Discovery of new solid phase sulfur oxidation catalysts using library screening[†]

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The discovery of a new solid-supported ligand 5 for the catalytic asymmetric oxidation of aryl alkyl sulfides in up to 72% ee using Ti(OⁱPr)₄ and aqueous H₂O₂ is reported.

The asymmetric synthesis of alkyl aryl sulfoxides has been the subject of much investigation, following the initial reports by Kagan¹ and Modena² on the use of a modified Sharpless reagent for the oxidation of alkyl aryl sulfides using alkyl hydroperoxides. More recent work has focussed on the use of H_2O_2 as the oxidant, with the first successful catalytic system discovered by Bolm using the combination of the amino alcohol-derived Schiff base **1** with vanadium.^{3,4} An oxidation catalyst that



combines high catalytic efficiency and high enantiomeric excess remains an important goal.⁵ The recent development of combinatorial methods for the discovery of new asymmetric catalysts offers a potential solution.⁶ The great success that has been achieved by Hoveyda and Snapper in various asymmetric C–C bond forming processes by parallel synthesis of peptide–Schiff base libraries⁷ suggested that an optimisation of the Bolm system using these techniques might be possible.

The apparent requirement for a hydroxy group in the ligand (presumably to coordinate to vanadium) suggested structure 2 as an appropriate generic ligand, which would be amenable to solid phase synthesis by standard coupling techniques. We planned on exploring five variables in this modular catalyst design, namely the solid support, amino acid 1, hydroxy amino acid 2, the salicylaldehyde and the choice of metal, with vanadium as the obvious starting point. Our initial library fixed the solid support as Wang, screened a series of L-amino acids (Gly, Ala, Val, Leu, Ile, Phe) as amino acid 1, serine and threonine as amino acid 2, and a series of salicylaldehyde derivatives [3,5-dibromosalicylaldehyde, 2-hydroxynaphthaldehyde, 3,5-di-tert-butylsalicylaldehyde (DtBS), 3,5-dichlorosalicylaldehyde, 5-nitrosalicylaldehyde and 3,5-dinitrosalicylaldehyde]. All the ligands were prepared in parallel using standard techniques. The library of 72 ligands was tested in the vanadium-catalysed oxidation of methyl phenyl sulfide 3a using hydrogen peroxide. We employed two different reaction protocols; in the first, 1 equiv. of VO(acac)₂ was simply added to a suspension of the ligand in CH_2Cl_2 , followed by addition of H_2O_2 and methyl phenyl sulfide **3a** (Scheme 1); in the second, the ligand was preincubated with a solution of VO(acac)₂, and the resin was then filtered and added to the reaction mixture. The latter protocol gave results that were as good as, or better than, the first protocol, so the latter protocol was used in all subsequent experiments.

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Scheme 1 Asymmetric oxidation of methyl phenyl sulfide.

The results from this initial screening indicated that all the ligands were good catalysts for the oxidation, with conversions to the sulfoxide 4 ranging from 56 to 93%, but with the best ee a modest 11% (Wang-Phe-Ser-DtBS). The corresponding threonine derivative (Wang-Phe-Thr-DtBS) gave racemic sulfoxide 4. As a final check, we also prepared the *allo*-threonine derivative (Wang-Phe-Thr*-DtBS),§ which gave excellent conversion to the sulfoxide, with an improved ee of 17%. Since these results were a substantial improvement on either threonine or serine, we felt that we had identified the optimum amino acid AA². We now attempted to optimise this ligand by use of the positional scanning method of Hoveyda and Snapper.7 A library of 18 salicylaldehyde derivatives was screened, and the results unfortunately confirmed that we had already identified the best component. Finally, we prepared another library (Wang-AA1-Thr*-DtBS) in which 19 different D- and L-amino acids were used as AA1, including those with and without functionality. This resulted in the discovery that the use of D-Phe gave a much improved ee of 23%, at a conversion of 89%. Thus, the optimised structure for the asymmetric oxidation of methyl phenyl sulfide 3a had the structure Wang-D-Phe-Thr*-DtBS 5. Although this ligand had the advantage that it could be rapidly assembled, and easily removed from the reaction mixture allowing straightforward product isolation, the ee was simply far too low to be useful.

At this stage, we felt it appropriate to explore whether metal ions other than vanadium might be more effective. We therefore screened a series of metals for their ability to catalyse the oxidation of methyl phenyl sulfide by aqueous hydrogen peroxide in the absence of added ligand, and unsurprisingly $Mo(v_1)$, $W(v_1)$, $V(v_1)$ and Ti(v) all proved effective (with Ti(v)interestingly being the least effective). When the ligand that had been optimised for the vanadium-catalysed oxidation was tested with these metals, it immediately became clear that the combination of Wang-D-Phe-Thr*-DtBS and $Ti(Oi-Pr)_4$ was a much more effective asymmetric catalyst, giving a reproducible ee of between 62 and 64% (*R*-isomer in excess), with high

[†] Electronic supplementary information (ESI) available: HPLC conditions. See http://www.rsc.org/suppdata/cc/b1/b108487a/



Scheme 2 Asymmetric oxidation of alkyl aryl sulfides.

Table 1 Asymmetric oxidation of alkyl aryl sulfides

Sulfide	\mathbb{R}^1	\mathbb{R}^2	Sulfoxid	le Conversion	n^a ee $(\%)^a$
3a	Ph	CH ₃	4a	100%	64
3b	Ph	Et	4b	96%	64
3c	Ph	Pr	4c	90%	57
3d	4-CH ₃ OC ₆ H ₄	CH_3	4d	85%	63
3e	4-ClC ₆ H ₄	CH ₃	4e	90%	58
3f	$4-BrC_6H_4$	CH ₃	4f	70%	53
3g	$4-O_2NC_6H_4$	CH ₃	4g	61%	64
3h	4-NCC ₆ H ₄	CH ₃	4h	90%	45
3i	2-Naphthyl	CH ₃	4i	87%	72
^a Conversions and ee values were measured using chiral phase HPLC.					

HPLC conditions are provided in the supplementary material.

conversion. Clearly the low rate of the background reaction is important. Schiff-base titanium complexes are effective for sulfur oxidation,^{8–10} and very recently it has been reported that Ti(salen) complexes can be very effective in the same process using hydrogen peroxide as the oxidant.¹¹

Since the behaviour of solid-supported ligands and their solution phase counterparts can differ, we converted the optimum ligand into the corresponding methyl ester **6** by treatment with NEt₃ in DMF–MeOH. Use of this solution phase ligand gave an identical 64% ee in the oxidation of methyl phenyl sulfide **3a** to the solid phase analogue (which is therefore a superior catalyst from a practical point of view).

Rather than screening all our previous libraries in the titanium-catalysed oxidation reaction, we tested the corresponding serine, threonine and *O-tert*-butyl threonine derivatives, Wang-D-Phe-Ser-DtBS (27% ee), Wang-D-Phe-Thr-DtBS (23% ee) and Wang-D-Phe-Thr(t-Bu)-DtBS (0% ee) in the titanium-catalysed oxidation of methyl phenyl sulfide **3a**. These results confirm both the importance of the free hydroxyl group and the influence of the stereogenic centre at C-3 of the *allo*-threonine residue.

In order to establish how strongly the titanium was complexed to the solid phase ligand, we incubated a solution of $Ti(Oi-Pr)_4$ in CH₂Cl₂ with the ligand **5**. The resin was then washed 5 times, and the titanium concentration in each of the washings was measured by ICP-AES. While some residual titanium was detectable in the first washing, in all the four subsequent washings the titanium concentration was below the background level (<1 ppm). This suggested that leaching of titanium from the resin was minimal, and that as a consequence the catalyst combination of ligand **5** and Ti might be reusable.



Provided the resin was not allowed to dry out, the catalyst could be reused without erosion of conversion or ee (first run, 62% ee, second run, 64% ee), although the ee did degrade with subsequent runs with the same sample of catalyst.

The ee of our catalyst system was comparable with the original results reported by Bolm, so we decided to investigate its scope in the oxidation of a variety of other alkyl aryl sulfides (Scheme 2), and our results are reported in Table 1. The ee values are remarkably consistent, and indicate the utility of the catalyst. Some overoxidation to the sulfone was observed in the case of 3d (13%) and 3g (22%), but in all other cases the amount of sulfone was less than 5%.

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Notes and references

‡ General procedure for solid phase asymmetric oxidation of sulfides. The solid phase ligand (0.015 mmol) was weighed into an Altech tube. Anhydrous CH₂Cl₂ (2.0 ml) was added, followed by the metal salt (0.05 mmol). After 20 min, the resin was filtered, and anhydrous CH₂Cl₂ (2.0 ml) was added to wash the resin. After one min the resin was filtered. A dry reaction tube with a magnetic stirrer was purged and filled with nitrogen three times. Then the resin was added in the reaction tube, followed by distilled CH₂Cl₂ (2.0 ml), the sulfide (1 mmol), and 30% H₂O₂ in water (1.1 mmol) and the mixture was stirred for 5-16 h, depending on the substrate. A sample (1-2 µl) was then removed, and diluted with 10% IPA-heptane, for analysis by HPLC.[†] To isolate the products, the reaction was worked up by quenching with 10% Na₂SO₃ solution (5 ml). The reaction mixture was extracted with Et₂O (2×10 ml), and the extracts were combined and dried (MgSO₄); the solvent was removed under reduced pressure. The crude product was purified by silica flash chromatography (Et₂O-MeOH 95:5) to leave the product as a white solid.

§ We found that use of Wang-Tle- Thr*-DtBS also gave an improved ee of 18%, but since resin loading of *tert*-leucine is less straightforward, we used commercially available Fmoc-L-phenylalanine resin for the subsequent libraries.

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