(Nonracemic) thiols and Zn\(^{II}\). Structural and catalytic aspects of some natural and non-natural zinc thiolates

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The catalytically active Zn\(^{II}\) ion of the enzyme horse liver alcohol dehydrogenase (HLADH) is well known to be co-ordinated to two thiolates and an imidazole. Attempts to prepare models of this catalytically active Zn\(^{II}\) complex are complicated by the great tendency of Zn\(^{II}\) thiolates to form oligomeric structures. Some approaches to monomeric structures are described. Work on this problem has led to spin-offs in the form of the use of \(\beta\)-aminothiols as ligands in the addition of diethylzinc to aldehydes. Monomeric zinc complexes are believed to be the active intermediates in this reaction. Excellent control over the enantioselectivity can be obtained. Methods developed in recent years for the synthesis of a variety of functionalized chiral nonracemic thiols open the way to the development of a catalytic chemistry of thiols in general and Zn\(^{II}\) thiolates in particular.

Introduction

Aggregation/cluster behaviour in certain organometallic systems contains the key to structural organization, chemical reactivity and catalysis.\(^1\) A clever recent example of control of the first aspect is that of Reinhoudt et al., wherein the directional aspects of co-ordinate bonds serve as a key to pre-planned structural organization of a metallodendrimer.\(^2\) Examples of control of the second and third aspects will follow in this article. A small but instructive segment of this broad area will be considered, namely complexes derived from interaction of Zn\(^{II}\) with thiols, and in a few cases sulfides.\(^3\) In the majority of the examples the thiols will be new compounds that derive from some of our work in recent years. The decision to focus this review on the combination of the zinc ion with thiols stems from experimental observation by us and others of interesting structural and catalytic possibilities. Links will be established with other systems of broad biochemical and chemical interest, for instance the interesting parallel with the rôle of zinc alkoxide compounds.\(^4\)

Consider first the Zn\(^{II}\) ion with its closed shell d\(^{10}\) configuration, small diameter (0.69 Å), strong electrophilicity and reluctance to engage in redox chemistry. Many examples of four (tetrahedral), five (trigonal or square bipyramidal) and six (octahedral) co-ordination numbers (stereochemistry) for Zn\(^{II}\) are known. The flexible zinc co-ordination sphere is adaptable to the demands of the ligands. Owing to the absence of crystal field stabilization effects, the stereochemistry of the ligands around the metal reflects ligand size together with electrostatic and covalent binding forces.\(^5\) Zn\(^{II}\) co-ordination complexes therefore often deviate strongly from regular geometries.\(^5,6\) Surely this must make the Zn\(^{II}\) ion suitable for enzyme active sites, where the co-ordinating amino acids can undergo small readjustments in position about the metal ion without shifting away owing to the restrictions provided by the protein secondary structure.\(^5,6\)

Zincate (ZnX\(^{2-}\)) ions are readily formed especially for X = OR, SR, Cl and Br. The Zn\(^{II}\) ion has a pronounced tendency to form cluster compounds with, in fact, virtually all anions capable of three-centre bonding. Superlative treatises on the chemistry and structural aspects of zinc compounds are available.\(^5\)

The interaction of thiols, thiolates and sulfides with Zn\(^{II}\) ions has in the past not been the stuff of addictive curiosity. Not much structural information is available on Zn\(^{II}\)-sulfide complexes apparently because the association is usually not strong enough to lead to well defined complexes. The chemistry of Zn\(^{II}\) with thiolates is better defined and entails typically either the formation of anionic aggregates,\(^7\) a common motif being [Zn(SR)\(_2\)]\(^{2-}\) as exemplified in the distorted (and on the NMR time scale fluxional) adamantyl-like structure 1, or neutral [Zn(SR)\(_2\)]\(^2+\) species like dimer 2.\(^6\) Less structurally hindered analogues of 2 probably can couple to form cubanes in analogy to zinc alkoxides for which these structures are better defined.\(^8\)

Ligand exchange on the Zn\(^{II}\) centres seems to be general\(^7\) although there appear to be no specific studies either of the relative rates of exchange of halide compared to alkoxide compared to thiolate or of the effect of structure and basicity (for alkoxides and thiolates) on the rates of exchange. From the qualitative information available we have the impression that these rates (in solution) span a range of several orders of magnitude from quite fast on the NMR time scale at ambient temperature to very slow on the same scale depending on, among other things, structural and electronic effects in the thiolates.

Higher order structures involving organic thiolates are known\(^7\) although not to the limit of the repeating unit of wurtzite 3 owing to the capping of the sulfurs with organic groups. Aggregation is by no means peculiar to zinc thiolates; similar chemistry is observed with Zn\(^{II}\) alkoxides, alkyls and halides.\(^5\)
The pronounced tendency towards aggregation results in a scarcity of examples of monomeric zinc thiolates. By reverse argument this scarcity indicates high reactivity. Important examples of monomeric complexes come from enzymes and regulatory peptides. One of the two Zn$^{II}$ centres in liver alcohol dehydrogenase has a formally negatively charged tetraco-ordinated Zn$^{II}$(cys)$_4$ centre; a similar centre is found in aspartate transcarbamoylase. These centres have, as far as is known, a structural but not catalytic function. Structurally analogous zinc thiolate centres can be created artificially in Desulforedoxin. Formally uncharged tetrahedral Zn$^{II}$(cys)$_2$(his)$_2$ centres are found in several ‘zinc finger’ regulatory proteins. Berg has recently emphasized that the role of zinc ions in general in stabilizing folded conformations of protein domains, seems to have been seriously underestimated.

Probably the best known catalytically active zinc thiolate is (the second) zinc centre in horse liver alcohol dehydrogenase, HLADH. This Zn$^{II}$ ion, co-ordinated to cys-46, cys-174 and his-67, bears in the resting state a water molecule as fourth ligand (4). In the catalytic process, this water is either replaced by substrate (alcohol or aldehyde), or addition to afford a pentavalent complex occurs. For a model system (not containing thiolate) that has been examined, the energy required for transition between four- and five-co-ordinate bonding in Zn$^{II}$ is small. This catalytically active zinc in HLADH may make good use of its amphoteric character in the reversible redox reaction catalysed by HLADH by acting either as an electrophile towards a carbonyl group to promote hydride acceptance from NADH or as a base in a zinc alcoholate to promote hydride donation from the alcoholate to NAD$^+$.

Models for the catalytically active zinc of HLADH

A long-standing interest in NADH chemistry and the desire to test the validity of some of the above ideas led us to try to prepare monomeric Zn$^{II}$ thiolate centres and to study their chemistry in order to understand better the role of the metal both in structural and catalytic capacity. This interest in zinc thiolates (and sulfides) was stimulated concurrently by the intense activity in the chemistry of alkylzincs with carbonyl compounds, whereby zinc alkoxides play an essential role.

The observation that neutral complexes 5 and 6 had been obtained as crystals and their structures determined by crystallographic techniques was an excellent precedent. Apparently the trisubstituted phenyl rings provide sufficient steric hindrance in both tetrahedral structures to prevent association. These complexes 5 and 6 seem to have no particular catalytic reactivity.

In an initial attempt tridentate ligand 7 was prepared as a mimic of the catalytically active site of HLADH. The aryl ‘roof’ and aliphatic ‘walls’ were anticipated to provide sufficient steric shielding to prevent dimerization. Things are not that simple. The Zn$^{II}$ complex of 7 was clearly oligomeric although the exact structure was never defined. The Co$^{III}$ complex, however, was monomeric and had spectral characteristics strongly resembling those of Co$^{III}$ substituted HLADH. The complex also possessed catalytic activity in that it mediated (poorly) the reduction of an activated carbonyl compound by N-benzyl-1,4-dihydonicotinamide.

The reaction of a more compact tridentate ligand, ‘pyridine dithiol’ 8a, with Zn$^{II}$ was next examined [eqn. (1)].

\[ \text{Zn}^{II} + 2 \text{NAD}^+ + \text{RCHO} \rightarrow \text{Zn}^{II} \text{NAD}^+ + \text{RCH}_2\text{OH} \]

The synthesis and use of ‘pyridine dithiols’ was first described by Holm and Berg; 8a was anticipated to be more sterically hindered than 7.

Despite the four bulky phenyl groups, 8a with ZnCl$_2$ nevertheless provided dimer 2, which has a cisoid structure with C$_2$ symmetry. Dimerization could be circumvented, however,
by locking the phenyl groups together via the large, flat fluorenyl groups of 8b; the monomeric complex 9 is readily soluble in organic solvents (in contrast to oligomers) and was characterized by NMR.

However, this structural success was catalytic overkill. The degree of steric shielding is apparently so great in complex 9 that nothing can approach the Zn\(^{II}\) centre. Neither co-ordination of additional ligands nor any activity as a mimic for the catalytically active Zn\(^{II}\) centre of liver alcohol dehydrogenase has been observed.

An intermediate between extremes is 8c, which is prepared by the base-induced addition of lutidine (2,6-dimethylpyridine) to adamantane thione.\(^{20}\) (Previous experience with far more circuitous routes to pyridine thiols\(^{8,19}\) nearly caused us to disregard this simple synthesis.) From preliminary experiments it appears that the adamantyl groups provide sufficient hindrance to prevent dimerization but leave a cavity (10) that is approachable by other ligands once the metal is encapsulated. Dithiol 8c is also a receptor for various metal cations as well as acids like HCl;\(^{20}\) the corresponding diol (-OH instead of -SH) also gives a stable complex with HCl\(^{21}\) and a pentavalent silyl derivative with dimethylsilyl dichloride.\(^{22}\) The chemistry of 8c and related compounds is currently being investigated actively.

Thiols and catalytic enantioselective reactions

Efforts to mimic the zinc catalytic centre of HLADH have so far been more successful from a structural than catalytic standpoint. Monomeric zinc thiolates are catalytically reactive, however. In our hands the catalytic potential of zinc thiolates has been better revealed through a different line of investigation, namely the chemistry of thiol analogues of \(\beta\)-amino alcohols, in particular thioephedrines.

Synthesis of these previously poorly defined thioephedrines is possible as outlined in eqns. (2) and (3).\(^{23}\) Ephedrine 11 and pseudoephedrine 15 readily undergo intramolecular S\(_{\text{N}}\)2 substitutions under Mitsunobu conditions to afford aziridines 12 and 16.\(^{24}\) These aziridines are ring-opened regioselectively in a clean S\(_{\text{N}}\)2 reaction with thiols. The end product 14 of reaction with thiol acids is not 13 but that of an S to N acyl shift. Pseudoephedrine 15 provides aziridine 16, which, although it reacts rather sluggishly, ultimately provides 17 and 18.

Ephedrine thiol 20 is obtained indirectly from 19; trapping as the condensation product allows one to avoid spontaneous oxidation to the disulfide. Removal of this protecting group under acidic conditions affords the HCl salt of 20 as a stable solid [eqn. (4)]. The free thiol is extremely sensitive to oxidation to the disulfide 21. Reductive cleavage of 19 with LiAlH\(_4\) provides \(N\)-isopropyl thioephedrine 22 or the corresponding disulfide 23. The \(N,N\)-dimethyl derivative 24 is obtained by cycloaddition of 12 with CS\(_2\) followed by reduction.

Our first investigation\(^{25}\) into the catalytic abilities of zinc thiolates was with the well studied addition of diethylzinc to benzaldehyde [eqn. (5)] to form 1-phenylpropan-1-ol 25 using the thioephedrines as inducers. Amino alcohols like ephedrine 11 and (\(+\))-DAIB 26 are well known as excellent inducers of the thioephedrines as inducers. Amino alcohols like ephedrine this reaction. The ‘on-off’ switch of this ligand accelerated\(^{16}\) process is convenient; no reaction with aldehyde in hydrocarbon solvent in the absence of inducer, reaction as soon as inducer is added.

Noyori\(^{16}\) has been instrumental in defining the mechanistic details of the reaction induced by amino alcohols. Crucial intermediates (carbon stereochemistry omitted for purposes of illustration) are 27, 28 and 29 and dimer 30 for the addition of R\(_2\)Zn to R\(^{\prime}\)CHO induced by R\(_2\)NCH\(_2\)CH\(_2\)OH [eqn. (6)]. The relative position of the equilibria, as well as the rates of conversion, depend—not surprisingly—on the structure of the amino alcohol ligand and the type of
aldehyde. Note that reactivity is centred about the monomeric not dimeric species.

Thioephedrines also induce the reaction of eqn. (4) very well. (R)-1-Phenylpropan-1-ol 25 is obtained in virtually quantitative yield in 94% ee with 20 as the inducer. In practice the more stable disulfides can better be used. In our experience aminothiols are highly sensitive to oxidation and are best handled as either the HCl salts or as the disulfides. The disulfides are activated in situ by attack of an ethyl group from diethylzinc on the disulfide linkage as illustrated in general terms in eqn. (7).

\[
\text{Et}_2\text{Zn} + \text{RSSR} \rightarrow \text{RSEt} + \text{RSZnEt} \quad (7)
\]

Other aminothiols have been reported to induce the diethylzinc addition. Kang and co-workers,²⁸,²⁹ have used both the free thiols 31 and 33 as well as the respective disulfides 32 and 34 to induce the addition of diethylzinc to aromatic as well as α-branched aliphatic aldehydes; ees of > 99% have been reported.† An interesting but puzzling sidelight is that a complex, formulated as 35, is reported to associate with various boranes leading ultimately to asymmetric reduction of meso-imides [eqn. (8)].³⁰ The mechanism of this reaction is not clear.

The thiols 31 and 33 are prepared via successive S₂2 reactions; mesylation of the N-alkylated ephedrine produces an aziridinium salt that is ring-opened by thiolate.

Ligand 36 described by van Koten et al.,³¹ readily forms a zinc complex 37 with zinc chloride, which with diethylzinc forms dimer 38 [eqn. (9)]. This is capable of inducing the addition of diethylzinc to aromatic aldehydes in up to 99% ee.

The information now available, although admittedly limited, gives us no reason to seek a mechanistic model for the aminothiol-induced additions of dialkylzincs fundamentally different from that given by Noyori and co-workers for amino alcohol-induced additions.³³,³³ The rôle of aggregation phenomena has been carefully defined by Noyori, who emphasizes the ‘softness’ (i.e. relatively low kinetic barriers to transitions between various intermediates) of the energy surface.³³

Based on analogy with β-amino alcohols, key intermediates [eqn. (10)] in thioephedrine-induced additions are expected to be monomer 39, dimer 40, tetramer 41 and catalytically active species 42 and 43. Again, the monomeric species are responsible for the reactivity. However, to our knowledge no examples of 39, 42 or 43 have yet been characterized unambiguously.

‡ After submission of this manuscript it was reported that aminothiols derived from proline are also excellent inducers of the addition of Et₂Zn to aldehydes.²⁹

The sense of enantioselection with aminothiols as inducers is analogous to the amino alcohols. The configuration at the thiol-bearing carbon determines the end configuration of 25; (1R,2S)-20 provides R-25 whereas the pseudoephedrine analogue (1S,2S)-25 provides S-25. (Note that in ref. 25 the enantiomers of the compounds used are illustrated.) This result
is consistent with transition states analogous to those suggested by Noyori. 32

Differences between amino alcohols and aminothiols appear, for example, in the investigation of nonlinear effects in asymmetric induction. 27 The nonlinear effects in asymmetric induction for N-methylephedrine and N-methylethioephedrine 24 have been compared. To our knowledge no investigations of the possible nonlinear behaviour of N-methylephedrine have ever been reported; this is striking in view of the powerful positive effects observed with (+)-DIAB. 26 Rather to our surprise we found no nonlinear effects with N-methylephedrine over the entire range of enantiomeric purities. On the other hand 24 led to a modest but unmistakable positive nonlinear effect; for example 50% ee in 24 led to 73% ee in 25.

Attempts to follow the aggregation behaviour of N-methylephedrine 24 by NMR spectroscopy were relatively unrewarding; observed effects were small and difficult to reproduce. Osmometric measurements were more informative. With a single equivalent of diethylzinc, N-methylephedrine gave a molecular weight of 770 (theoretical for monomer, see generic structure 30, 274), corresponding roughly to a 1:1 mixture of dimer and tetramer. On the other hand 24 with an equivalent amount of diethylzinc gave an observed molecular weight of 1215, which corresponds nicely with tetramer 41. An extra equivalent of diethylzinc completely breaks up this latter aggregate (observed molecular weight 364, theoretical for monomer 43, 413). Extra diethylzinc also breaks up the N-methylephedrine aggregate (observed molecular weight 425, theoretical molecular weight 397). The origin of the nonlinear effects with 24 is likely a tetramer 41 formed from two meso-dimers. The stability of this meso-tetramer must be greater than that of the heterochiral tetramer so that it is not broken apart by the excess of diethylzinc.

What is clearly needed to test for dramatic nonlinear effects is a sterically rigid aminothiol, for instance the—as far as we are aware unknown—thiol analogue of DIAB. 26 Unfortunately our efforts to prepare this compound have so far failed. We have greater hope for 44, the alcohol analogue of which has now been prepared. 33

The wider possibilities for applications of thiols in (catalytic) synthesis require emphasis. These possibilities have become greater in recent years owing to reasonable breakthroughs in the synthesis of various functionalized chiral nonracemic thiols. These synthetic approaches are summarized. First, routes have been developed for the synthesis in optically pure form of α-mercapto acids; such compounds are very sensitive to racemization.

Diazotization of various amino acids 45 in the presence of chloride (or bromide) ions leads to α-halogeno acids 46 with retention of configuration. Substitution by the caesium salts of thiobenzoic or thioacetic acids in DMF proceeds virtually without racemization to give 47, which, with care, can be deacylated with ammonia to afford enantiomerically pure 48 [eqn. (11)]. 34 The mercapto analogue of lactic acid, ‘thiolactic acid’ 48a 34-36 has received considerable attention now that it is available in enantiopure form.§

Access to 48a has been improved and simplified further via a recently modified synthetic method that allows entry to either enantiomer via the single cheap starting material (S)-lactic acid 49. This is illustrated in eqn. (12). 37 The use of pig liver esterase (PLE) for ester hydrolysis is a major improvement; there is little risk of partial racemization during work-up.

Optically pure α-mercapto acids can serve as the precursors for a wide variety of di- or tri-functionalized thiols or thiol derivatives. A simple, and racemization free, approach is illustrated with 48a in eqn. (13). The 1,3-thiazolidin-4-ones (50a-d) are formed in excellent yield by condensation; reduction of 50a to 51a also proceeds smoothly. For example, condensation product 50c is obtained more than 90% § It is interesting that 48a seems not to form spontaneously a thiolactide, analogous to the lactide of lactic acid. Polymerization of lactic acid is normally carried out via the lactide but for 48a polymerization is reported to occur via the S-carboxy anhydride. 36

\[ \text{[eqn. (11)]:} \]

\[ \text{[eqn. (12)]:} \]

\[ \text{[eqn. (13)]:} \]
diastereoisomerically pure as the cis compound. A single recrystallization provides pure material. In the CuI-catalysed addition of diethylzinc to cyclohexenone (a reaction in which it is extremely difficult to control the enantioselectivity), 50c is remarkably effective as ligand and affords the 1,4-addition product in 62% ee. These reactions have been thoroughly investigated by A. de Vries in the group of Prof. B. L. Feringa, with whom we collaborate. A method to obtain α-substituted-α-mercapto acids 54 is via cis-1,3-oxathiolanones 52 as illustrated to provide cis-53, again with 48a, in eqn. (14). 59

use of a tertiary butyl group from pivaldehyde to retain optical activity during alkylation was introduced by Seebach et al. 40

The availability now of a wide variety of optically pure thiols makes it possible to study not only the induced addition of diethylzinc but also many other reactions including those with both transition and main group metals. Enantioselectivity of oxidation of some of these chiral nonracemic thiols by flavin model compounds has also been examined. 43 Dependable routes to α-mercapto acids means the availability of routes to mercatoposphines [R, R', C(SH)CH, PR], by reduction of the carboxy group followed by substitution by PR, to mercaptoamines prepared by the same approach using amide (-NR instead of phosphate) or, for example, to heterocycles like 50 followed by reductive ring-opening to analogues of 51. A collection of thiol-containing ligands is now available for study in catalytic enantioselective synthesis or as chiral building blocks. Possibilities for application outside of organozinc chemistry parallel and complement those of the corresponding amino alcohols.

Relatively simple and conformationally flexible structures can give surprisingly good results in these induced reactions of diethylzinc. For example, thiol 51, prepared from 48a, aniline and isobutyraldehyde followed by reduction, affords 25 in quantitative yield and 69% ee. 42

Conclusions and prospects

The original idea to prepare structural models of the catalytically active zinc site in HLADH has not led so far to a perfect structural and catalytic mimic. That is not too surprising: there is a price to be paid for total neglect of accompanying peptide. An entirely successful mimic will catalyse the reduction of a carbonyl or imine group by NADH or a model thereof and will also catalyse the oxidation of the product alcohol by NAD⁺ or a suitable model thereof. The latter reaction is more difficult, but certainly not impossible, 40 to mimic. A good mimic will also work (and be soluble—no mean task!) in aqueous or partially aqueous solution.

We clearly suggest, despite the disparity of the reactions and reaction conditions, that there are useful parallels to be drawn between the problems associated with design of a suitable model for the catalytically active ZnII of HLADH and zinc thiolate-induced reactions with, for example, dialkylzincs. The enzyme by virtue of its tertiary structure successfully isolates a monomeric and catalytically active zinc dithiolate that can undergo rapid ligand exchange at free co-ordination positions and which probably can readily change co-ordination numbers from four to five. 44 Simple ‘pyridine dithiols’ like 8c and optically active 44 promise to combine the necessary degree of steric hindrance to prevent (complete) dimerization while maintaining chemical reactivity.

It is instructive to note how well the ZnII ion can preserve electrophilic character despite co-ordination to strong bases. The calculation 37 that the energy of the carbonyl LUMO of formaldehyde is lowered from 4.01 eV to 2.76 eV on complexation to 39 (alkyl, alkoxide and tertiary amine as ligands) is entirely consistent with the operation of the zinc ion as a strong electrophile that makes the carbonyl carbon more receptive to attack by a nucleophile such as ethyl from diethylzinc (or hydride from NADH)?

Within the realms of organic chemistry it is clear that ZnII complexes of β-aminothiols can act as efficient activators in some organometallic reactions. The balance between monomeric, dimeric and tetrameric structures is obviously of great importance for reactivity and selectivity. There is currently some sensitivity to structural and chemical changes. The properties of these complexes will differ somewhat from those of the corresponding β-amino alcohols. The thiol is a weaker acid and sulfur is more readily polarizable than oxygen. This will probably result in a somewhat more electrophilic zinc ion.

The possibilities for applications of chiral thiols, the synthesis of which has been discussed here, goes further than complexation with Zn2+. A number of chiral nonracemic thiols can now be synthesized in optically active form. Our experience has been that with normal precautions (hood, closed systems, glassware immediately put in basic solution) odour is not a problem. We see good opportunities for application of chiral nonracemic thiols and sulfides in various metal catalysed processes. The (in general) greater stability of sulfides to oxidation than phosphines makes their use attractive. We have, for example, recently shown that sulfides derived from ring-opening of 12 with thiols can serve as excellent ligands in Pd catalysed allylations. 44

Acknowledgements

R. P. H. has received partial support from the Netherlands Organization for Scientific Research (NWO) administered through the Office for Chemical Research (SON).

¶ In an effort to gain insights into the differences between ZnII complexes of amino alcohols and aminothiols, we are calculating (R. W. J. Zijlstra, work in progress) the energies and geometries of the intermediates analogous to those calculated by Yamakawa and Noyori 16b for aminoethanol-induced additions of dimethylzinc to formaldehyde. However, in our study geometries have been optimized using DFT routines as implemented in GAUSSIANT, using a 6-31G basis for Zn and a 4-31G basis for all other elements. Orbital symmetries and energies have been obtained from a RHF calculation using the DFT optimized geometries in a 6-31G++ basis set for all elements. For the complex of 2-aminoethanol with dimethylzinc we obtain virtually the same bond lengths and bond angles and forms of HOMO and LUMO orbitals reported in ref. 16(c) (unpublished). The corresponding calculation for the analogous complex with 2-mercaptoethanol leads to the conclusion that the hybridization of Zn lies between sp and sp³, as indicated by the S-Zn-C bond angle (153.9° compared to 158.0° for the oxygen case). However, the HOMO (-8.54 eV) is centred solely on sulfur and is the lone pair. This HOMO lies some 1.5 eV higher in energy than for the oxygen analogue, which is delocalized over the O-Zn-C σ bonds and lies (is mostly located on oxygen and carbon).

We hope that this work, in which all other pertinent intermediates will also be calculated, will clarify the implications of this remarkable difference in frontier orbital character between the oxygen and sulfur analogues.

References

20 J. Butler, R. Hulst, A. J. Bouter, R. Stroetinga, B. Koning and R. M. Kellogg, to be submitted; this article deals with syntheses of pyridine diols and thiols, complexes of these ligands with HCl, and the enantioselective ring-opening of epoxides with complexed HCl.
33 R. Stroetinga, R. Hulst and R. M. Kellogg; the alcohol analogue of 44 will be described in the work under ref. 20.
38 A. H. M. de Vries, B. L. Feringa, R. P. Hof and R. M. Kellogg, manuscript in preparation.