Chiral Sulfoxide Ligands in Catalytic Asymmetric Cyanohydrin Synthesis

Gareth J. Rowlands*

The Chemical Laboratories, The University of Sussex, Falmer, Brighton, BN1 9QJ, UK
Fax +44(1273)677196; E-mail: g.rowlands@sussex.ac.uk

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Abstract: A novel chiral sulfoxide-containing ligand for the catalytic addition of trimethylsilylcyanide to aldehydes is reported. The sulfoxide moiety was found to be vital for reactivity.

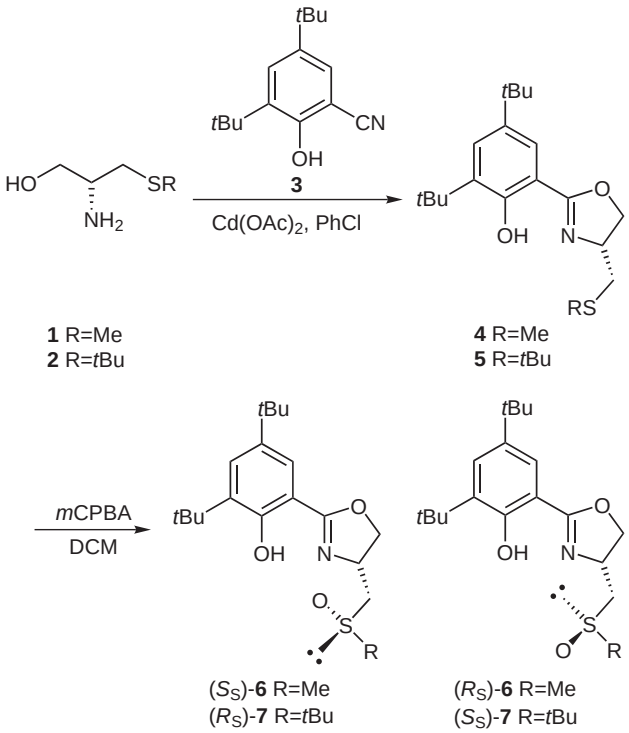
Key words: aldehydes, catalysis, cyanohydrins, chiral sulfoxides

The asymmetric synthesis of cyanohydrins is currently an area of intense study due to the highly versatile nature of this structural motif.[1,2] Existing methods for the preparation of cyanohydrins include both enzymatic[2,3] and chemical processes.[2,4] Of the latter, chiral Lewis acid catalysis is probably the most exploited. As more empirical data becomes available it is increasingly becoming clear that the majority of these catalysts operate via a dual activation mechanism[5,6] in which the catalyst activates both the carbonyl substrate and the incoming nucleophilic cyanide moiety. Research to exploit this greater understanding of the mechanism has culminated in the bifunctional catalysts of Shibasaki,[7] the peptide-based Schiff catalysts of Hoveyda[8] and the dimeric salen complexes of Belokon' and North.[9] In this paper we report our exploratory results utilising chiral sulfoxide-containing titanium-oxazoline complexes for the asymmetric synthesis of cyanohydrins.

Sulfoxides are an attractive Lewis basic functional group. There exists a plethora of methods for synthesising enantiomerically pure chiral sulfoxides[10] and they are efficient electron-donors, forming complexes with a variety of metals.[11] Yet their use in asymmetric catalytic processes remains largely unexplored.[12,13] Hiroi has made significant contributions in which sulfoxides have been employed as the binding site between metal and ligand.[14] Yet, with the exception of ligands for the addition of diethylzinc to aldehydes,[13,15] they have not been used as Lewis bases in catalysis. Considering that sulfoxides have a centre of chirality on the donor and not just in the ligand scaffold this appears remiss.

The paucity of examples of sulfoxides in such a role presumably reflects their relatively low Lewis-donicity as reflected in solvent basicity scales.[16] Sulfoxides are considerably less electron donating than phosphoramides,[17] the most prevalent Lewis base catalysts but are better than amides such as dimethylformamide that have found use in Lewis base catalysis.[18] We felt that the potential issue of the reduced Lewis basicity could be overcome by designing a catalyst that operated via a dual activation pathway. The synergistic activation of the carbonyl substrate by a Lewis acid in conjunction with even weak activation of the incoming nucleophile by the sulfoxide could offer a synthetically useful reaction. This, in conjunction with known nucleophilicity of sulfoxides towards silicon,[19] led us to examine the cyanosilylation of aldehydes.

The ligands were based on the phenolic oxazoline scaffold.[20] This offers a discreet metal-ligand bond via the alkoxide, a well-defined chiral scaffold in the oxazoline moiety[21] and ease of introduction of the sulfur substituent via cysteine derivatives. The incorporation of a second chiral centre in to the ligand would result in the formation of diastereoisomers on oxidation of the sulfide to the sulfoxide, potentially facilitating separation of the two chiral sulfoxides. One possible shortcoming with these ligands was the potential for internal coordination between the sulfoxide and the Lewis acid and subsequent catalyst deactivation. For such an exploratory study this risk was deemed acceptable.



Scheme 1

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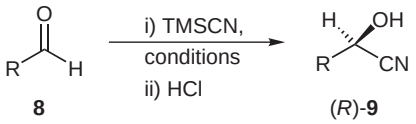
Phenolic oxazoline **4** was prepared from commercially available *S*-methyl-L-cysteine via reduction[22] to the alcohol **1** followed by condensation[23] with the readily accessible nitrile **3** (Scheme 1).[24] Oxidation of sulfide **4** with MCPBA gave a 1:1 mixture of diastereotopic sulfoxides **6**. Unfortunately, it proved impossible to isolate both in diastereomerically pure form, only (S_S)-**6**, which was eluted first, could be purified. The relative stereochemistry at sulfur was confirmed by X-ray crystallography.



8 (*R*)-**9**

Scheme 2

The reaction of benzaldehyde **8** (R = Ph) with trimethylsilylcyanide in the presence of a chiral titanium complex, prepared in situ from Ti(*i*-PrO)$_4$ and a diastereomeric mixture of sulfoxides favouring the *R*-sulfoxide (70% de), was examined first (Scheme 2; Table 1). The optimum solvent was found to be dichloromethane, which gave both superior yields and enantiomeric excess (entry 1; Table 1) when compared to toluene (entry 2; Table 1) or tetrahydrofuran (entry 3; Table 1) at –35 °C. Altering the temperature of the reaction produced the expected results, raising the temperature (entry 4; Table 1) resulted in increased reactivity but with reduced selectivity. Whilst at a lower temperature (entry 5; Table 1) the reaction was slower but the enantiomeric excess increased. The stoichiometry of the catalyst also appeared to effect the efficiency of the reaction. If the loading was lowered (entry 6; Table 1) then the rate of reaction decreased and there was a slight reduction in selectivity. Alternatively, increasing the loading (entry 7; Table 1) resulted in increased selectivity.

More interesting results were obtained when the diastereomeric excess of the sulfoxide was altered. Increasing the proportion of the *S*-sulfoxide in the ligand mixture resulted in a steady decrease in the enantiomeric excess of the product **9** but with no observable effect on the rate of reaction. If pure *S*-sulfoxide (S_S)-**6** was utilised the selectivity actually reversed, albeit with considerably worse selectivity than the R_S-diastereoisomer (entry 8; Table 1). The initial belief, based on related chiral

Table 1 Optimisation of the Cyanosilylation of Benzaldehyde

Entry	Ligand	Mol%	Temp. (°C)	Solvent	Time (h)	Yield (%)	ee[a] (%)
1	**6**[b]	9	–35	CH_2Cl_2	12	>90	40 *(R)*
2	**6**[b]	9	–35	toluene	12	20	10 *(R)*
3	**6**[b]	9	–35	THF	12	60	20 *(R)*
4	**6**[b]	9	0	CH_2Cl_2	8	76	20 *(R)*
5	**6**[b]	9	–84	CH_2Cl_2	48	52	49 *(R)*
6	**6**[b]	4.5	–35	CH_2Cl_2	48	71	33 *(R)*
7	**6**[b]	100	–35	CH_2Cl_2	12	79	49 *(R)*
8	(S_S)-**6**	9	–35	CH_2Cl_2	12	78	12 *(S)*
9	(S_S)-**7**	9	–35	CH_2Cl_2	12	72	47 *(R)*
10	(S_S)-**7**	9	–84	CH_2Cl_2	60	>95	54 *(R)*
11	(S_S)-**7**	100	–84	CH_2Cl_2	60	>95	60 *(R)*
12	(S_S)-**7**	9	–84	CH_2Cl_2[c]	24	>95	54 *(R)*
13	(R_S)-**7**	9	–35	CH_2Cl_2	12	63	22 *(S)*
14	**10**	9	–35	CH_2Cl_2	12	40	7 *(R)*
15	**10**	9	–84	CH_2Cl_2	96	0	–
16	**11**	9	–84	CH_2Cl_2	168	40	27 *(R)*
17	**12**	9	–84	CH_2Cl_2	66	0	–
18	**12**	9	–35	CH_2Cl_2	12	27	26 *(R)*

[a] Ee determined from the ^{1}H NMR spectrum of the methoxyphenylacetic acid derivative. Absolute configuration by optical rotation
[b] 70% de favouring (*R*)-configuration at sulfur
[c] Reaction performed 3.5 times more concentrated

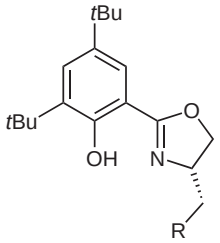
Schiff base-titanium alkoxide catalysts,[25] that the stereochemistry of the oxazoline ring was the dominant stereodirecting group was clearly wrong. The optimum catalyst structure requires the stereochemistry of both the oxazoline and the sulfoxide to be matched.

In order to further investigate the intriguing influence of the sulfoxide moiety the *tert*-butyl derivatives[26] **7** were synthesised. We anticipated that the steric bulk would improve the selectivity of the reaction and that the increased inductive effect of the *tert*-butyl group would augment the Lewis basicity of the sulfoxide. Pleasingly the diastereomeric sulfoxides **7** were readily separable by column chromatography.[27] X-ray crystallography revealed the first eluted diastereoisomer to be the (R_S)-**7**.

Initial results, utilising the *S*-configured sulfoxide (S_S)-**7**, indicated a slight improvement in selectivity (entry 9; Table 1). More encouraging was the increase in reactivity at low temperature with concomitant increase in selectivity (entry 10; Table 1). This suggests that the Lewis basicity of the sulfoxide is an important factor in the reactivity of these complexes. As with the methyl derivative, use of a stoichiometric amount of the complex led to increased selectivity (entry 11; Table 1). In order to reduce the reaction time of the catalytic variant at low temperature, the concentration of the reaction was increased which led to a pleasing 97% yield with 54% ee in just 24 hours (entry 12; Table 1).

Once again the effect of the sulfoxide was investigated. Use of the opposite configuration of sulfoxide (R_S)-**7** led to a reversal in selectivity (entry 13; Table 1). Unsure as to the extend of the sulfoxide moiety's role in the cyanosilylation we examined three control ligands bereft of the Lewis basic group (Figure 1). Both **10** and **11**, derived from phenylalaninol and leucinol respectively, showed considerably reduced reactivity and selectivity. Under the standard conditions, **10** furnished only 40% cyanohydrin in a meagre 7% ee (entry 14; Table 1). Cooling the reaction to –84 °C resulted in no reaction even after 96 hours (entry 15; Table 1). Ligand **11** faired slightly better giving cyanohydrin **9** but only after 168 hours at –84 °C (entry 16; Table 1). Clearly the sulfoxide moiety is not an innocent steric spectator in the cyanosilylation reaction. We then opted to study the sulfone **12** derived from the complete oxidation of **5**. It was thought that this would mimic the sterics of the analogous sulfoxide **7** whilst sufficiently reducing the Lewis basicity[16] to reveal more information about any electronic effects. Interestingly the catalyst derived from sulfone **12** (Figure 1) was completely inactive at –84 °C (entry 17; Table 1). Repeating the reaction at –35 °C furnished the desired cyanohydrin in a mere 27% and 26% ee (entry 18; Table 1). These results reinforced the conclusion that the sulfoxide was playing an active role in the catalysis.

To investigate the scope of the reaction with regard to substrate structure a variety of aldehydes were subjected to the optimised conditions[28] (Scheme 2; Table 2). Whilst most aldehydes could be converted in moderate to good



10 R=Ph, **11** R=*i*Pr, **12** R=*t*BuSO$_2$

Figure 1

yields it was found that the catalyst was sensitive to steric effects (entries 3, 4 and 9; Table 2). The electronics of the aromatic ring also had a great effect on the selectivity of the reaction. Electron-donating substituents gave the best enantiomeric excesses (entries 2 and 6; Table 2) whilst electron-withdrawing substituents resulted in very poor selectivities (entries 3 and 5; Table 2). Inexplicably both aldehydes containing an α-proton (entries 10 and 11; Table 2) resulted in a reversal of absolute configuration of the cyanohydrin.

Table 2 Asymmetric Cyanosilylation of Aldehydes with Ligand (S_S)-**7**

Entry	Aldehyde	Yield (%)[a]	ee (%)[b]
1	Benzaldehyde	85	54 (*R*)
2	4-Methoxybenzaldehyde	80	57 (*R*)
3	2-Nitrobenzaldehyde	48	10 (*R*)
4	Mesitaldehyde	15	15 (*R*)[c]
5	4-Nitrobenzaldehyde	51	0
6	3,5-Dimethoxybenzaldehyde	72	61 (*R*)
7	2-Naphthaldehyde	80	40 (*R*)
8	Cinnamaldehyde	78	50 (*R*)
9	Trimethylacetaldehyde	26	40 (*R*)[c]
10	2-Methylpropionaldehyde	87	37 (*S*)
11	Heptanal	62	37 (*S*)

[a] All reactions were carried out according to experimental procedure.[28,]

[b] Ee determined by ^{1}H NMR of the methoxyphenylacetic acid derivative and absolute configuration by optical rotation.

[c] Absolute stereochemistry was estimated by analogy.

The mechanistic details of the process are uncertain at present. ^{1}H NMR of the titanium complex indicates that the phenol moiety displaces one *iso*-propoxide unit as indicated by both the absence of the phenol hydroxyl peak at 12 ppm and the integration of the *iso*-propoxide signals. The *iso*-propanol thus generated could facilitate the formation of a low concentration of hydrogen cyanide that could catalyse the reaction. The difference in reactivity

between (S_S)-**7** and **10**–**12** would suggest that this is not the case. Therefore it is evident that the sulfoxide moiety plays an integral role in catalysis.[29] Whilst we have evidence that the sulfoxide moiety can participate in the desired dual activation pathway,[30] it seems unlikely that it is in this example. The absolute stereochemistry of the major cyanohydrin product was the same regardless of the presence of the Lewis base (Table 1; entry 10 vs. 16). Alternatively, the sulfoxide could be coordinated to the metal centre to give a coordinatively saturated titanium complex. ^{1}H NMR of the titanium complex of the methyl sulfoxide **6** showed a downfield shift in the methyl singlet compared to the free ligand consistent with coordination. The sulfoxide moiety does not displace an *iso*-propoxide unit as ^{1}H NMR clearly indicates the presence of three *iso*-propoxide units within the complex. The sulfoxide could then behave as a hemi-labile ligand,[31] forming a vacant site on the titanium that would allow facile coordination and activation of the aldehyde. Such an explanation does not satisfactorily explain the selectivity differences between the two sulfoxide configurations. Interestingly, Feng[6] recently reported *N*-oxide titanium complexes catalysed the cyanosilylation of ketones. Whilst they propose a dual activation pathway their complexes can also undergo internal coordination. It is clear that further study is required to elucidate the mechanism of the sulfoxide-mediated process.

In conclusion, a novel sulfoxide containing ligand for the cyanosilylation of aldehydes has been developed. The reaction is mechanistically interesting as a result of the crucial role played by the Lewis basic sulfoxide in catalyst activity. Work to modify the chiral scaffold to improve the enantioselectivity and to extend the use of sulfoxides in Lewis base promoted reactions[32] is currently underway and will be reported in due course.

Acknowledgement

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(27) Sulfoxide (S_S)-**7**: ^{1}H NMR (300 MHz, $CDCl_3$) 12.21 (1 H, br s,), 7.53 (1 H, d, *J* = 1.5 Hz), 7.44 (1 H, d, *J* = 2.5 Hz), 4.93–4.82 (1 H, m), 4.61 (1 H, t, *J* = 9.5 Hz), 4.29 (1 H, t, J 9.0 Hz), 2.84 (1 H, dd, *J* = 12.5 Hz, 6.5 Hz), 2.68 (1 H, dd, *J* = 12.5 Hz, 7.5 Hz), 1.42 (9 H, s), 1.28 (9 H, s), 1.26 (9 H, s); ^{13}C NMR (75 MHz, $CDCl_3$) 167.7 (C), 157.3 (C), 140.7 (C), 137.0 (C), 128.9 (CH), 122.8 (CH), 109.7 (C), 71.9 (CH_2), 62.2 (CH), 53.8 (C), 51.4 (CH_2), 35.5 (C), 34.7 (C), 31.9 (CH_3), 29.8 (CH_3), 23.2 (CH_3); MS (EI) *m/z* = 393, 337, 322, 274, 250, 217, 205, 149, 57.
Sulfoxide (R_S)-**7**: ^{1}H NMR (300 MHz, $CDCl_3$) 12.15 (1 H, s), 7.52 (1 H, d, *J* = 2.5 Hz), 7.42 (1 H, d, *J* = 2.5 Hz), 4.91–4.81 (1 H, m), 4.58 (1 H, t, *J* = 9.0 Hz), 4.40 (1 H, dd, *J* = 9.0 Hz, 7.0 Hz), 3.00 (1 H, dd, *J* = 12.5 Hz, 3.5 Hz), 2.59 (1 H, dd, *J* = 12.5 Hz, 10.0 Hz), 1.40 (9 H, s), 1.27 (9 H, s), 1.25 (9 H, s); ^{13}C NMR (75 MHz, $CDCl_3$) 167.9 (C), 157.2 (C), 140.7 (C), 137.1 (C), 128.9 (CH), 122.7 (CH), 109.5 (C), 71.0 (CH_2), 61.4 (CH), 54.1 (C), 51.1 (CH_2), 35.5 (C), 34.7 (C), 31.9 (CH_3), 29.8 (CH_3), 23.1 (CH_3).
(28) Typical procedure: Ti(*i*-PrO)$_4$ (0.013 mL, 0.04 mmol, 0.09 equiv) was added to a solution of (S_S)-**7** (0.018 g, 0.05 mmol, 0.1 equiv) in CH_2Cl_2 (0.78 mL) at room temperature. The resultant pale yellow solution was stirred at room temperature for 1 hour whereupon it was cooled to –78 °C. Benzaldehyde (0.049 mL, 0.47 mmol, 1.0 equiv) was added and the solution stirred for a further 30 min. TMSCN (0.095 mL, 0.71 mmol, 1.5 equiv) was then added and the reaction vessel transferred to a –84 °C freezer for 60 h. $HCl_{(aq)}$ (3 M; 3 mL) was added and the mixture vigorously stirred at room temperature for 2 h. The layers were separated and the aqueous phase extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The cyanohydrin **9** was isolated by column chromatography (petroleum ether:ether, 3:1).
(29) At –84 °C there was no reaction between benzaldehyde and TMSCN in the presence of either 10% Ti(*i*-PrO)$_4$ or 10% Ti(*i*-PrO)$_4$ + 10% DMSO after 48 h. On warming to –20 °C complete reaction was observed in the presence of just 10% Ti(*i*-PrO)$_4$ in 12 h whilst the reaction had only gone to 60% completion in the presence of 10% Ti(*i*-PrO)$_4$ + 10% DMSO over the same period. Again this indicates that the ligand is essential for activity. The decrease in the rate of reaction in the presence of DMSO could possibly be the result of the formation of a coordinatively saturated octahedral complex with resultant loss in Lewis acidity. This would require two equivalents of DMSO per titanium centre thus resulting in only 5% active catalyst being present. Stoichiometry of the catalyst has already been shown to effect the rate (Table 1; entry 6).
(30) Three aluminium complexes were studied in cyanosilylation reaction of benzaldehyde. One formed from 2,2′-biphenol gave 58% conversion, one with a phenyl sulfone substituent in the *ortho* position of 2,2′-biphenol gave 75% conversion whilst the phenyl sulfoxide substituted 2,2′-biphenol gave 92% conversion. This suggests that the sulfoxide is activating the TMSCN and that it is not purely an electronic effect making the aluminium centre more Lewis acidic. Work to convert this to a chiral system is currently underway.
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