Synthesis of Bis(4-methylphenylsulfonimidoyl)methane – The First 'Free' Geminal Bis(sulfoximine)

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Abstract: The synthesis of the first 'free' geminal bis(sulfoximine) bis(4-methylphenylsulfonimidoyl)methane is described. Herein we present two different synthetic routes leading either to the racemate or the enantiomerically pure compound. This representative of a new substance class can be regarded as a chiral analogue of the bis(iminophosphorane)s which are used as ligands in rare-earth-metal-catalyzed hydroamination reactions.

Key words: sulfoximine, asymmetric catalysis, ligands, elimination, oxidative cleavage, sulfur, zinc, chirality

Bis(iminophosphorane)s are used as ligands in various metal-catalyzed reactions, for example, the polymerization of ethane[1–3] or the ring-opening polymerization of lactides[4,5] and ε-caprolactam.[6–9] Furthermore, the rare-earth-metal complexes of iminophosphoranes serve as catalysts in hydroamination reactions.[10–13] Since 2001 a number of bis(iminophosphorane) rare-earth-metal complexes have been prepared by Roesky et al. starting from precursor **1** (Figure 1).[14]

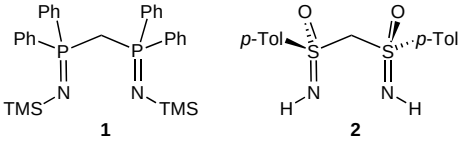
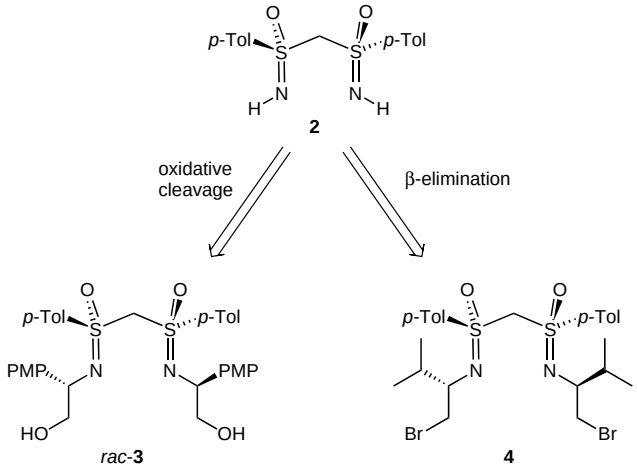


Figure 1 Comparison of bis(iminophosphorane) **1** and the 'free' geminal bis(sulfoximine) **2**

The application in intramolecular hydroamination–cyclization reactions of terminal aminoalkenes delivered the corresponding azacycles in almost quantitative yields.[15] Naturally, due to the achirality of the ligand, all products were formed as racemic mixtures.

To render the process enantioselective we were interested in chiral analogues of the bis(iminophosphorane)s. Some years ago we[16,17] and others[18–22] demonstrated the applicability of sulfoximines in general and bis(sulfoximine)s[17] in particular as chiral ligands in metal-catalyzed reactions. Based on our work with the latter compounds we anticipated that bis(sulfoximine)-based ligands such as **2** may act as a chiral equivalent of the bis(iminophosphorane) **1**. Both structures are characterized by an acidic methylene bridge and heteroatom-bound imino functions as possible coordination sites.

For the sake of maximum structural flexibility we envisioned the synthesis of the double N-unsubstituted ('free') parent compound **2** which has proven to be highly reluctant to its synthesis.[17] Herein we describe two different routes for its preparation starting from bis(sulfoximine)s *rac*-**3** (PMP = 4-methoxyphenyl) and **4**, respectively (Scheme 1).



Scheme 1 Retrosynthetic analysis bis(sulfoximine) **2**

The first route relies on an oxidative cleavage of the new bis(sulfoximine) *rac*-**3** derived from the non-natural amino acid *rac*-**5** (Scheme 2). Its reduction and O-protection delivered the TMS-protected amino alcohol *rac*-**6** in good yields.

Following the established synthetic procedure developed in our group,[23,24] the cyclic sulfonimidate *rac*-**8** was obtained by sulfinylation and diastereoselective cyclization via the epimers *rac*-**7** in good yield and diastereomeric ratio.

After removal of the minor diastereomer by crystallization, the sulfonimidate was opened by methyllithium, the product deprotonated with LiHMDS and treated with another equivalent of *rac*-**8**. The resulting bis(sulfoximine) *rac*-**3** was obtained in a very good yield with a diastereomeric ratio of 11:1 favoring the C_2-symmetric isomer which was isolated in diastereomerically pure form by flash chromatography (Scheme 3).

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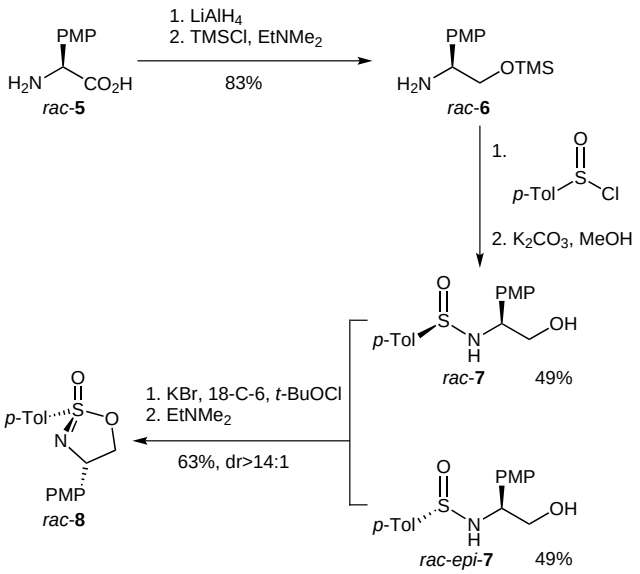
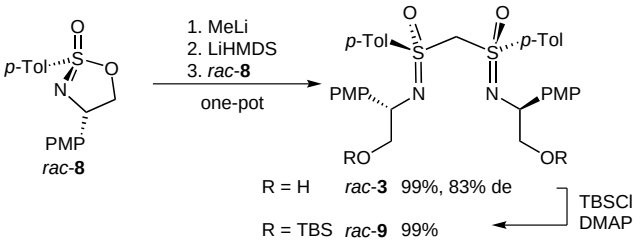


Scheme 2 Synthesis of the cyclic sulfonimidate *rac*-**8**

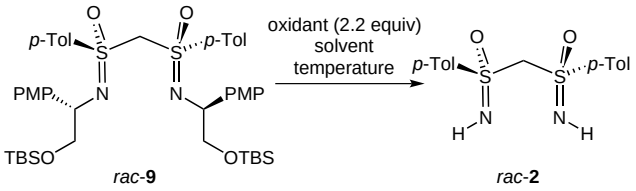


Scheme 3 Synthesis of the bis(sulfoximine) *rac*-**3** and its OTBS-protected derivative *rac*-**9**

After protection as TBS-ether yielding *rac*-**9**, the key step involving the oxidative cleavage with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) was studied (Table 1). Treating the substrate *rac*-**9** with 1.05 equivalents DDQ per PMP group under standard conditions[25,26] (CH_2Cl_2/H_2O = 20:1, r.t.) instantaneously gave a dark colored solution indicating the formation of a charge-transfer complex. After 20 minutes the starting material was completely consumed accompanied by precipitation of DDQH. $NaHCO_3$ workup turned out to be rather sluggish, for which reason we took advantage of the basicity of the sulfoximine moiety and extracted the reaction product with 5 M HCl into the aqueous phase. Re-extraction after pH adjustment gave the desired highly crystalline bis(sulfoximine) *rac*-**2** albeit in poor 8% yield (Table 1, entry 1).

No other sulfoximine-containing components could be isolated from the aqueous acidic phase. TLC analysis of the organic phase indicated considerable decomposition. The application of chloranil ($C_6O_2Cl_4$, Table 1, entry 2) as a less powerful oxidation agent was equally unsuccessful as was a solvent change to THF (Table 1, entry 3). A substantial improvement was achieved at lower temperatures (Table 1, entry 4) but most successful was the application of a biphasic reaction system (CH_2Cl_2/5 M HCl) to immediately remove the basic product from the reacting system (Table 1, entry 5). We were pleased to find no evidence for partial epimerization under the given reaction conditions.

Table 1 Optimization of the Oxidative Cleavage Reaction



Entry	Solvent	Ratio	Oxidant	$t_{initiation}$	Temp (°C)[a]	Yield (%)
1[b]	CH_2Cl_2–H_2O	20:1	DDQ	–	20	8
2	*p*-xylene	–	$C_6O_2Cl_4$	–	138	–
3	THF–H_2O	10:1	DDQ	–	20	<5
4	CH_2Cl_2–H_2O	20:1	DDQ	–	0	27
5	CH_2Cl_2–HCl[c]	1:2	DDQ	20 min[d]	20	54

[a] Reaction temperature after initiation, 16 h.
[b] 2.1 equiv DDQ were used.
[c] Degassed solvents under argon
[d] –20 °C in pure CH_2Cl_2, then addition of HCl.

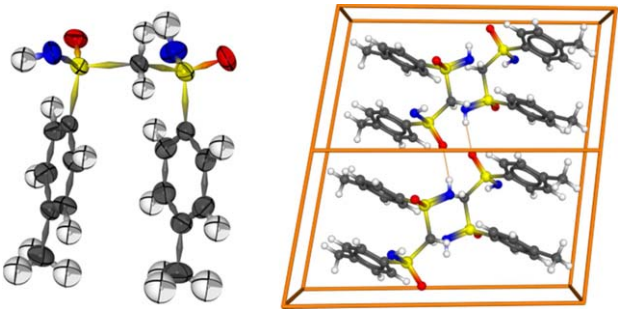
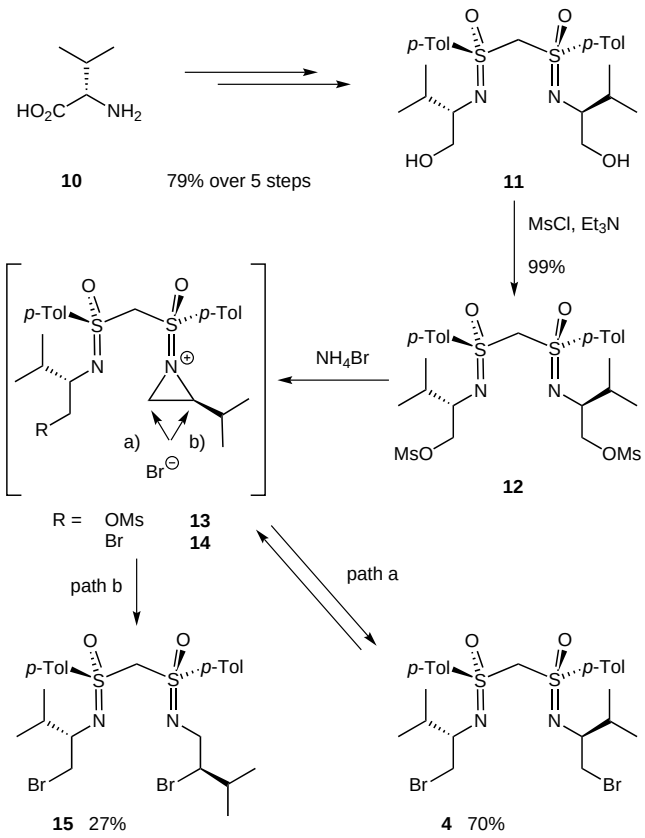


Figure 2 Solid-state structure of *rac*-**2** (left: 50% probability anisotropic thermal ellipsoids; right: plot of 1 × 2 × 1 unit cells)

We succeeded in growing single crystals of *rac*-**2** that were suited for a crystal structural analysis (Figure 2). It crystallizes in the centrosymmetric space group $P\bar{1}$ with two symmetry-related molecules (**2**/*ent*-**2**) present in the unit cell.

In contrast to the crystal structure of OTBS-protected **11** (Scheme 4),[17] which displays an almost C_2-symmetric conformation, the solid-state conformation of *rac*-**2** features an asymmetric, almost coplanar arrangement of both aromatic rings. These tolyl substituents form columnar stacks with adjacent molecules, which are additionally held together via S=O···HN=S hydrogen bonds ($d_{H\cdots O}$ = 2.159 Å).

Simultaneously, we developed another route to the title compound in enantiomerically pure form including a metal-induced β-elimination. Towards this end L-valine (**10**)

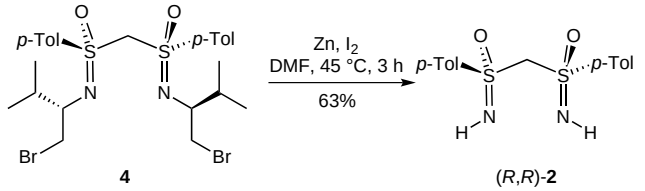


Scheme 4 Synthesis of the brominated bis(sulfoximine)s **4** and **15** starting from enantiomerically pure L-valine (**10**)

was converted in five steps into the known bis(sulfoximine) **11** in 79% yield (Scheme 4).[17]

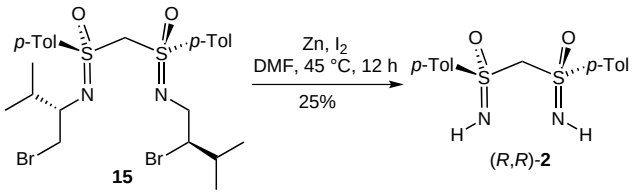
Mesylation followed by halogenation with NH_4Br delivered the dibrominated compound **4** in 70% yield, albeit accompanied by 27% of the isomeric compound **15**. This observation is in accordance with the initial formation of aziridinium ions **13** or **14** which can be attacked either via path a) or path b). Furthermore, the formation of the rearranged product **15** can be observed in solutions of **4** after a few days most probably via the intermediate **14**.

With this halogenated compound **4** in hand we tried the zinc-induced β-elimination using Huo's method.[27] After optimization of the reaction conditions the 'free' geminal bis(sulfoximine) (*R*,*R*)-**2** was obtained in good yields and in enantiomerically pure form (Scheme 5).[28]



Scheme 5 Zinc-induced β-elimination of the brominated bis(sulfoximine) **4** to the title compound (*R*,*R*)-**2**

We also used the rearranged compound **15** for the elimination reaction and obtained the desired bis(sulfoximine) in moderate yield after a prolonged reaction time (Scheme 6).



Scheme 6 Zinc-induced β-elimination of the rearranged halogenated bis(sulfoximine) **15**

In conclusion we have developed two different synthetic routes for the first geminal 'free' bis(sulfoximine) **2** including its preparation in enantiomerically pure state (*R*,*R*)-**2**. This new kind of ligand represents a chiral analogue of bis(iminophosphorane)s and may therefore be suited as a ligand for asymmetric hydroamination reactions employing rare-earth metals as central atoms. Moreover, compound **2** offers the opportunity to modify both the acidic methylene bridge and the 'free' NH's to obtain a whole family of new sulfoximine-based ligand systems. Work along these lines is in progress.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(28) **Reaction Procedure for the Zinc-Induced β-Elimination:** In a Schlenk flask, zinc dust (10.1 g, 155 mmol, 12 equiv) was suspended in dry DMF (12.9 mL) and elemental iodine (6.88 g, 27.1 mmol, 2.1 equiv) was added at 0 °C. After disappearance of the brown color the brominated bis(sulfoxmine) **4** (8.00 g, 12.9 mmol), dissolved in dry DMF (32 mL), was added dropwise to the grey suspension via cannula, and the reaction mixture was stirred at 45 °C for 3 h. After complete conversion (controlled by TLC) the excess zinc was removed by filtration over a pad of Celite. The solvent was removed by vacuum distillation and freeze-drying with toluene (3 × 250 mL). The residue was taken up in CH_2Cl_2 (130 mL), the organic phase was washed with a sat. NH_4Cl solution (130 mL) and 0.1 M EDTA solution (130 mL). Drying over Na_2SO_4 and removal of the solvent delivered the crude product as a pale yellow oil. The pure bis(sulfoximine) was obtained by recrystallization from toluene (2.45g, 63%). $[\alpha]_D^{25}$ –59.1 (*c* 1.05, CH_2Cl_2); mp 132–133 °C (from toluene); EA calcd for $C_{13}H_{18}N_2O_2S_2$: C, 55.87; H, 5.63; N, 8.69; found: C, 55.79; H, 5.57; N, 8.53. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.90 (4 H, d, *J* = 8.4 Hz, 4-H), 7.32 (4 H, d, *J* = 8.4 Hz, 3-H), 4.53 (2 H, s, 6-H), 4.12 (2 H, br s, NH), 2.43 (6 H, s, 1-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 145.04 (C-2), 137.18 (C-5), 129.86 (C-3), 128.89 (C-4), 77.00 (C-6), 21.59 (C-1) ppm.

