Asymmetric Synthesis of α-Substituted β-Amino Sulfones by aza-Michael Addition / α-Alkylation

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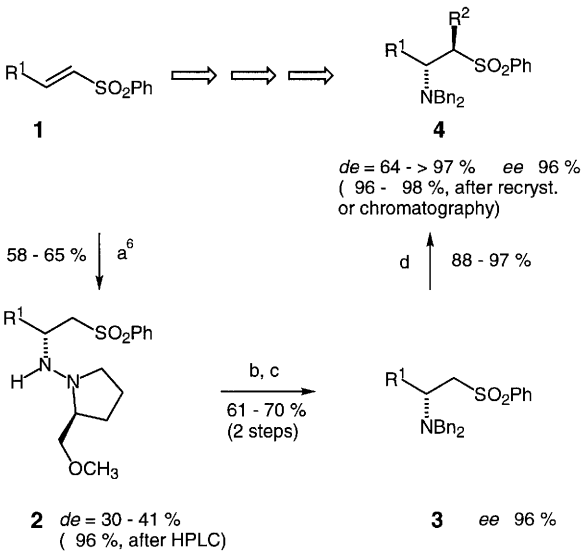
Abstract: The aza-Michael addition of (*S*)-1-amino-2-methoxymethyl-pyrrolidine (SAMP) to alkenyl sulfones (*E*)-**1**, followed by reductive N-N bond cleavage with BH_3·THF and *N*-benzylation yields *N*-benzyl-protected β-amino sulfones (*R*)-**3** with high enantiomeric excesses (*ee* ≥ 96 %). Subsequent α-alkylation of (*R*)-**3** with various electrophiles leads to α-alkyl-β-amino sulfones (*R*,*R*)-**4a-e** in excellent yields (88-97 %) and finally high diastereomeric (*de* = 96 - ≥ 98 %) and enantiomeric purity (*ee* ≥ 96 %). The absolute configuration was determined by X-ray structural analysis and confirmed by NMR spectroscopy (NOE-experiments).

Key words: asymmetric synthesis, Michael addition, α-alkylation, amines, sulfones, alkenyl sulfones

Since sulfones are capable of undergoing a variety of synthetically important transformations, their synthesis and utility has recently received much attention.[1] For instance, sulfones allow α-functionalization, their replacement by other functional groups, and removal by reductive cleavage. In addition, the ease of α-deprotonation allows sulfone anions to take part, for example, in cyclopropanations,[2] aldol-type reactions[3] and α-alkylations,[4] which have been widely used in total synthesis of bioactive compounds.

Cyclic and acyclic β-amino sulfones are known to undergo electrophilic substitutions α to the sulfone group.[5] However, to our knowledge the asymmetric synthesis of acyclic α-substituted β-amino sulfones has not been described. We have recently demonstrated the enantioselective synthesis of β-amino sulfones by aza-Michael addition to alkenyl sulfones.[6] Conjugate addition of (*S*)-1-amino-2-methoxymethylpyrrolidine (SAMP)[7] to (*E*)-alkenyl sulfones (*E*)-**1a-c** has been shown to afford Michael adducts (*R*,*S*)-**2a-c** in the presence of catalytic amounts of ytterbium trifluoromethanesulfonate ($Yb(OTf)_3$) in moderate yields and with moderate to good diastereoselectivities. The epimers could be separated by preparative HPLC to yield virtually diastereomerically pure β-hydrazino sulfones.

We now wish to report an important extension of our previous protocol by α-alkylation to generate two neighbouring stereogenic centres. In order to reach this goal, the prozection of the β-amino function was changed. Thus, after removal of the chiral auxiliary with excess BH_3·THF,[8] subsequent *N*,*N*-dibenzylation[9] allowed access to *N*,*N*-dibenzyl-protected β-amino sulfones (*R*)-**3a-c** in good yields (61 - 70 % over two steps), which were finally alkylated to afford the title compounds (Scheme 1, Table 1).



Scheme 1. *Reagents and Conditions:* a) $Yb(OTf)_3$ (0.1 equiv), THF, add **1** (1.0 equiv), add SAMP, (1.5 equiv), reflux, 3 d; b) BH_3·THF (10 equiv, 1.0 M in THF), THF, reflux, 5 h; rt, HCl (4.0 M), 2 h; c) BnBr (3.0 equiv), Na_2CO_3 (6.0 equiv), CH_2Cl_2/H_2O (4:1), reflux, 2 d; d) LDA (1.3 equiv), TMEDA (1.3 equiv), –78 °C, add (*R*)-**3**, 4 h, R^2X (1.4 equiv, neat, **4a**,**b**,**e**: MeI, **4c**: EtI, **4d**: BnBr) –78 °C → rt, 14 h.

Table 1. Diastereo- and enantioselective synthesis of (*R*,*R*)-**4a-e** by α-alkylation of *N*,*N*-dibenzyl-protected β-amino sulfones (*R*)-**3a-c**.

4	R^1	R^2	yield [a] [%]	*de* [b] [%]	*ee* [c] [%]	$[\alpha]_D^{25}$ [c, $CHCl_3$]
a	Me	Me	91	70 (≥ 98)	≥ 96	– 1.5 (1.43)
b	Et	Me	95	> 97	≥ 96	+ 54.7 (1.30)
c	Et	Et	97	68 (> 97)	≥ 96	+ 19.9 (1.23)
d	Et	Bn	88	64 (> 97)	≥ 96	+14.9 (2.11)
e	BOM [d]	Me	97	68 (≥ 96)	≥ 96	– 12.1 (1.16)

[a] Yield of α-alkylation step (**3** → **4**). [b] Determined by NMR spectroscopy (**4b-e**) and GC analysis (**4a**). The numbers in parentheses refer to the *de*-value after isolation of the major diastereomer by recrystallization (**4a**,**c**,**d**) or column chromatography (**4e**). [c] Based on *de*-values of the corresponding Mosher amides (NMR) of the free amines assuming no overall racemization under subsequent reaction conditions as confirmed by chiral HPLC (Chiralpak AD) of compounds **4b** and **4e**. [d] Benzyloxymethyl.

In a typical experiment the *N*,*N*-dibenzyl-β-amino sulfone (*R*)-**3** was metalated with LDA in the presence of TMEDA. The corresponding electrophile R^2X (methyl iodide, ethyl iodide or benzyl bromide, respectively) was added affording products (*R*,*R*)-**4a-e** after work-up and purification as colorless oils in excellent yields (88 - 97 %), good to high diastereomeric excesses (*de* = 64 - > 97 %) and excellent enantiomeric excesses (*ee* ≥ 96 %). The major diastereomer of each of the products (*R*,*R*)-**4a-e** could be obtained practically diastereomerically pure (*de* ≥ 96 - ≥ 98 %) after isolation of the main epimer by recrystallization ((*R*,*R*)-**4a**,**c**,**d**) or column chromatography ((*R*,*R*)-**4e**), respectively.

The relative and absolute configuration of the newly formed stereogenic centres of the major diastereomer is based on the X-ray structural analysis of crystalline (*R*,*R*)-**4b**.[10] This result was confirmed by NOE-analysis of compounds (*R*,*R*)-**4b** and (*R*,*R*)-**4e**.[11]

In summary, we have synthesized α-alkylated β-amino sulfones **4** of high diastereo- and enantiomeric purity by α-alkylation of *N*,*N*-dibenzyl-protected β-amino sulfones **3**, readily available through aza-Michael addition. These compounds are interesting synthetic intermediates for the creation of enantiopure acyclic and cyclic carbon frameworks with a nitrogen-bearing stereogenic centre and applications in the asymmetric synthesis of bioactive compounds can be envisaged.

General Procedure for the Preparation of Compounds **3** and **4**:[12,13]

(*R*)-**3a-c**: The β-hydrazino sulfones (*R*,*S*)-**2a-c** (10 mmol) were dissolved in THF (100 mL) under an atmosphere of argon. BH_3·THF[8] (100 mmol, 1.0 M in THF) was added, and the rection mixture was heated at reflux for 5 h. After cooling to room temperature the solution was slowly quenched with HCl (4.0 M, 30 mL) and stirred for 2 h at room temperature. The solvent was evaporated under reduced pressure, and the residue was carefully treated with a saturated aqueous solution of Na_2CO_3. The aqueous phase was extracted 3 times with diethyl ether/CH_2Cl_2 (3:1), and the combined organic layers were washed with brine. After drying over Na_2SO_4 the solvent was removed under reduced pressure. Without further purification, the crude product was subjected to reaction with benzyl bromide or with (*R*)-Mosher's acid in order to determine the enantiomeric excess of the amine.

To obtain the *N*,*N*-dibenzyl-β-amino sulfones (*R*)-**3a-c**, the crude amines were dissolved in a mixture of CH_2Cl_2 and water (4:1, 100 mL), and Na_2CO_3 (60 mmol) and BnBr (30 mmol) was added at room temperature.[9] The reaction mixture was heated under reflux for 2 d. After separation of the organic layer the aqueous phase was extracted with CH_2Cl_2, and the combined organic layer was washed with saturated aqueous solution of Na_2CO_3 and then brine. After drying over $MgSO_4$ the solvent was evaporated, and the products were purified by chromatography (SiO_2, diethyl ether/pentane) to obtain (*R*)-**3a-c** as colourless solids.

(*R*,*R*)-**4a-e**: The *N*,*N*-dibenzyl-β-amino sulfones (*R*)-**3a-c** (5 mmol) were dissolved in THF (25 mL) and added to a solution of LDA (6.5 mmol) at –78 °C. TMEDA (6.5 mmol) was added, and the reaction mixture was stirred at –78 °C for 4 h. The corresponding electrophile (7.0 mmol, neat) was slowly added and the solution was stirred for 1 h at –78 °C and then overnight at room temperature. After quenching with pH 7-buffer the aqueous phase was extracted three times with diethyl ether. The combined organic layer was washed with brine, dried over $MgSO_4$, and the solvent was removed under reduced pressure. The products were purified by chromatography (SiO_2, diethyl ether/pentane). Products (*R*,*R*)-**4a-d** were isolated in crystalline form and product (*R*,*R*)-**4e** was obtained as a colourless oil.

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(10) Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 115145. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk). b) Software for preparing the ball-and-stick plot representation: Ball & Stick Version 2.2, Falk, A.; Müller, N.; Schoppel, G.; Webb, L., Linz (Austria), Stafford (UK).
(11) **4b**: NOE's were observed between $CH_3CH_2 \rightarrow CH_3CH$, $CH_2Ph \rightarrow CH_3CH$, $CH_2Ph \rightarrow CH_3CH$ and $SO_2Ph_{ortho} \rightarrow CH_3CHN$.
4e: NOE's were observed between $CH_2Ph \rightarrow CH_3CH$, $CH_3CH \rightarrow CHN$ and $SO_2Ph_{ortho} \rightarrow CHN$.
(12) Selected analytical and spectroscopic data of compounds **2**, **3** and **4**:
(*R*,*S*)-**2b**: $[\alpha]_D^{25} = -109.5$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, C_6D_6): δ 0.67 (t, 3H, *J* = 7.5 Hz, CH_3CH_2), 1.42-1.60 (m, 4H, $CHCH_2CH_2CH_2$ / CH_3CHH / $CHCHHCH_2CH_2$), 1.65-1.74 (m, 1H, CH_3CHH), 1.76-1.83 (m, 1H, $CHCHHCH_2CH_2$), 2.19-2.24 (m, 1H, CHHN), 2.62 (m, 1H, OCH_2CHN), 2.92 (dd, 1H, *J* = 14.3, 3.1 Hz, $CHHSO_2Ph$), 3.05 (dd, 1H, *J* = 14.3, 8.2 Hz, $CHHSO_2Ph$), 3.18 (s, 3H, CH_3O), 3.23-3.29 (m, 2H, CHHN / CHHO), 3.34 (m, 1H, CHNH), 3.57 (dd, 1H, *J* = 9.16, 3.97 Hz, CHHO), 6.97-7.81 (m, 5H, Ph); ^{13}C NMR (125 Hz, C_6D_6): δ 9.0, 21.3, 26.0, 27.0, 54.7, 56.6, 58.5, 58.8, 65.9, 75.6, 128.1, 129.2, 133.3, 140.8; MS: *m/z* 326 (M^+), 281, 266, 214, 171, 155, 143, 141, 129, 125, 114, 111, 84; IR (neat): 3387, 3063, 2965, 2930, 2876, 2827, 1585, 1459, 1447, 1384, 1346, 1305, 1239, 1193, 1148, 1086, 1025, 999, 972, 921, 876, 804, 751, 719, 690, 597, 570, 533 cm^{-1}; Anal. calcd. for $C_{16}H_{26}N_2O_3S$: C 58.87, H 8.03, N 8.58. Found: C 58.42, H: 7.62, N: 8.80.
(*R*)-**3b**: $[\alpha]_D^{25} = +40.28$ (*c* 2.16, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.88 (t, 3H, *J* = 7.0 Hz, CH_3), 1.65 (m, 2H, CH_3CH_2), 2.96 (dd, 1H, *J* = 13.5, 8.2 Hz, $CHHSO_2Ph$), 3.07 (m, 1H, $CHCH_2$), 3.22 (d, 2H, *J* = 13.7 Hz, CHHPh), 3.49 (dd, 1H, *J* = 13.5, 2.2 Hz, $CHHSO_2Ph$), 3.67 (d, 2H, *J* = 13.7 Hz, CHHPh), 7.18-7.85 (m, 15H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$): δ 11.3, 25.6, 53.3, 54.9, 56.1, 127.0, 128.0, 128.9, 129.2, 129.3, 139.0, 139.8; MS: *m/z* 393 (M^+), 364, 302, 238, 196, 105, 91, 77; IR (KBr): 2972, 2923, 1602, 1494, 1380, 1359, 1301, 1199, 1146, 1083, 1028, 836, 791, 745, 698, 622, 589, 566, 548 cm^{-1}; Anal. calcd. for $C_{24}H_{27}NO_2S$: C 73.25; H 6.92; N 3.56. Found: C 72.83; H 6.98; N 3.41.
(*R*,*R*)-**4b**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.89 (t, 3H, *J* = 7.2 Hz, CH_3CH_2), 1.24-1.38 (m, 1H, CH_3CHH), 1.35 (d, 3H, *J* = 7.3 Hz, CH_3CH), 1.54-1.66 (m, 1H, CH_3CHH), 3.29 (d, 2H, *J* = 13.4 Hz, CHHPh), 3.38 (dd, 1H, *J* = 11.6, 2.8 Hz, CH_2CH), 3.52 (q, 1H, *J* = 7.3 Hz, $CHSO_2Ph$), 3.79 (d, 1H, *J* = 13.4 Hz, CHHPh), 7.17-8.80 (m, 15H, Ph); ^{13}C NMR (125 MHz, $CDCl_3$): δ 11.5, 11.6, 20.8, 53.4, 56.4, 58.1, 126.9, 128.0, 128.6, 128.9, 129.0, 133.5, 137.7, 139.4; MS: *m/z* 407 (M^+), 378, 316, 238, 105, 91; IR (neat): 3062, 3028, 2873, 1601, 1494, 1448, 1304, 1240, 1146, 1085, 1027, 1001, 962, 912, 867, 848, 750, 699, 668, 625, 572, 551, 522 cm^{-1}; Anal. calcd. for $C_{25}H_{29}NO_2S$: C 73.67, H 7.17, N 3.44. Found: C 73.47, H 7.09, N 3.40.
(13) All new compounds showed suitable spectroscopic data (IR, MS, NMR) and correct elemental analyses or high-resolution mass spectra.

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