2471.8(3) Å$^3$, $Z = 4$, $\rho_{calcd} = 1.469$ g cm$^{-3}$, $R1 = 0.048$ based on $F$, $wR2 = 0.133$ based on $F^2$. Maximum and minimum heights in the final difference Fourier map are 0.578 and $-0.378$ e Å$^{-3}$. 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-101870. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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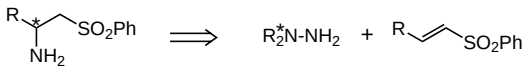
## Enantioselective Synthesis of β-Amino Sulfones by aza-Michael Addition to Alkenyl Sulfones**

Dieter Enders,* Stephan F. Müller, and Gerhard Raabe

*Dedicated to Professor Elias J. Corey on the occasion of his 70th birthday*

The use of sulfones in organic synthesis has become increasingly important in recent years. This has been due to versatile synthetic transformations involving sulfones, for example functionalization in the $\alpha$ position by electrophilic substitution, replacement of the sulfone group with other functional groups, and reductive cleavage of the sulfone group. Furthermore, $\alpha,\beta$-unsaturated sulfones are excellent Michael acceptors and react with a number of carbon and heteroatom nucleophiles, such as alcohols, thiols, and amines.[1] The aza-Michael addition involving C–N bond formation has proven to be a particularly useful synthetic tool.[2] The conjugate addition of an enantiopure ammonia equivalent **B**, bearing a readily cleaved chiral auxiliary, to alkenyl sulfones **C** should provide a novel enantioselective access to synthetically valuable $\beta$-amino sulfones **A**.




**A** **B** **C**

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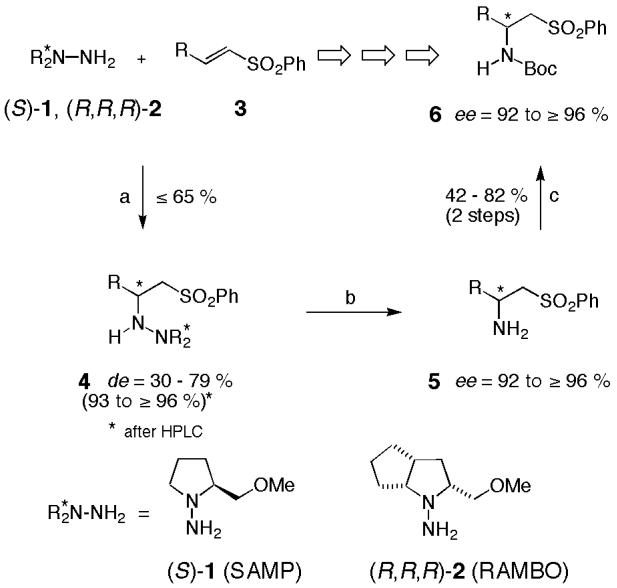
Enantiopure $\beta$-amino sulfones play an important role in physiological processes.[3] Additionally, they readily undergo electrophilic substitution in the $\alpha$ postion and have, for instance, been used as intermediates in the synthesis of $\alpha$-amino acids,[4, 5] amino alcohols,[6] substituted uridines and adenosines,[7] alkaloids,[8] $\beta$-lactams,[9] and nitrogen heterocycles.[10, 11] As early as the 1960s Stirling and McDowell investigated the kinetics of the intermolecular addition of achiral amines to alkenyl sulfones.[12] Today, there exist several procedures for intramolecular[6, 8, 13] and intermolecular[7, 10, 11, 14] aza-Michael additions to alkenyl sulfones. However, to our knowledge the enantioselective aza-Michael addition with a nitrogen nucleophile bearing chirality information, which may subsequently be cleaved, has not been described. We now report the synthesis of the title compounds by asymmetric conjugate addition with (*S*)-1-amino-2-methoxymethylpyrrolidine (SAMP, (*S*)-**1**)[15] as a chiral ammonia equivalent; this species has already been proven to be of great value in asymmetric synthesis. As shown in Scheme 1,




Scheme 1. Enantioselective synthesis of $\beta$-amino sulfones by aza-Michael addition on alkenyl sulfones. a) 1.5 equiv of nitrogen nucleophile (*S*)-**1** or (*R*,*R*,*R*)-**2** per equiv of sulfone **3**, $Yb(OTf)_3$ (0.1 equiv), THF, room temperature (RT) for 20 d (procedure A) or heating at reflux for 3 d (procedure B); b) $BH_3 \cdot THF$ (10.0 equiv, 1N in THF), THF, reflux, 5 h; HCl (4N), RT, 2 h; c) $Boc_2O$ (10.0 equiv), $Et_3N$, MeOH, RT, 2 d. OTf = trifluoromethanesulfonate.

conjugate addition of (*S*)-**1** to (*E*)-alkenyl sulfones (*E*)-**3a–e** afforded Michael adducts (*R*,*S*)-**4a–e** in the presence of catalytic amounts of ytterbium trifluoromethanesulfonate ($Yb(OTf)_3$)[16] in moderate chemical yields and with moderate to good diastereoselectivities. The epimers could be separated by preparative HPLC to yield virtually diastereomerically pure $\beta$-hydrazino sulfones (*R*,*S*)-**4a–e** ($de = 93$ to greater than 96%, Table 1). The absolute configuration of the newly formed stereogenic center of the major diastereomer was determined by X-ray structural analysis of crystalline (*R*,*S*)-**4b** (Figure 1).[17, 18]

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Table 1. Yields and diastereomeric excesses of $\beta$-hydrazino sulfones **4** prepared by conjugate addition of SAMP to (*E*)-alkenyl sulfones **3**.

| Product | R[a] | Yield [%][b] | Method | *de* [%][c, d] |
|---|---|---|---|---|
| (*R*,*S*)-**4a** | Et | 42 | A | 64 ($\geq$96) |
| (*R*,*S*)-**4a** | Et | 58 | B | 40 ($\geq$96) |
| (*R*,*S*)-**4b** | *i*Pr | 25 | A | 79 ($\geq$96) |
| (*R*,*S*)-**4b** | *i*Pr | 52 | B | 43 ($\geq$96) |
| (*R*,*S*)-**4c** | *i*Bu | 34 | A | 54 (93) |
| (*R*,*S*)-**4c** | *i*Bu | 58 | B | 44 (93) |
| (*R*,*S*)-**4d** | *c*Hex[e] | 6 | A | 61 ($\geq$96) |
| (*R*,*S*)-**4d** | *c*Hex | 35 | B | 50 ($\geq$96) |
| (*R*,*S*)-**4e** | BOM[f] | 32 | A | 36 ($\geq$96) |
| (*R*,*S*)-**4e** | BOM | 65 | B | 30 ($\geq$96) |

[a] 2-Aryl-substituted alkenyl sulfones are not suitable as Michael acceptors in the aza-analogous conjugate addition. [b] Yield of isolated **4**. The yield based on the conversion is usually 90–95%. [c] The *de* values were determined by $^1$H NMR spectroscopy (Varian Gemini 300-MHz spectrometer). [d] The numbers in parentheses refer to the *de* value after resolution of the diastereomers by HPLC ($SiO_2$, diethyl ether/pentane 3/1). [e] cHex = cyclohexyl. [f] BOM = benzyloxymethyl.

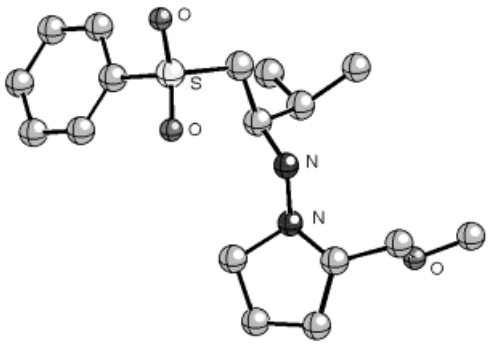


Figure 1. Structure of $\beta$-amino sulfone (*R*,*S*)-**4b**.[19]

Alternatively, (*R*,*R*,*R*)-2-amino-3-methoxymethyl-azabicyclo[3.3.1]octane (RAMBO, (*R*,*R*,*R*)-**2**), first synthesized as its enantiomer SAMBO by Martens et al.,[20] can be employed as the nitrogen nucleophile. This compound may be obtained by a five-step reaction sequence[21] from the benzyl ester of (*R*,*R*,*R*)-2-azabicyclo[3.3.0]octane-3-carboxylic acid, a precursor to the angiotensin converting enzyme (ACE) inhibitor Ramipril from the Hoechst AG.[22] With (*R*,*R*,*R*)-**2** as a nucleophile, considerably higher selectivities were obtained than with (*S*)-**1**. The separation of the diastereomers by means of HPLC was also feasible in this case (Table 2).

Table 2. Yields and diastereomeric excesses of $\beta$-hydrazino sulfones **4** prepared by conjugate addition of RAMBO to (*E*)-alkenyl sulfones **3** (procedure A).

| Product | R[a] | Yield [%][b] | *de* [%][c,d] |
|---|---|---|---|
| (*S*,*R*,*R*,*R*)-**4a** | Et | 46 | 82 ($\geq$96) |
| (*S*,*R*,*R*,*R*)-**4b** | *i*Pr | 21 | $\geq$96 |
| (*S*,*R*,*R*,*R*)-**4c** | *i*Bu | 32 | 90 ($\geq$96) |
| (*S*,*R*,*R*,*R*)-**4d** | *c*Hex | 29 | 94 |
| (*S*,*R*,*R*,*R*)-**4e** | BOM | 29 | 90 |
| (*S*,*R*,*R*,*R*)-**4f** | *n*Bu | 45 | 86 ($\geq$96) |

[a] 2-Aryl-substituted alkenyl sulfones are not suitable as Michael acceptors in the aza-analogous conjugate addition. [b] Yield of isolated **4**. The yield based on the conversion is usually 90–95%. [c] The *de* values were determined by $^1$H NMR spectroscopy (Varian Gemini 300-MHz spectrometer). [d] The numbers in parentheses refer to the *de* value after resolution of the diastereomers by HPLC ($SiO_2$, diethyl ether/pentane 3/1).

Reductive cleavage of the chiral auxiliary from $\beta$-hydrazino sulfones (*R*,*S*)-**4a–e** with $BH_3 \cdot THF$[23] in refluxing THF afforded $\beta$-amino sulfones (*R*)-**5a–e** without racemization. Treatment with di-*tert*-butyldicarbonate ($Boc_2O$) and triethylamine in methanol gave the N-Boc-protected $\beta$-amino sulfones **6** (*ee* = 92 to greater than 96%) without prior purification of the amines **5** (Table 3). After N–N bond cleavage the chiral auxiliary (*S*)-2-methoxymethyl-pyrrolidine could be recovered as the N-Boc derivative and—after deprotection, nitrosation, and reduction—reused as a chiral ammonia equivalent.

Table 3. Yields, optical rotations, and enantiomeric excesses of N-Boc-protected $\beta$-amino sulfones **6**.

| Product | R | Yield [%][a] | $[\alpha]_D^{25}$ (*c*, $CHCl_3$) | *ee*[b] [%] |
|---|---|---|---|---|
| (*R*)-**6a** | Et | 60 | −2.1 (0.78) | $\geq$96 |
| (*R*)-**6b** | *i*Pr | 42 | −12.9 (0.31) | $\geq$96 |
| (*R*)-**6c** | *i*Bu | 73 | +7.1 (1.25) | 92 |
| (*R*)-**6d** | *c*Hex | 58 | −8.1 (0.16) | $\geq$96 |
| (*R*)-**6e** | BOM | 82 | −9.7 (0.57) | $\geq$96 |

[a] Yield determined over two steps. [b] The *ee* values were determined from the *de* values of the corresponding Mosher amides by $^1$H NMR spectroscopy (Varian Gemini 300-MHz spectrometer).[24]

Similarly, cleavage of the chiral auxiliary from $\beta$-hydrazino sulfones (*S*,*R*,*R*,*R*)-**4a–f** (Table 2) synthesized with (*R*,*R*,*R*)-**2** proceeded without racemization.[25] By replacing SAMP by RAMBO, both enantiomers of the title compounds could be accessed.

In summary, the described asymmetric aza-Michael addition with C–N bond formation opens up an efficient approach to synthetically valuable and virtually enantiopure $\beta$-amino sulfones.[26]

## *Experimental Section*

**4a–f**: The alkenyl sulfone **3a–f** (5.0 mmol) was added dropwise to a solution of $Yb(OTf)_3$ (0.31 g, 0.50 mmol) in THF (10 mL) under an atmosphere of argon at room temperature. After the mixture was stirred for 15 min, the nitrogen nucleophile (*S*)-**1** or (*R*,*R*,*R*)-**2** (7.5 mmol) was added dropwise to the colorless to light yellow solution, and the mixture was stirred for 20 d at room temperature (procedure A) or 3 d under reflux (procedure B). The solution was then poured into pentane/diethyl ether (2/1, 150 mL) and filtered through celite. The solvent was evaporated under reduced pressure, and the residue was purified by column chromatography or HPLC ($SiO_2$, pentane/diethyl ether) to provide the major diastereomer. Products **4a–f** were isolated as colorless oils, and (*R*,*S*)-**4b** was obtained in crystalline form (m.p. 63 °C).

(*R*)-**5a–e**: The $\beta$-hydrazino sulfones (*R*,*S*)-**4a–e** (Table 1) were dissolved in THF (20 mL per mmol) under an atmosphere of argon. $BH_3 \cdot THF$ (10 equiv, 1.0 N in THF) was added, and the reaction mixture was heated at reflux for 5 h. After the mixtrure had cooled to room temperature, hydrochloric acid (4 N, 3 mL per mmol) was slowly added and the solution was stirred for 2 h at room temperature. The solvent was evaporated under reduced pressure, and the residue was treated with a saturated aqueous solution of $Na_2CO_3$. The aqueous phase was extracted with dichloromethane/diethyl ether (3/1), and the combined organic layer was washed with brine. After drying of the solution over $Na_2SO_4$ the solvent was evaporated in vacuo. Without further purification, the crude product (*R*)-**5a–e** was subjected to reaction with $Boc_2O$ or with (*R*)-Mosher's acid in order to determine the enantiomeric excess of the amine.

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(*R*)-**6a–e**: The crude $\beta$-amino sulfones (*R*)-**5a–e** were dissolved in methanol (30 mL per mmol), and $Boc_2O$ (10 equiv) and triethylamine (ca. 3 mL per mmol) were added at 0 °C. The reaction mixture was stirred for 2 d. The solvent was evaporated under reduced pressure, and the residue was diluted with diethyl ether. The mixture was washed with a saturated aqueous solution of $NH_4Cl$ and then brine, and dried over $MgSO_4$. The solvent was evaporated, and the products were purified by chromatography ($SiO_2$, diethyl ether/pentane). The products (*R*)-**6a–e** were obtained as colorless solids.

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[17] Crystal structure analysis of (*R*,*S*)-**4b** ($C_{17}H_{28}O_3N_2S$): orthorhombic, space group $P2_12_12_1$ (no. 19), $a = 8.2728(4)$, $b = 10.3874(5)$, $c = 22.205(1)$ Å, $V = 1908.14$ Å$^3$, $Z = 4$, $M_{calcd} = 340.49$, $\rho_{calcd} = 1.185$ g cm$^{-3}$. Crystals were obtained from dichloromethane/*n*-hexane, crystal dimensions ca. $0.3 \times 0.3 \times 0.3$ mm$^3$, Enraf-Nonius CAD4 diffractometer, $Cu_{K\alpha}$ radiation (graphite monochromator, $\lambda = 1.54179$ Å. The structure was solved with direct methods (Gensin, Gentan, from Xtal3.2).[18] Some of the hydrogen positions could be localized, the remaining were calculated. Reflections observed [$I > 2\sigma(I)$]: 1826, parameters refined: 208; $R = 0.056$, $R_w = 0.046$; min./max. residual electron density $-0.4/+0.3$e Å$^{-3}$. The configuration at C8 was determined with respect to the known configuration at C3. 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-102345. 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).

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[25] The starting material for the synthesis of RAMBO—(*R*,*R*,*R*)-azabicyclo[3.3.0]octane-3-carboxylic acid benzyl ester hydrochloride, which was supplied by the Hoechst AG – showed an *ee* value of 80% (determined by $^1$H NMR spectroscopy from the *de* value of the corresponding Mosher amide).

[26] All new compounds showed suitable spectroscopic data (IR, MS, NMR) and correct elemental analysis or high-resolution mass spectra.

# A Novel High-Nuclearity Luminescent Gold(I)–Sulfido Complex**

Vivian Wing-Wah Yam,* Eddie Chung-Chin Cheng, and Kung-Kai Cheung

There has been growing interest in the study of $Cu^I$, $Ag^I$, and $Au^I$ complexes, and in particular polynuclear systems. This stems from the tendency of these metal ions to form clusters and aggregates as a result of weak metal–metal interactions[1] and the recent demonstration that a number of these aggregates exhibit rich luminescence behavior.[2] Recently, our group showed[3] that unsubstituted chalcogenides, with their well-known ability to exhibit a variety of bridging

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