2** Removal of the chiral auxiliary to form the methyl sulfonates (\( R,R \))-4
Confirmation that the cleavage of the auxiliary occurred without epimerization at the \( \alpha \)-position of the sulfonyl group was obtained after the cleavage of compound 2d, which consists of only the two major diastereomers in a ratio of 84:16 (Table 1). After treatment with Pd(OAc)\(_2\) and diazomethane the ratio of the resulting diastereomers of the methyl sulfonate remained the same. This result also proves that the two major diastereomers of the Michael addition are in an anti and syn relationship to each other. The diastereomeric ratio could be easily increased to 97:3 via recrystallization from a diethyl ether–pentane mixture.

We were interested in converting the nitro group into a carboxylic acid derivative via the Meyer reaction in order to demonstrate the versatility of the nitro group to obtain another useful bifunctional building block. Our preliminary results of the cleavage of the auxiliary showed that an increase of reaction time increased also the amount of the Meyer product. Thus, compounds 2a–e were refluxed in an ethanolic solution containing Pd(OAc)\(_2\) and diazomethane the ratio of the resulting diastereomers of the methyl sulfonate remained the same. This result also proves that the two major diastereomers of the Michael addition are in an anti and syn relationship to each other. The diastereomeric ratio could be easily increased to 97:3 via recrystallization from a diethyl ether–pentane mixture.

To confirm that the cleavage of the auxiliary occurs without racemization at the \( \alpha \)-position of the sulfonyl or the newly formed ester group, compound 2b was prepared at 0 °C to obtain a mixture of all diastereomers. Removal of the auxiliary, under the Meyer conditions, yielded 6b as a mixture of stereoisomers. By comparison of the analytical HPLC data of the induced sample (\( R,R \))-6b with the isomeric mixture of 6b none of the other possible stereoisomers could be detected. This also proves that the reaction occurs without racemization and hence we can assume that the relative configuration of the stereogenic centres is analogous to the nitro counterparts 4a–e. Thus, by making a seemingly small change in the cleavage conditions a new bifunctional class of compounds can be envisioned which may be difficult to reach via a different synthetic route. Those compounds bearing the same diester fragment like 6 are found, for example, in the synthesis of side-chain-modified sulfonic analogues of aspartic acids\(^{18}\) or as products after the ozonolysis and oxidative workup of curacin A\(^{19}\).

In conclusion, we have developed a very efficient asymmetric synthesis of \( \alpha,\beta \)-disubstituted \( \gamma \)-nitro methyl sulfonates leading to excellent de- and ee-values. By making appropriate changes to the cleavage conditions the corresponding \( \beta \)-sulfonato carboxylic acid esters 6a–d were obtained with high diastereomeric and enantiomeric excesses demonstrating the versatility of this methodology. Furthermore, additional transformations of the nitro group can be envisioned thus providing an array of useful bifunctional building blocks.

All moisture-sensitive reactions were carried out by using standard Schlenk techniques unless stated otherwise. Solvents were dried and purified by conventional methods prior to use. THF was freshly distilled from sodium–lead alloy under argon. Reagents of commercial quality were used from freshly opened containers or purified by common methods. BuLi (1.6 M in hexane) was purchased from Merck, Darmstadt. Preparative column chromatography used Merck silica gel 60, particle size 0.040–0.063 mm (230–240 mesh, flash). Analytical TLC used silica gel 60 F\( \text{254} \) plates from Merck, Darmstadt.

### Table 2  Removal of the Chiral Auxiliary to Form the \( \gamma \)-Nitro Methyl Sulfonates (\( R,R \))-4

<table>
<thead>
<tr>
<th>Product</th>
<th>( R^1 )</th>
<th>( R^2 )</th>
<th>Yield (%)</th>
<th>de (%)(^b)</th>
<th>ee (%)(^b)</th>
<th>([\alpha]_D^{25}) (c, CHCl(_3))</th>
</tr>
</thead>
<tbody>
<tr>
<td>(( R,R ))-4a</td>
<td>H</td>
<td>Et</td>
<td>71</td>
<td>≥98</td>
<td>≥98</td>
<td>33.1 (0.72)</td>
</tr>
<tr>
<td>(( R,R ))-4b</td>
<td>H</td>
<td>n-Pr</td>
<td>70</td>
<td>≥98</td>
<td>≥98</td>
<td>25.3 (1.15)</td>
</tr>
<tr>
<td>(( R,R ))-4c</td>
<td>H</td>
<td>i-Pr</td>
<td>49</td>
<td>≥98</td>
<td>≥98</td>
<td>49.6 (0.73)</td>
</tr>
<tr>
<td>(( R,R ))-4d</td>
<td>Ph(CH(_2))(_2)</td>
<td>76</td>
<td>68 (93)(^c)</td>
<td>≥98</td>
<td>24.4 (0.62)</td>
<td></td>
</tr>
<tr>
<td>(( R,R ))-4e</td>
<td>t-Bu</td>
<td>Et</td>
<td>63</td>
<td>≥98</td>
<td>≥96</td>
<td>27.6 (0.81)</td>
</tr>
</tbody>
</table>

\(^a\) Measured by \(^1\)H NMR and \(^13\)C NMR.
\(^b\) Based on the de values of the Michael adducts 2a–e.
\(^c\) In brackets after recrystallization.

### Table 3  Removal of the Chiral Auxiliary and Meyer Reaction to Form the \( \beta \)-Alkoxy carbonyl Methyl Sulfonates (\( R,R \))-6

<table>
<thead>
<tr>
<th>Product</th>
<th>( R^1 )</th>
<th>( R^2 )</th>
<th>Yield (%)</th>
<th>de (%)(^a)</th>
<th>ee (%)(^a)</th>
<th>([\alpha]_D^{25}) (c, CHCl(_3))</th>
</tr>
</thead>
<tbody>
<tr>
<td>(( R,R ))-6a</td>
<td>Et</td>
<td>Et</td>
<td>94</td>
<td>≥98</td>
<td>≥98</td>
<td>17.5 (1.08)</td>
</tr>
<tr>
<td>(( R,R ))-6b</td>
<td>n-Pr</td>
<td>Et</td>
<td>84</td>
<td>≥98</td>
<td>≥98</td>
<td>6.0 (1.00)</td>
</tr>
<tr>
<td>(( R,R ))-6c</td>
<td>i-Pr</td>
<td>Et</td>
<td>87</td>
<td>≥98</td>
<td>≥98</td>
<td>14.7 (1.01)</td>
</tr>
<tr>
<td>(( R,R ))-6d</td>
<td>i-Pr</td>
<td>i-Pr</td>
<td>95</td>
<td>≥98</td>
<td>≥98</td>
<td>12.6 (1.04)</td>
</tr>
</tbody>
</table>

\(^a\) Measured by \(^1\)H NMR and \(^13\)C NMR.
\(^b\) Based on the de values of the Michael adducts 2a–e.
\(^c\) Determined by HPLC using a chiral stationary phase (Daicel OD, n-heptane–i-PrOH, 98:2).
Darmstadt. Optical rotation values were measured on a Perkin–Elmer P241 polarimeter. Microanalyses were obtained with a Vario EL element analyzer. Mass spectra were acquired on a Finnigan SSQ7000 (CI 100 eV; EI 70 eV) spectrometer. High resolution mass spectra were recorded on a Finnigan MAT95 spectrometer. IR spectra were taken on a Perkin–Elmer FT/IR 1760. 1H and 13C NMR spectra were recorded on Gemini 300 or Varian Inova 400 and all measurements were performed with tetramethylsilane as internal standard. Melting points were determined on a Tottoli melting point apparatus and are uncorrected.

Michael Adducts (R,R)-2a–e; General Procedure 1 (GP 1)
The enantipure sulfonate 1 (1.0 equiv) was dissolved in anhydrous THF (20 mL per mmol sulfonate). The solution was cooled to between −95 °C and −90 °C. After 30 min BuLi (1.0 equiv) was added dropwise. The solution was stirred for an additional 1 h, after which the nitroalkene (1.5 equiv) was added dropwise over a period of 30 min. The mixture was allowed to stir at −95 °C to −90 °C for 1–3 h. The reaction was quenched by adding pH 7 buffer (2 mL per mmol sulfonate). The mixture was partitioned between CH2Cl2 and H2O. The aq layer was extracted with CH2Cl2 until TLC control of the extract indicated no presence of the product. The combined organic layers were dried (MgSO4), filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO2; Et2O–n-pentane) to give the product mixture.

Removal of the Chiral Auxiliary to Give the a,β-Disubstituted γ-Nitro Methyl Sulfonates (R,R)-4a–e; General Procedure 2 (GP2)
The Michael adduct 2 was dissolved in a solution of EtOH–H2O (20:2 mL per 0.7 mmol). To the solution was added Pd(OAc)2 (20 mol%) and the mixture was refuxed until the yel-

(R,R)-2-Nitromethyl-1-phenylpentane-1-sulfonic Acid Ester (R,R)-2b According to GP1 the sulfonate 1a (474.3 mg, 1.14 mmol) was deprotonated with BuLi (0.72 mL, 1.6 M) and allowed to react with (E)-nitropent-1-ene (201.0 mg, 1.75 mmol in 1.5 mL THF) for 2 h. Work-up and flash chromatography (EtO–n-pentane, 1:3:1) gave (R,R)-2b.

Yield: 547.8 mg (90%); colorless foam; dr 5:9:86, ds 86% (HPLC).

\( \text{H NMR (400 MHz, CDCl}_3\):} \delta = 0.89 \text{ (3, H, J = 7.4 Hz, CH}_3\text{CH}_2\) 1.15–1.27 (m, 1 H, CHCHH\text{CH}_3\) 1.31 \text{[3, H, (O)C(CH)]}, 1.36 \text{[3, H, (O)C(CH)]}, 1.46 \text{[3, H, (O)C(CH)]}, 1.56 \text{[3, H, (O)C(CH)]}, 1.65–1.76 (m, 1 H, CHCHH\text{CH}_3\) 3.14–3.24 (m, 1 H, CHCHH\text{CH}_3\), 3.85 (dd, 1 H, J = 6.0, 8.5 Hz, CHCH\text{OC}], 4.04 (dd, 1 H, J = 6.8, 8.5 Hz, CHCH\text{OC}], 4.09 (dd, 1 H, J = 4.3, 8.7 Hz, CH\text{OC}][CH\text{OC}][CH\text{OC}], 4.14 \text{[1, H, J = 4.1 Hz, CH\text{OC}][CH\text{OC}][CH\text{OC}], 4.27 (dt, 1 H, J = 4.1, 6.6 Hz, CH\text{OC}][CH\text{OC}][CH\text{OC}], 4.66 (dd, 1 H, J = 8.5 Hz, CHCH\text{OC}], 4.69 (dd, 1 H, J = 4.7, 8.5 Hz, CH\text{OC}], 4.72 (dd, 1 H, J = 6.0, 13.7 Hz, CHH\text{NO}], 4.78 (dd, 1 H, J = 6.6, 13.7 Hz, CHH\text{NO}], 5.67 [1, H, J = 3.6 Hz, CH\text{OC}], 7.39–7.45 (m, 3 H, Ar\text{H}], 7.46–7.50 (m, 2 H, Ar\text{H}).

13C NMR (100 MHz, CDCl3): \delta = 9.7 \text{[CH}_3\text{CH}_2\) 25.1, 26.1, 26.5, 26.6 \text{[O(C)CH]], 39.8 \text{[CHCHCH}_3\), 65.2 \text{[CH2O]}, 68.6 \text{[CHSO3]], 74.5 \text{[CHCHCH\text{OC}], 74.8 \text{[CH3CH\text{OC}], 76.7 \text{[CH2O(CH)CH]OC}], 77.3 \text{[CH2O(CH)CH]OC}], 77.7 \text{[CH2O(CH)CH]OC}], 103.4 \text{[CH2O(CH)]}, 110.0 \text{[O(C)CH]], 113.6 \text{[O(C)CH]], 128.9, 129.4, 129.9 \text{(AC\text{H}, 130.3 \text{(AC\text{H}.)}}

MS (CL 100 eV, isobutane): m/z (%) = 518 (11) [M]+, 517 (26) [M]+ + 2, 516 (100) [M]+, 500 (8), 458 (7), 192 (9).

Anal. Calc. For C_{37}H_{33}O_{22}S (515.57): C, 53.58; H, 6.45; N, 2.72. Found: C, 53.39; H, 6.43; N, 2.55.

Removal of the Chiral Auxiliary to Give the α,β-Disubstituted β-Alkoxycarbonyl Methyl Sulfonates (R,R)-6a–d; General Procedure 3 (GP3)
The Michael adduct 2 (1 mmol) was dissolved in EtOH (30 mL). To the solution was added Pd(OAc)2 (20 mol%) and the mixture was refluxed for 7 days. The palladium residues were removed by filtration and the filter cake was washed twice with EtOH. The filtrate was treated with an ethereal solution of diazomethane until the yellow color persisted. The solvent was evaporated under reduced pressure and the crude product was purified by flash column chromatography (SiO2; Et2O–n-pentane).

\( \text{IR (KBr)}: 2980 \text{ (vs), 2937 (s), 2883 (s), 1555 (vs), 1496 (w), 1456 (s), 1437 (m), 1374 (vs), 1319 (m), 1256 (s), 1217 (vs), 1168 (vs), 1118 (vs), 1070 (vs), 1019 (vs), 932 (m), 874 (s), 847 (s), 773 (w), 739 (w), 702 (s), 625 (m), 598 (m), 518 (m) cm}^{-1}\)
(R,R)-3-Methyl-2-nitromethyl-1-phenylbutane-1-sulfonic Acid Ester ([R,R]-2c)

According to GP1 the sulfonate 1a (478.0 mg, 1.15 mmol) was deprotonated with BuLi (0.63 mL, 1.6 M) and allowed to react with (E)-3-methyl-1-nitrobut-1-ene [224.0 mg, 1.95 mmol in THF (2.0 mL)] for 1 h. Work-up and flash chromatography (EtO₂⁻n-pentane, 1:4–1:1) gave ([R,R]-2c).

Yield: 511.4 mg (84%); colorless solid; mp 128 °C; dr 4:10:86, 1b.¹¹C NMR (75 MHz, CDCl₃, major diastereomer): δ = 25.4, 26.4, 26.8, 26.9 [(O)₂C(CH₂)₃], 30.3 (ArCH₂CH₃), 32.3 (ArCH₂CH₂), 38.5 (CH₃COO), 65.6 (CH₂OO), 69.0 (CHSO₃) 74.8 [(CH₂O)C(O)], 75.5 (CH₂O), 77.1 [(CH₂O)CH(O)CH(O)C(O)H], 77.7 [(CH₂O)CH(O)C(O)CH₃], 78.0 (CH(O)CO), 103.8 [(CH₂O)C(O)₃], 110.5 [(O)₂C(CH₃)₃], 110.3 (O)₂C(CH₃)₃, 126.7, 128.5, 129.9, 129.5, 130.0, 135.4 (ArCH₢), 140.2 (ArCO).

MS (Cl, 100 eV, isobutane): m/z (%) = 594 (2) [M⁺ + 3], 593 (4) [M⁺ + 2] 592 (20) [M⁺ + 1], 261 (18), 259 (9), 243 (9), 237 (7), 203 (100), 185 (6).


(R,R)-1-(4-tert-Butylphenyl)-2-nitromethylbutane-1-sulfonic Acid Ester ([R,R]-2e)

According to GP1 the sulfonate 1b (489.7 mg, 1.04 mmol) was deprotonated with BuLi (0.66 mL, 1.6 M) and allowed to react with (E)-1-nitrobut-1-ene [160.0 mg, 1.58 mmol in THF (1.5 mL)] for 1 h. Work-up and flash chromatography (EtO₂-n-pentane, 1:3–1:1) gave ([R,R]-2e).

Yield: 543.7 mg (91%); colorless foam; dr 3:10:87 87% (¹³C NMR). The major diastereomer was separated by preparative HPLC; δ ≈ 98% ([¹³C NMR]; [α]₂⁺ + 807.0 (c 0.94, CHCl₃).

IR (KBr): 2981 (s), 2938 (m), 2915 (m), 1562 (vs), 1497 (w), 1457 (m), 1430 (w), 1385 (vs), 1369 (m), 1240 (s), 1211 (vs), 1177 (vs), 1166 (vs), 1125 (s), 1047 (vs), 1034 (ms), 1017 (vs), 938 (w), 884 (vs), 856 (s), 835 (s), 790 (w), 709 (s), 650 (w), 588 (vs), 598 (m), 521 (m), 508 (m) cm⁻¹.

¹³C NMR (100 MHz, CDCl₃): δ = 16.0 [CH₂CH₃], 20.5 [CH₂CH₂], 25.2, 26.1, 26.5, 26.6 [(O)₂C(CH₃)₂], 28.0 [CH₂CH₂], 43.1 [CH₂CO₂], 65.1 (CH₂OC), 69.7 (CHSO₃), 73.1 [CH₂OCH₂], 74.3 [(O)₂C(O)], 76.6 [CH₂OC(O)CH₂O], 77.3 [CH₂OCH(O)CH₂O], 77.6 (CH₂O), 103.5 [CH₂O], 110.0, 113.5 [(O)₂C(CH₃)], 129.0, 129.4, 129.7 (ArCH₢), 131.3 (ArC₢).

1H NMR (400 MHz, CDCl₃): δ = 0.66 [d, 3 H, J = 6.8 Hz, CH₂CH₃], 0.95 [d, 3 H, J = 7.1 Hz, CH₂CH₃], 1.34 [s, 3 H, (O)₂C(CH₃)₂], 1.36 [s, 3 H, (O)₂C(CH₃)₂], 1.44 [s, 3 H, (O)₂C(CH₃)₂], 1.59 [s, 3 H, (O)₂C(CH₃)₂], 1.80 (deut, 1 H, J = 3.0, 6.9 Hz, CH₂CH₃), 3.35–3.42 (m, 1 H, CH₂CH₃NO₂), 3.64 (dd, 1 H, J = 6.3, 8.5 Hz, CH(OH)CO₂), 4.04 (dd, 1 H, J = 6.9, 8.8 Hz, CH₂CO₂), 4.13 (dd, 1 H, J = 3.8, 8.8 Hz, CH₂OC(O)CH₂OC(O)), 4.26–4.32 (m, 2 H, CH₂OC(O)CH₂OC(O)), 4.51 (d, 1 H, J = 10.2 Hz, CHSO₃), 4.59 (dd, 1 H, J = 5.5, 14.9 Hz, CH₂NO₂), 4.70 (dd, 1 H, J = 4.6, 8.8 Hz, CH₃O), 5.11 (dd, 1 H, J = 4.9, 14.8 Hz, CH₂NO₂), 5.72 [d, 1 H, J = 3.9 Hz, CH₂O], 7.41–7.45 (m, 3 H, ArH), 7.48–7.51 (m, 2 H, ArH).

PAPER

Asymmetric Michael Addition of Chiral Lithiated Sulfonates to Nitroalkenes

Yield: 154.4 mg (71%); colorless solid; mp 59–60°C; de ≥ 98% \(^{(1)}\) (H NMR. \(^{13}\)C NMR, ee ≥ 98% (based on the ds value of the Michael adduct); \([\text{rl}]_{D}^{25} +3.1 (c 0.72, \text{CHCl}_3).\)

IR (KBr): 2980 (w), 2892 (w), 1555 (vs), 1456 (w), 1440 (w), 1385 (s), 1356 (vs), 1335 (s), 1297 (w), 1228 (m), 1165 (vs), 1134 (w), 984 (vs), 851 (w), 833 (s), 782 (s), 735 (m), 700 (s), 623 (m), 586 (m) cm\(^{-1}\).

\(^{13}\)NMR (300 MHz, CDCl\(_3\)): \(
\delta = 0.89 (3 \text{ H}, J = 7.4 \text{ Hz}, \text{CH}_2\text{CH}_3), 1.16–1.32 (1 \text{ m}, \text{CHICHICHI}), 1.58–1.73 (1 \text{ m}, \text{CHICHICH}), 2.99–3.12 (3 \text{ m}, \text{H, } \text{CH(CH)}_3\text{NO})\), 3.62 (2 \text{ s}, 3 \text{ H, SOCH}_3\text{), 4.56 (d, 1 \text{ H}, J = 9.0 Hz, CHSO}_3\text{), 4.71 (dd, 1 \text{ H}, J = 5.5, 14.0 Hz, CHNHO}, 4.84 (dd, 1 \text{ H}, J = 5.5, 14.0 Hz, CHNHO), 7.40–7.50 (m, 5 \text{ H}, \text{ArH}).\)

\(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \(
\delta = 10.2 (\text{CH}_2\text{CH}_3), 21.3 (\text{CH}_2\text{CH}_3), 39.7 (\text{CH}_2\text{CH}_3\text{NO}), 57.4 (\text{CH})_7\text{CH}_2\text{NO})\), 67.1 (CHSO\(_3\)), 74.7 (CH\(_3\text{CH}_2\text{NO})\), 129.2, 129.6, 129.8 (ArCH), 130.9 (ArC).

MS (CI, 100 eV, isolobate): \(m/z\% = 290 (5) [\text{M} + 3], 289 (12) [\text{M} + 2], 288 (84) [\text{M} + 1], 193 (12), 192 (100), 174 (10), 145 (10).


\((R.R')-2\text{-Nitromethyl-1,4-diphenylbutane-1-sulfonic Acid Methyl Ester ([}R.R']-4d)\)

According to GP2 the Michael adduct \((R.R')-2c\) (246.8 mg, 0.47 mmol) was refluxed in a solution of EtOH–H\(_2\)O containing Pd(OAc)\(_2\) (23.2 mg, 0.14 mmol) for 23 h. Work-up and flash chromatography (EtO\(_2\)-n-pentane, 1:9–1:4) gave \((R.R')-4c\).

Yield: 174.4 mg (76%); colorless solid; de 68% \(^{(1)}\) H NMR, \(^{13}\)C NMR, de 93% (after recyclization from EtO\(_2\)-n-pentane 1:1 at –24°C). \(^{13}\)C NMR, ee ≥ 98% (based on the ds value of the Michael adduct); \([\text{rl}]_{D}^{25} +24.4 (c 0.62, \text{CHCl}_3).\)

IR (KBr): 2950 (m), 1602 (m), 1571 (vs), 1543 (vs), 1497 (m), 1456 (s), 1430 (m), 1384 (s), 1363 (vs), 1238 (m), 1273 (63), 1169 (vs), 1042 (w), 1030 (w), 989 (vs), 926 (w), 910 (w), 854 (m), 818 (s), 777 (s), 749 (s), 734 (s), 697 (vs), 644 (w), 597 (m), 580 (vs), 541 (w), 510 (m), 465 cm\(^{-1}\).

\(^{13}\)NMR (400 MHz, CDCl\(_3\), major diastereomer): \(\delta = 1.50–1.61 (1 \text{ m, 1 H, ArCH(CH}_2\text{CH}_2\text{)}, 1.86–1.97 (1 \text{ m, 1 H, ArCH}_2\text{CH}_2\text{), 2.49–2.68 (2 \text{ H, 2 H, ArCH}_2\text{CH}_2\text{), 3.02–3.11 (1 \text{ m, 1 H, CHCH}_2\text{NO})\), 3.60 (s, 3 \text{ H, SOCH}_3\text{), 4.61 (d, 1 \text{ H}, J = 8.7 Hz, CHSO}_3\text{), 4.70 (dd, 1 \text{ H}, J = 5.7, 14.0 Hz, CHNHO), 6.95–7.00 (2 \text{ m, 2 H, ArH}), 7.15–7.26 (3 \text{ m, 3 H, ArH}, 7.36–7.44 (cm, 5 \text{ H, ArH}).\)

\(^{13}\)C NMR (100 MHz, CDCl\(_3\), major diastereomer): \(\delta = 29.9 (\text{ArCH}_2\text{CH}_2\text{), 32.2 (ArCH}_2\text{CH}_2\text{), 37.7 (\text{CHCl}_3\text{), 57.3 (SOCH}_3\text{), 67.0 (CHSO}_3\text{), 74.8 (CHNHO), 128.3, 128.1, 128.4, 129.0, 129.5, 129.6 (ArCH), 130.5, 139.6 (ArC).\)

MS (CI, 100 eV, isolobate): \(m/z\% = 366 (7) [\text{M} + 3], 365 (19) [\text{M} + 2], 364 (100) [\text{M} + 1], 268 (21), 223 (22), 221 (28), 191 (5), 190 (42), 143 (12), 107 (6).


\((R.R')-3\text{-Methyl-2-nitromethyl-1-phenylbutane-1-sulfonic Acid Methyl Ester ([}R.R']-4e)\)

According to GP2 the Michael adduct \((R.R')-2e\) (416.1 mg, 0.73 mmol) was refluxed in a solution of EtOH–H\(_2\)O containing Pd(OAc)\(_2\) (31.0 mg, 0.14 mmol) for 21 h. Work-up and flash chromatography (EtO\(_2\)-n-pentane, 1:9–1:4) gave \((R.R')-4e\).

Yield: 157.5 mg (63%); colorless solid; mp 87–88°C; de ≥ 98% \(^{(1)}\) H NMR, \(^{13}\)C NMR, de ≥ 96% (based on the ds value of the Michael adduct); \([\text{rl}]_{D}^{25} +27.6 (c 0.81, \text{CHCl}_3).\)

IR (KBr): 2966 (s), 2939 (m), 2908 (w), 2875 (w), 1610 (w), 1554 (vs), 1512 (w), 1466 (m), 1432 (m), 1417 (w), 1385 (m), 1352 (v), 1331 (m), 1272 (m), 1256 (w), 1200 (m), 1169 (vs), 1126 (w), 1114

According to GP3 the Michael adduct ([R,R]-2a) (515.6 mg, 1.0 mmol) was refluxed in EtOH (98%: 30 mL) containing Pd(OAc)$_2$ (44.3 mg, 0.2 mmol) for 7 d. Work-up and flash chromatography (Et$_2$O-n-pentane, 1:3) gave ([R,R]-6a).

Yield: 283.2 mg (94%); colorless oil; de ≥ 98% (1H NMR, 13C NMR), ee ≥ 98% (based on the ds value of the Michael adduct); [ol]$_{D}^{25}$ +1.08 (c 1.08, CHCl$_3$).

IR (KBr): 3064 (w), 2977 (s), 2939 (m), 2884 (w), 1723 (vs, Cs$_2$CO$_3$), 1460 (m), 1381 (s), 1354 (vs), 1300 (w), 1266 (w), 1162 (m), 1092 (m), 981 (w), 840 (m), 815 (s), 787 (s), 728 (m), 705 (s), 611 (m), 581 (s), 512 (w), 462 (w) cm$^{-1}$.

1H NMR (300 MHz, CDCl$_3$): δ = 0.81 (t, 3 H, J = 7.42 Hz, CH$_3$(CH$_3$)), 1.10–1.25 (m, 4 H, CH$_2$(CH$_3$)), 1.29 (t, 3 H, J = 7.14 Hz, OCH(CH$_3$)), 3.27 [dt, 1 H, J = 3.57, 10.98 Hz, SO$_2$CH(Ph)CH$_2$], 3.61 (s, 3 H, CH$_3$OSO$_2$), 4.22 (q, 2 H, J = 7.14 Hz, OCH$_2$CH$_3$), 4.56 (d, 1 H, J = 10.99 Hz, SO$_2$CH(Ph)CH$_2$), 5.70–7.50 (m, 5 H, ArH).

13C NMR (75 MHz, CDCl$_3$): δ = 13.8 (CH$_3$(CH$_3$)), 14.4 (OCH$_2$CH$_3$), 20.1 (CH$_2$(CH$_3$)$_2$), 33.3 (CH$_3$(CH$_3$)$_2$), 45.8 (SO$_2$CH(Ph)CH$_3$), 57.4 (CH$_3$OSO$_2$), 61.5 (OCH$_2$CH$_3$), 68.5 (SO$_2$CH(Ph)CH$_2$), 129.5, 129.8, 130.0 (ArCH), 131.9 (ArC), 173.9 (C=O).

MS (EL, 70 eV): m/z (%) = 314 (2) [M$^+$], 219 (92), 173 (20), 145 (100), 135 (99), 117 (36), 91 (68).

Anal. Calc. for C$_{12}$H$_{20}$SO$_5$ (343.43): C, 55.96; H, 7.34; N, 4.08. Found: C, 55.84; H, 7.28; N, 3.88.

(R,R)-2-(1-Methoxysulfonyl-1-phenylmethyl)-3-methylbutyric Acid Ethyl Ester ([R,R]-6b)

According to GP3 the Michael adduct ([R,R]-2b) (529.6 mg, 1.0 mmol) was refluxed in i-PROH (98%: 30 mL) containing Pd(OAc)$_2$ (44.3 mg, 0.2 mmol) for 7 d. Work-up and flash chromatography (Et$_2$O-n-pentane, 1:3) gave ([R,R]-6b).

Yield: 312.0 mg (95%); colorless solid; mp 90°C; de ≥ 98% (1H NMR, 13C NMR), ee ≥ 98% (based on the ds value of the Michael adduct); [ol]$_{D}^{25}$ +12.6 (c 1.64, CHCl$_3$).

IR (KBr): 2972 (s), 2938 (m), 2881 (w), 1715 (vs, Cs$_2$CO$_3$), 1466 (m), 1389 (s), 1374 (m), 1356 (vs), 1273 (s), 1251 (m), 1195 (s), 1164 (vs), 1106 (vs), 980 (vs), 926 (m), 809 (s), 785 (vs), 778 (s), 706 (s), 612 (w), 587 (w), 513 (w), 461 (w) cm$^{-1}$.

1H NMR (300 MHz, CDCl$_3$): δ = 0.74 [d, 3 H, J = 6.92 Hz, CH$_2$(CH$_3$)$_2$], 0.92 [d, 3 H, J = 7.17 Hz, CH$_3$(CH$_3$)$_2$], 1.31 [d, 3 H, J = 6.18 Hz, OCH$_2$(CH$_3$)$_2$], 1.32 [d, 3 H, J = 6.17 Hz, OCH$_2$(CH$_3$)$_2$], 1.70 [m, 1 H, CH$_2$(CH$_3$)$_2$], 3.31 [dd, 1 H, J = 3.96, 11.62 Hz, SO$_2$CH(Ph)CH$_2$], 3.65 (s, 3 H, CH$_3$OSO$_2$), 4.74 (q, 2 H, J = 7.14 Hz, OCH$_2$CH$_3$), 5.13 [d, 1 H, J = 11.84 Hz, SO$_2$CH(Ph)CH$_2$], 7.41 (m, 5 H, ArH).

Acknowledgement

This work was supported by the Deutsche Forschungsgemeinschaft (SFB 380, Graduiertenkolleg 440) and the Fonds der Chemischen Industrie. We thank Degussa AG, BASF AG and Bayer AG for the donation of chemicals. The X-ray structure determination by Dr. J. Industrie. The NOE-measurements by donation of chemicals. The X-ray structure determination by Dr. J. Runsink, RWTH-Aachen, are gratefully acknowledged. W. Bats, University of Frankfurt, and the NOE-measurements by Dr. J. Runsink, RWTH-Aachen, are gratefully acknowledged.

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(13) The experimental data will be reported in a separate full paper on the α-alkylations.

13C NMR (75 MHz, CDCl3): δ = 15.7 [CH(CH3)CH2], 21.3 [CH(CH3)2], 21.7 [OCH(CH3)2], 22.0 [OCH(CH3)2], 27.9 [CH3CH2CHO], 49.5 [SO2CH(Ph)CH], 57.0 [CH2OSO2], 67.0 [SO2CH(Ph)CH], 68.5 [OCH(CHOH)CH], 128.60, 129.0, 130.3 (ArCH), 130.1 (ArC), 170.6 (C=O).

MS (EI, 70 eV): m/z (%): 328 (4) [M+], 269 (8), 233 (75), 191 (100), 173 (81), 145 (64), 131 (68), 105 (19), 91 (83), 69 (18), 57 (8).