

## Schiff-Base Ligands Carrying Two Elements of Chirality: Matched-Mismatched Effects in the Vanadium-Catalyzed Sulfoxidation of Thioethers with Hydrogen Peroxide

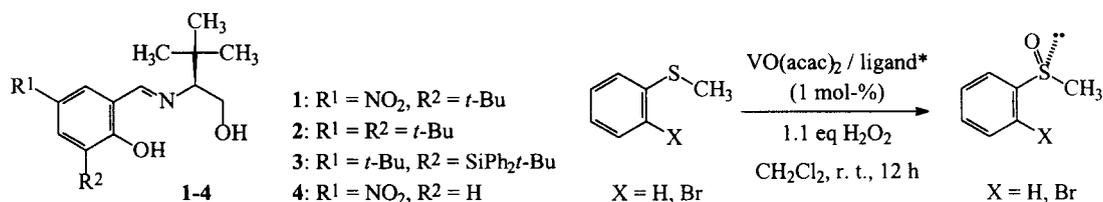
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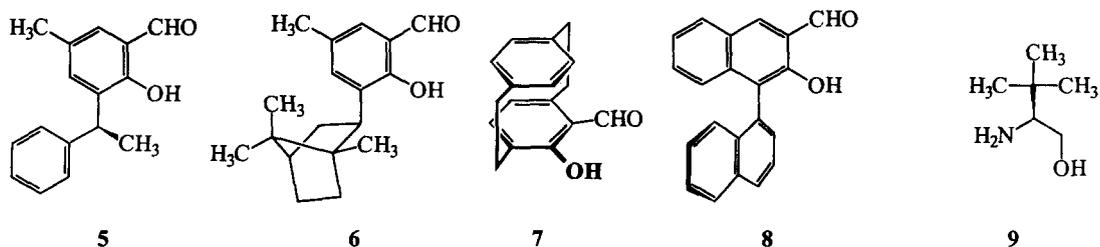
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**Abstract:** Eight chiral Schiff-base ligands were prepared from (*S*)-*tert*-leucinol and four chiral, racemic salicylic aldehydes. The resulting pairs of diastereomers were separated by preparative HPLC and applied to the vanadium-catalyzed asymmetric sulfoxidation of thioethers with hydrogen peroxide. The product enantioselectivities revealed matched-mismatched effects that depended strongly on the structures of the chiral salicylic aldehydes. In particular, thioanisole and 2-bromothioanisole could be oxygenated in almost quantitative yields and with enantiomeric excesses up to 78 % ee. The latter values are the highest ones ever achieved for these substrates using transition metal catalysts and hydrogen peroxide as terminal oxidant. © 1998 Elsevier Science Ltd. All rights reserved.

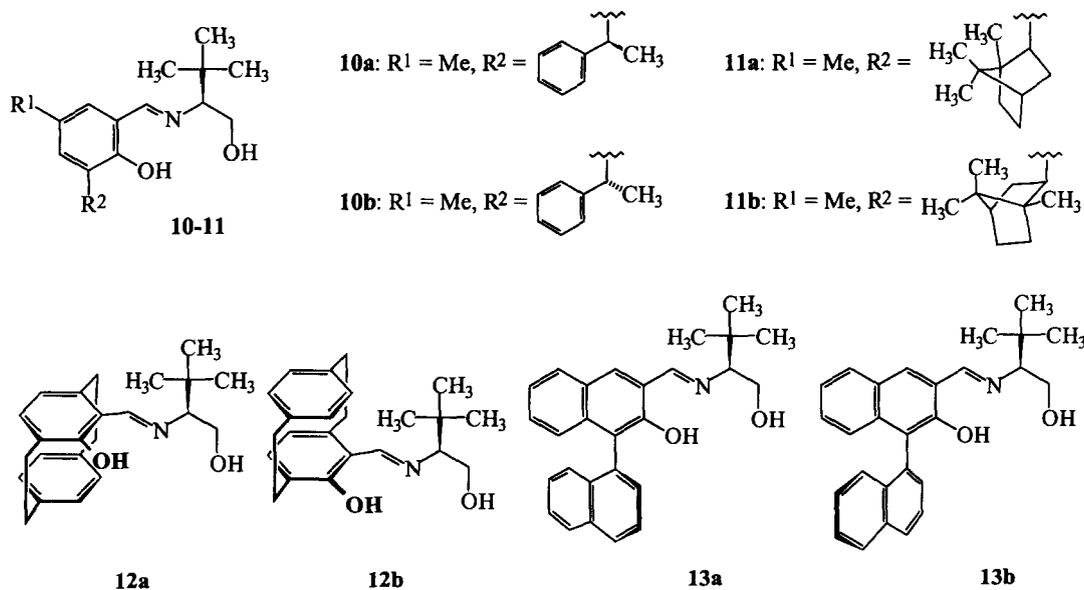
Enantiomerically pure sulfoxides are of considerable value as auxiliaries or intermediates in asymmetric synthesis<sup>1</sup>. A common way for their preparation exists in Andersen's method, i.e. the reaction of Grignard reagents with chiral sulfonates<sup>2</sup>. An attractive alternative is the catalytic asymmetric oxidation of prochiral thioethers<sup>3</sup>. Much progress has been made in recent years, particularly by using enzymes<sup>4</sup> or chiral complexes of titanium<sup>5</sup>, manganese<sup>6</sup> and vanadium<sup>7</sup> as catalysts. In 1995, Bolm and Bienewald reported a new and very promising catalytic system<sup>8</sup>: At catalyst loadings of as little as 1 %, the vanadium complexes of the Schiff-base ligands 1-4 effected the asymmetric sulfoxidation of thioethers, using hydrogen peroxide as terminal oxidant. For example, in the case of thioanisole as substrate, almost quantitative yields (94 %) and good enantiomeric excesses (70 %) could be achieved when the ligand 1 was employed<sup>8</sup>.



The Schiff-base ligands 1-4 contain one center of chirality, derived from the amino acid (*S*)-*tert*-leucine. We reasoned that the enantioselectivity of the highly efficient vanadium catalysts could be further enhanced by introducing an additional element of chirality into the salicylic aldehyde moiety. Thus, the racemic aldehydes *rac*-5-8 were reacted with enantiomerically pure (*S*)-*tert*-leucinol (9). The aldehydes 5-8 are of central (5,6)<sup>9</sup>, planar (7)<sup>10</sup> and axial chirality (8)<sup>11</sup>.



The corresponding imines **10-13** were formed in quantitative yields. Clearly, two diastereomeric Schiff-bases (**10-13a,b**) resulted from each racemic mixture of aldehydes. As it turned out, they could easily be separated by preparative HPLC<sup>12</sup> (> 99 % de at > 95 % recovery). The configurational assignment of the salicylic aldehyde moieties in **12-13a,b** rests on the separate synthesis of the Schiff-bases, starting from enantiomerically pure aldehydes, and comparison of these materials with those obtained from the HPLC-separation. So far, the configurational assignment is purely arbitrary in the cases of **10,11a,b**<sup>9</sup>.



In a standard sulfoxidation experiment, the catalyst was prepared *in situ* by dissolving 318  $\mu\text{g}$  (1.20  $\mu\text{mol}$ ) of VO(acac)<sub>2</sub> and 1.80  $\mu\text{mol}$  of the ligand in 400  $\mu\text{l}$  of dichloromethane. The mixture was stirred at room temp. for 12 h. Thioanisole (14.9 mg, 120  $\mu\text{mol}$ ) and diphenyl ether [15.3 mg, 90.0  $\mu\text{mol}$  (internal GC-standard)] were added. After stirring for an additional 15 min, 30 % hydrogen peroxide (16.7  $\mu\text{l}$ , 132  $\mu\text{mol}$ , 1.10 eq.) was added. The reactions proceeded smoothly. After 12 h, methyl phenyl sulfoxide was formed in the yields and enantiomeric excesses summarized in Table 1. In just the same way, *o*-bromothioanisole was oxidized. Sulfones were formed only to a minor extent (< 5 %). For comparison, the result obtained by Bolm and Bienewald<sup>8</sup> using ligand **2** is included in Table 1, too (entry 10).

**Table 1:** Asymmetric sulfoxidation of thioanisole and *o*-bromothioanisole<sup>a,b</sup>.

entry	ligand	thioanisole		<i>o</i> -bromothioanisole	
		yield [%]	ee [%] <sup>c,d</sup>	yield [%]	ee [%] <sup>c,e</sup>
1	<b>10a</b>	85	45 ( <i>S</i> )	96	49 ( <i>S</i> )
2	<b>10b</b>	87	49 ( <i>S</i> )	95	59 ( <i>S</i> )
3	<b>11a</b>	93	39 ( <i>S</i> )	96	52 ( <i>S</i> )
4	<b>11b</b>	91	70 ( <i>S</i> )	97	78 ( <i>S</i> )
5	<b>12a</b>	78	2 ( <i>R</i> )	85	4 ( <i>R</i> )
6	<b>12b</b>	82	48 ( <i>S</i> )	92	46 ( <i>S</i> )
7	<b>13a</b>	87	56 ( <i>S</i> )	45	10 ( <i>S</i> )
8	<b>13b</b>	85	71 ( <i>S</i> )	41	19 ( <i>S</i> )
9	<b>13b</b>	92 <sup>f</sup>	78 <sup>f</sup> ( <i>S</i> )		
10	<b>2</b>	73	59 ( <i>S</i> )		

- a) Reactions were performed as described in the text. Ratio VO(acac)<sub>2</sub>:ligand:substrate:hydrogen peroxide = 1:1.5:100:110.
- b) Yields and enantiomeric excesses were determined by capillary GC using an octakis-(2,6-di-*O*-pentyl-3-*O*-butyryl- $\gamma$ -cyclodextrin) capillary column (Lipodex E, 25 m).
- c) The configuration of the major enantiomer is quoted in parentheses.
- d) The configuration of the major enantiomer was determined by co-injection of enantiomerically pure (*S*)-(-)-methyl phenyl sulfoxide.
- e) The configuration of the major enantiomer was determined by isolation of the sulfoxide and comparison of its sign of optical rotation [(-)] with literature data<sup>13</sup>.
- f) The reaction was run at 0 °C.

The data summarized in Table 1 allow for the evaluation of the effects exerted by additional elements of chirality: (a) Additional center(s) of chirality (**10,11a,b**): In the case of **10a,b**, the stereochemical outcome of the reactions is clearly dominated by the chirality of the *tert*-leucinol moiety (entries 1,2). The configuration of the salicylic aldehyde is of no significant influence. Comparison with entry 10 demonstrates that sufficient bulkiness of the substituent *ortho* to the phenolic hydroxyl group is of greater importance than mere chirality. In line with this assumption, a 2-*exo*-bornyl substituent at this position (**11a,b**) is of strong influence, and a pronounced matched-mismatched effect results (entries 3,4). In fact, the "matched" ligand **11b** afforded the highest enantioselectivity in the *o*-bromothioanisole series (78 % ee, entry 4). (b) Additional chiral plane: The strongest "mismatched" effect could be observed in the case of the cyclophane ligand **12a**: Almost no enantioselectivity is retained (entry 5). In fact, (*R*)-sulfoxides are formed in very low ees instead of the (*S*)-sulfoxides observed with all other ligands. Unfortunately, a "matched" effect of similar strength was not observed in the case of the diastereomeric ligand **12b** (entry 6). (c) Additional chiral axis: For the sulfoxidation of thioanisole, the binaphthyl system **13b** turned out to be the most efficient ligand: the corresponding sulfoxide is formed in up to 78 % ee (entries 8,9). To the best of our knowledge, this is the highest enantioselectivity ever achieved in the sulfoxidation of thioanisole using transition metal catalysts and hydrogen peroxide as terminal oxidant. The diastereomeric ligand **13a** affords methyl phenyl sulfoxide of significantly lower ee (56 %,

entry 7). Most interestingly, neither one of the axially chiral ligands **13a,b** gave satisfying results in the case of *o*-bromothioanisole (entries 7,8). The relatively low yields and marginal enantioselectivities point to unfavorable non-bonding interactions between the bromo substituent and the binaphthyl moiety of the ligand. Unfortunately, since the structure of the oxygen transferring species within the catalytic cycle is not known to date, a serious interpretation of this effect does not yet appear to be possible.

In summary, we herein report the most efficient ligands known to date for the vanadium-catalyzed asymmetric sulfoxidation of thioanisole and *o*-bromothioanisole, using hydrogen peroxide as terminal oxidant. These particular ligands (**11b**, **13b**) were found by a systematic study of the combinations of (*S*)-*tert*-leucinol with chiral salicylic aldehydes. We are convinced that this broad screening approach will enable us to optimize other transition metal/Schiff-base catalyst systems.

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