Enantioselective Sulfide Oxidation with H_2O_2: A Solid Phase and Array Approach for the Optimisation of Chiral Schiff Base-Vanadium Catalysts

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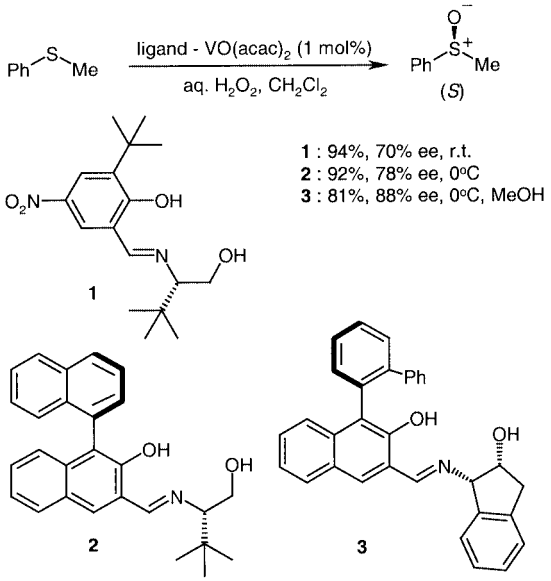
Abstract: Two libraries of chiral Schiff base ligands were synthesised and screened in the vanadium-catalysed oxidation of alkyl aryl sulfides with hydrogen peroxide as terminal oxidant. The vanadium-chiral Schiff base complex **10**, readily prepared from 3,5-diiodo-salicylaldehyde and (*S*)-*tert*-leucinol, was found to be highly enantioselective. Optically active sulfoxides could thus be obtained in good yields with up to 97% ee.

Key words: asymmetric catalysis, Schiff bases, hydrogen peroxide, enantioselective sulfoxidation, supported catalysts

Enantiopure sulfoxides are an important class of compounds as synthetic intermediates for asymmetric transformations,[1] as chiral ligands in enantioselective catalysis[2] and as bioactive ingredients in the pharmaceutical industry.[3] The asymmetric oxidation of prochiral sulfides[4] has become the method of choice for the synthesis of optically active sulfoxides since Kagan[5] and Modena[6] independently reported high enantioselectivities using modified versions of the Sharpless epoxidation system: alkyl hydroperoxide/titanium tetraisopropoxide/diethyl tartrate.

Although originally stoichiometric, catalytic versions of this titanium-mediated reaction were later described[7] and new catalytic systems have emerged.[8–11] Current efforts are devoted to the development of oxidation reactions using hydrogen peroxide as terminal oxidant, as this is a cheap, readily available, environmentally benign and atom efficient reagent.[9–11] In this respect, the catalytic system of a vanadium-chiral Schiff base **1** described by Bolm in 1995 is particularly attractive for its simplicity, high activity (0.01–1 mol% of catalyst) and good enantioselection in asymmetric sulfide oxidation with H_2O_2, giving up to 70% ee for thioanisole oxidation (Scheme 1).[10a] Improvements of the selectivity were later achieved using more complex Schiff bases bearing extra chirality on the fragment derived from the aldehyde. Thus binaphthyl-derived ligand **2**[10b] and biphenyl-derived ligand **3**[10e] afforded methyl phenylsulfoxide in 78% and 88% ee respectively. In this latter case, the enantioselectivity was further improved by the addition of a slight amount of methanol, which probably affects the equilibrium between the peroxovanadium species.[12]

As part of our interest in simple oxidation systems using H_2O_2 as terminal oxidant, we were attracted by Bolm's protocol and decided to launch a systematic study to optimise the Schiff base-derived catalyst structure. Our approach was to rapidly generate libraries of simple chiral Schiff bases using solid phase chemistry and parallel synthesis and to screen them in the enantioselective vanadium-catalysed sulfide oxidation. In this paper, we report our results from these screenings and highlight in particular that the enantiocontrol is dictated mainly by a single stereocentre on the Schiff base ligand and that the preferred catalysts, synthesised in only one or two steps from commercially available materials, lead to some of the best ee's reported to date.



Scheme 1

We first synthesised a library of solid-supported Schiff bases **7** derived from a large range of readily available chiral amines and supported salicylaldehyde **6** (Scheme 2). The coupling of a salicylaldehyde unit onto a solid support was achieved by the synthesis of acid precursor **5** and alkylation of its cesium salt with Merrifield

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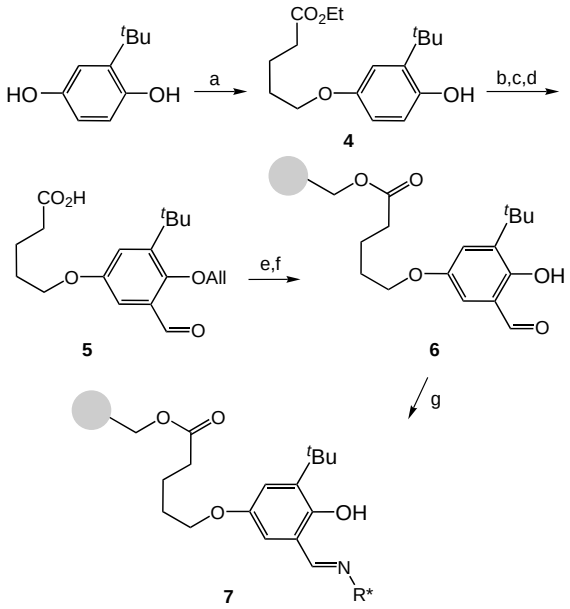
resin. Acid **5**[13] was prepared in 4 steps from *tert*-butylhydroquinone, by selective alkylation with ethyl-5-bromovalerate, ortho-directed formylation[14] of phenol **4**, allyl-protection of the free phenol (which was rendered necessary for clean coupling to the resin), and saponification of the ethyl ester. A deallylation reaction with 10 mol% $Pd(PPh_3)_4$ and morpholine led to the supported salicylaldehyde **6**, the structure of which was confirmed by MAS-NMR. Various chiral amines, mainly diversely substituted aminoalcohols, were then condensed with aldehyde **6**. The structures of the resulting imines **7** were checked by MAS-NMR as conventional aldehyde colour tests on resin provided ambiguous results.[15]

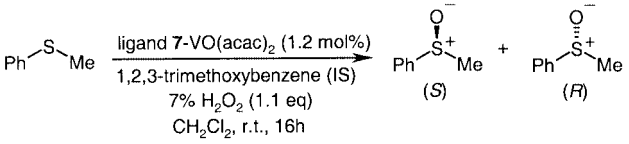


Scheme 2 *Reagents and conditions*: a) ethyl-5-bromovalerate, K_2CO_3, KI, CH_3CN, 55 °C; b) $MgCl_2$, Et_3N, CH_3CN, r.t. then $(CH_2O)_n$, 40 °C; c) allyl bromide, K_2CO_3, DMF, r.t.; d) $LiOH.H_2O$, dioxane-H_2O (1:1), r.t., 47% (4 steps); e) Merrifield resin (0.74 mmol/g), Cs_2CO_3, KI, DMF, 50 °C; f) $Pd(PPh_3)_4$, morpholine, CH_2Cl_2, r.t.; g) chiral amine, CH_2Cl_2, r.t.

We next screened our library of 29 chiral supported ligands in the vanadium-catalysed asymmetric oxidation of thioanisole, after pre-optimisation of the reaction conditions for this triphasic catalytic system.[16] Representative examples of the library results are reported in Table 1. Poor enantioselectivities were observed when no hydroxyl function was present on the amine backbone (ligands **7a** and **7b**, Table 1, entries 1 and 2 vs. 9), when the aminoalcohol was monosubstituted by another heteroatomic group (alcohol, amide, ester, *cf* ligand **7c**, Table 1, entry 3), with 1,1,2-trisubstituted aminoalcohols, *trans*-1,2-disubstituted aminoalcohols (ligand **7l**, Table 1, entry 12 vs. 13) and *trans*-1,2-disubstituted aminosulfonamides (ligand **7k**, Table 1, entry 11). In contrast, higher enantioselectivities were reached with aminoalcohols substituted with alkyl or aromatic groups (Table 1, entries 4–10) and *cis*-1,2-disubstituted aminoalcohols (Table 1, entries 13–15). The selectivity increased with the steric hindrance of the substituent α to the amine, from 21% ee with a methyl group (Table 1, entry 5) to 52% ee with a *tert*-butyl group (Table 1, entry 10). Interestingly, the position of the chiral centre, α or β to the amine, did not affect the selectivity (Table 1, entry 4 vs. 5). It is also worth noting that mainly the (*S*) enantiomers of the sulfoxide were formed with both ligands **7d** and **7e** bearing methyl substituents of opposite configuration. These results demonstrate firstly the role of the hydroxyl function in the chelation with vanadium and secondly the importance of substitution on only one face of the resulting vanadium-tridentate Schiff base complex for enantioselectivity.

The best enantioselectivities were obtained with (*S*)-*tert*-leucinol-derived ligand **7j** (52% ee) and (1*R*,2*S*)-*cis*-aminoindanol-derived ligand **7o** (48% ee) containing the same amines as the best ligands reported in the literature (*cf* ligands **1**–**3**) and represent the best results so far in the sulfide oxidation with solid-supported vanadium catalysts. Control experiments were performed in solution phase with Schiff bases prepared by condensation of the ethyl ester analogue of aldehyde **6** and L-*allo*-threonine, (1*R*,2*S*)-*cis*-aminoindanol or (*S*)-*tert*-leucinol. Comparable results in terms of selectivity order were obtained with 54%, 59% and 63% ee respectively (compared to 40%, 48% and 52% ee with supported ligands **7m**, **7o** and **7j**), and validated our solid phase approach for the optimisation of catalyst structures. The loss of enantioselectivity from solution phase to solid phase catalysis has previously been reported for other asymmetric transformations[17] and might be explained by the lower accessibility of the catalytic sites on solid support.

Table 1 Thioanisole Oxidation with Supported Vanadium-Schiff Bases **7** as Catalysts and Aqueous H_2O_2 as Oxidant



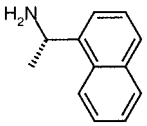
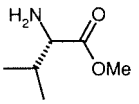
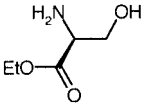
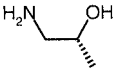
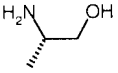
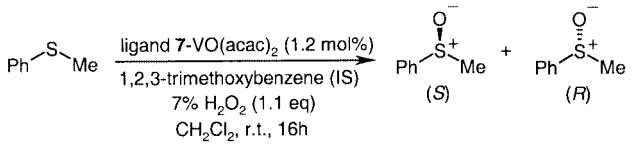
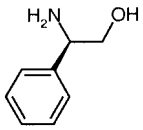
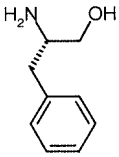
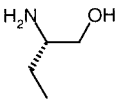
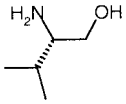
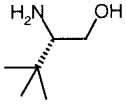
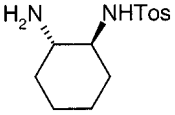
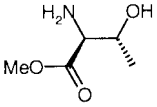
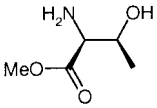
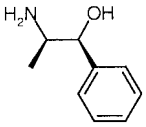
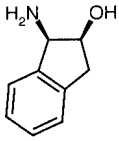
Entry	Ligand	Amine[a]	Yield[b]	ee[b]	Conf.[c]
1	**7a**		82	4	S
2	**7b**		71	6	*S*
3	**7c**		74	6	*R*
4	**7d**		77	20	S
5	**7e**		78	21	*S*

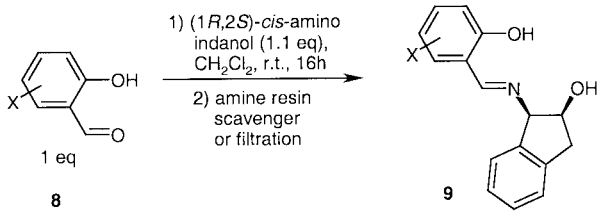
Table 1 Thioanisole Oxidation with Supported Vanadium-Schiff Bases **7** as Catalysts and Aqueous H_2O_2 as Oxidant (continued)



Entry	Ligand	Amine[a]	Yield[b]	ee[b]	Conf.[c]
6	**7f**		74	23	*R*
7	**7g**		78	32	S
8	**7h**		72	34	*S*
9	**7i**		71	39	*S*
10	**7j**		76	52	*S*
11	**7k**		73	6	S
12	**7l**		87	6	R
13	**7m**		82	40	*R*
14	**7n**		85	39	*R*
15	**7o**		83	48	R

[a] Amine condensed on supported salicylaldehyde **6**.
[b] Determined by chiral HPLC of the crude mixture with 1,2,3-trimethoxybenzene as internal standard (IS) (Chiralcel OD-H, 5% EtOH in heptane, 1 mL/min, 227 nm). Retention times: 4.2 min (thioanisole), 7.1 min (internal standard), 11.7 min (*R*-methyl-phenylsulfoxide), 13.1 min (*S*-methyl-phenylsulfoxide), 14.3 min (methyl-phenylsulfone). The sulfone was obtained as by-product in ~10–20% yield, along with some unreacted thioanisole (up to 10%).
[c] Configuration of the major enantiomer.

We then focused on the aldehyde part of the Schiff base ligand and decided to screen different aldehyde structures by parallel synthesis of a library of chiral Schiff bases in solution. To build the library, we chose *cis*-aminoindanol rather than *tert*-leucinol (best leads from the previous screening) because of the possibilities this aromatic aminoalcohol offers for further structural modifications. Moreover, at the time of the study, there was no example in the literature of selective *cis*-aminoindanol-derived ligands for asymmetric sulfide oxidation. Chiral Schiff bases **9** were prepared by condensation of 44 diversely substituted salicylaldehydes with (1*R*,2*S*)-*cis*-aminoindanol (Scheme 3). After 16 h, the imines that had precipitated were simply filtered. For those still in solution, the excess aminoalcohol was scavenged with *N*-methyl isatoic anhydride polystyrene resin. The purity of the crude Schiff bases was checked by HPLC and ^{1}H NMR and for 41 out of the 44 found to be satisfactory (>90%) and suitable for screening without further purification.



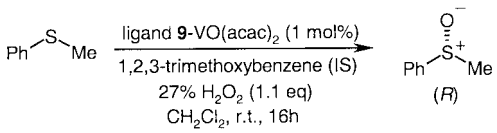
Scheme 3 Synthesis of a library of *cis*-aminoindanol-derived Schiff base ligands **9**

All 41 chiral Schiff bases were tested in the vanadium-catalysed oxidation of thioanisole and representative results are reported in Table 2. Ligand **9a** without a substituent on the aromatic ring of the aldehyde part gave 55% ee (Table 2, entry 1), which constituted our reference value in assessing the influence of substituents on the selectivity. Surprisingly, bulky substituents such as a *tert*-butyl group in *ortho* position to the phenol did not improve the selectivity (Table 2, entries 4, 8, 10). Ligand **9j**, derived from the same aldehyde as the one in Bolm's best ligand **1**, led to the same result as the unsubstituted equivalent **9a** (55% ee, Table 2, entry 10). In contrast, a smaller alkyl substituent such as a methyl group (ligand **9c**, Table 2, entry 3) afforded the sulfoxide with a better enantioselectivity of 67% ee. To cross-check these findings, we synthesised the isopropyl- and phenyl-substituted analogues (*ortho* to the phenol), of intermediate steric hindrance, and we obtained intermediate selectivities of 59% and 63% respectively, as might be expected.

However, no general conclusions can be drawn as the enantioselectivity often results from a combination of both steric and electronic effects of the substituents. For example, the substitution of a methyl group by a more electron-donating methoxy group induced the opposite effect of decreasing the enantioselectivity (41% ee, Table 2, entry 5). The importance of electronic effects is further illustrated with ligands **9b** and **9f**; the presence of a halogen substituent improves the selectivity from 55% to 64%

(Table 2, entry 1 vs. 2) and from 41% to 66% (Table 2, entry 5 vs. 6). More generally, the presence of one or more halogen atoms on the aldehyde aromatic ring was beneficial irrespective of their positions (Table 2, entries 9 vs. 10, 2 vs. 1, 6 vs. 5). Unexpectedly, good enantioselectivities were observed with ligands **9k** and **9l** (67% and 73%, Table 2, entries 11 and 12), derived from unsubstituted naphthaldehydes. Overall, the best enantioselectivities were achieved with the 3,5-diiodo-substituted ligand **9g** (70% ee, Table 2, entry 7) and with the naphthaldehyde-derived ligand **9l** (73% ee, Table 2, entry 12). **9l** is more selective than Bolm's ligand **1** even with no substitution on the aldehyde aromatic system.

Table 2 Thioanisole Oxidation with Vanadium-Schiff Bases **9** Catalysts and Aqueous H_2O_2 as Oxidant[a]



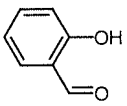
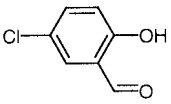
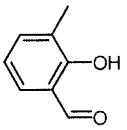
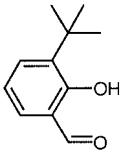
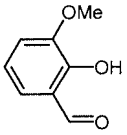
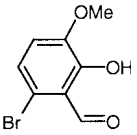
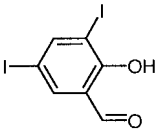
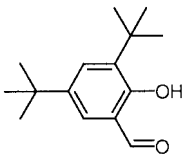
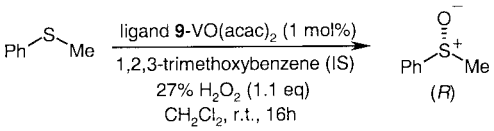
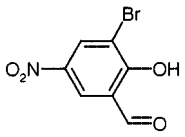
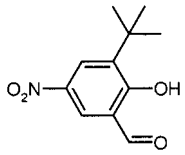
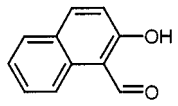
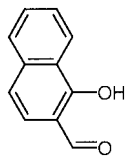
Entry	Ligand	Aldehyde[b]	Yield[c]	Ee[c]
1	**9a**		83	55
2	**9b**		73	64
3	**9c**		82	67
4	**9d**		80	54
5	**9e**		82	41
6	**9f**		88	66
7	**9g**		85	70
8	**9h**		79	53

Table 2 Thioanisole Oxidation with Vanadium-Schiff Bases **9** Catalysts and Aqueous H_2O_2 as Oxidant[a] (continued)



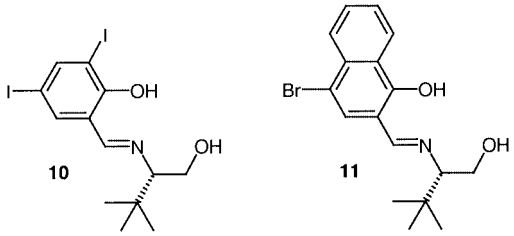
Entry	Ligand	Aldehyde[b]	Yield[c]	Ee[c]
9	**9i**		86	64
10	**9j**		85	55
11	**9k**		83	67
12	**9l**		80	73

[a] All reactions were performed with 1.5 mol% of ligand (7.5 mmol), 1 mol% of $VO(acac)_2$ (5 mmol), 0.2 equiv of 1,2,3-trimethoxybenzene (0.1 mmol), 1 equiv of thioanisole (0.5 mmol) and 1.1 equiv of 27% H_2O_2 (60 mL) in 1 mL of CH_2Cl_2.
[b] Aldehyde condensed on (1*R*,2*S*)-*cis*-aminoindanol.
[c] Determined by chiral HPLC of the crude mixture with 1,2,3-trimethoxybenzene as internal standard (Chiralcel OD-H, 5% EtOH in heptane, 1 mL/min, 227 nm).

To complete this study, we synthesised a set of pure ligands derived from the best hits of each library (all combinations between (*S*)-*tert*-leucinol or (1*R*,2*S*)-*cis*-aminoindanol on one hand and 3,5-diiodosalicylaldehyde or 1-hydroxy-2-naphthaldehyde on the other). We also included ligands derived from 4-bromo-1-hydroxy-2-naphthaldehyde[18] as this aldehyde combines the main features of the two best aldehydes from the screening. In order to find the best reaction conditions with these optimal ligands, we examined different reaction parameters such as the temperature, the addition of alcohol and the metal/ligand ratio. In general, the thioanisole oxidation is more enantioselective at lower temperature (0 °C) for most ligands whereas methanol as an additive is only beneficial in some cases, mainly with (1*R*,2*S*)-*cis*-aminoindanol derivatives. No significant change was observed by modifying the ratio vanadium/ligand from 1:1 to 1:2.

From this optimisation work, ligands **10**[20] and **11**[21] (see Figure) emerged as the best candidates for the vanadium-catalysed enantioselective oxidation of sulfides. Finally, a series of experiments was carried out with ligand **10** and different amounts of oxidant (from 0.9 equiv to 1.4 equiv

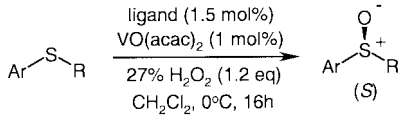
of H_2O_2), which revealed that the enantioselectivity reached a maximum value when approximately 1.2 equiv of oxidant was added (88% ee from the crude mixture). This was 7–9% higher than the ones measured for the reactions with 0.9 equiv and 1.4 equiv of H_2O_2.



Figure

With these new optimised conditions,[22] we performed the vanadium-catalysed oxidation of various alkyl aryl sulfides with our best ligands **10** and **11** (Table 3). The corresponding sulfoxides were obtained in good isolated yields with enantioselectivities of greater than 89%, and up to 97% for methyl naphthylsulfoxide. In particular, ligand **10** afforded methyl phenylsulfoxide in 81% yield and 90% ee, which are comparable results to those obtained with the more complex ligand **3**. These are the best results reported so far with simple chiral Schiff bases bearing only one chiral centre.

Table 3 Oxidation of Alkyl Aryl Sulfides with the Preferred Vanadium Catalysts using Aqueous H_2O_2 as Oxidant[a]



Entry	Ar	R	Ligand	Yield[b]	ee[c]
1	C_6H_5	Me	**10**	81	90
2	*p*-ClC_6H_4	Me	**10**	85	89
3	*p*-$MeOC_6H_4$	Me	**10**	78	91
5	C_6H_5	Et	**10**	76	92
6	2-Naphthyl	Me	**10**	78	97
7	C_6H_5	Et	**11**[d]	74	90
8	2-Naphthyl	Me	**11**[d]	86	92

[a] All reactions were performed twice and gave reproducible results.
[b] Isolated yields after column chromatography on silica gel (EtOAc–cyclohexane).
[c] Determined by chiral HPLC: methyl phenylsulfoxide (Chiralcel OD-H, 5% EtOH in heptane), ethyl phenylsulfoxide (Chiralcel OD-H, 7% EtOH in heptane), *p*-chlorophenyl methylsulfoxide (Chiralcel OB-H, 20% IPA in heptane), *p*-methoxyphenyl methylsulfoxide (Chiralcel AS, 40% IPA in heptane), methyl naphthylsulfoxide (Chiralcel OD-H, 5% EtOH in heptane).
[d] Reaction carried out with MeOH (20 μL) added at the same time as the sulfide.

In conclusion, we have been able to optimise Bolm's catalytic system for the oxidation of alkyl aryl sulfides by a systematic screening of the different components of the Schiff base ligand. We report the best enantioselectivities so far with supported vanadium-Schiff base complexes and demonstrate that high enantioselectivities can be achieved with simple and readily available (1–2 steps) chiral Schiff bases bearing only one chiral centre, such as imine **10**.

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(13) Compound **5**: ^{1}H NMR ($CDCl_3$, 250 MHz) δ = 10.30 (s, 1 H), 7.15 (m, 2 H), 6.08 (ddt, 1 H, *J* = 17.0, 10.5, 5.0 Hz), 5.52 (dd, 1 H, *J* = 17.0, 1.5 Hz), 5.33 (dd, 1 H, *J* = 10.5, 1.5 Hz), 4.46 (br. d, 2 H, *J* = 5.0 Hz), 3.98 (br. t, 2 H, *J* = 5.0 Hz), 2.46 (br. t, 2 H, *J* = 7.0 Hz), 1.85 (m, 4 H), 1.41 (s, 9 H); ^{13}C NMR ($CDCl_3$, 62 MHz) δ = 190.4, 179.2, 156.5, 154.8, 145.6, 132.7, 130.3, 122.5, 117.5, 108.3, 79.9, 67.7, 35.2, 33.5, 30.7 (3 C), 28.5, 21.4; MS (ES) *m/z* = 335 (M + H^+), 279, 251, 233.

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(15) Chiral amino acids failed to react with supported salicylaldehyde **6**.

(16) Typical procedure: Solid supported Schiff base **7** (6 μmol, 0.012 equiv) was weighed in an Alltech tube and the resin was swollen in CH_2Cl_2 for 1 h. A 0.04 M solution of $VO(acac)_2$ in CH_2Cl_2 (1 mL, 40 μmol) was added and the mixture was shaken for 1 h. The solution was filtered and the resin washed with CH_2Cl_2 (5 × 2 mL) and transferred into a reaction test tube. A 0.5 M solution of thioanisole (1 mL, 0.5 mmol, 1 equiv) and 1,2,3-trimethoxybenzene (0.1 mmol, 0.2 equiv, internal standard) in CH_2Cl_2 was added, followed by 7% H_2O_2 in H_2O (240 μL, 1.1 equiv). The reaction mixture was stirred for 16 h and analysed by chiral HPLC (Chiralcel OD-H, 5% EtOH in heptane, 1 mL/min, 227 nm). Retention times: 4.2 min(thioanisole), 7.1 min (internal standard), 11.7 min (*R*-methyl-phenylsulfoxide), 13.1 min (*S*-methyl-phenylsulfoxide), 14.3 min (methyl-phenylsulfone).

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(18) 4-Bromo-1-hydroxy-2-naphthaldehyde was prepared by bromination of 1-hydroxy-2-naphthaldehyde with *N*-bromosuccinimide according to a literature procedure[19] and isolated in 60% yield. Spectroscopic data: ^{1}H NMR ($CDCl_3$, 250 MHz) δ = 12.60 (s, 1 H), 9.92 (s, 1 H), 8.49 (d, 1 H, *J* = 8.5 Hz), 8.19 (d, 1 H, *J* = 8.5 Hz), 7.80 (t, 1 H, *J* = 8.5 Hz), 7.80 (s, 1 H), 7.63 (t, 1 H, *J* = 8.5 Hz); ^{13}C NMR ($CDCl_3$, 62 MHz) δ = 195.2, 161.3, 135.5, 131.8, 129.4, 127.2, 126.9, 125.8, 124.8, 114.8, 112.1.

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(20) Compound **10**: ^{1}H NMR ($CDCl_3$, 250 MHz) δ = 14.85 (br. s, 1 H), 8.10 (s, 1 H), 8.00 (d, 1 H, *J* = 2.0 Hz), 7.51 (d, 1 H, *J* = 2.0 Hz), 3.99 (dd, 1 H, *J* = 11.5, 2.5 Hz), 3.69 (dd, 1 H, *J* = 11.5, 9.5 Hz), 3.07 (dd, 1 H, *J* = 9.5, 2.5 Hz), 1.00 (s, 9 H); ^{13}C NMR ($CDCl_3$, 62 MHz) δ = 166.5, 164.6, 149.9, 141.0, 117.0, 92.6, 78.2, 75.9, 61.8, 32.9, 26.8 (3 C); MS (ES) *m/z* = 474 (M + H^+).

(21) Compound **11**: ^{1}H NMR ($CDCl_3$, 250 MHz) δ = 13.57 (br. s, 1 H), 8.39 (d, 1 H, *J* = 8.0 Hz), 7.98 (d, 1 H, *J* = 8.0 Hz), 7.70 (m, 1 H), 7.67 (t, 1 H, *J* = 8.0 Hz), 7.49 (t, 1 H, *J* = 8.0 Hz), 7.01 (s, 1 H), 4.06 (dd, 1 H, *J* = 11.5, 3.0 Hz), 3.76 (br. t, 1 H, *J* = 10.5 Hz), 3.16 (m, 1 H), 1.07 (s, 9 H); ^{13}C NMR ($CDCl_3$, 62 MHz) δ = 177.1, 162.2, 135.9, 131.5, 130.7, 127.7, 126.1, 125.5, 109.4, 107.0, 75.2, 62.3, 33.5, 27.2 (3 C); MS (ES) *m/z* = 350 and 352 (M + H^+).

(22) Typical experimental procedure: To a 0.03 M solution of ligand in CH_2Cl_2 (0.25 mL, 7.5 μmol, 0.015 equiv) was added a 0.02 M solution of $VO(acac)_2$ in CH_2Cl_2 (0.25 mL, 5 μmol, 0.01 equiv) and the resulting mixture was stirred at r.t. for 30 min. A 1 M solution of sulfide in CH_2Cl_2 (0.5 mL, 0.5 mmol, 1 equiv) was added and after 30 min stirring at r.t., the reaction mixture was cooled down to 0 °C. After 15 min at 0 °C, 27% H_2O_2 in H_2O (65 μL, 1.2 mmol, 1.2 equiv) was added dropwise. The mixture was stirred at 0 °C for 16 h and the solvent evaporated. The crude residue was purified by column chromatography (silica gel, EtOAc–cyclohexane).