doi:10.1246/cl.2012.974

Asymmetric Sulfoxidation of Thioanisole by Helical Ti(IV) Salan Catalysts

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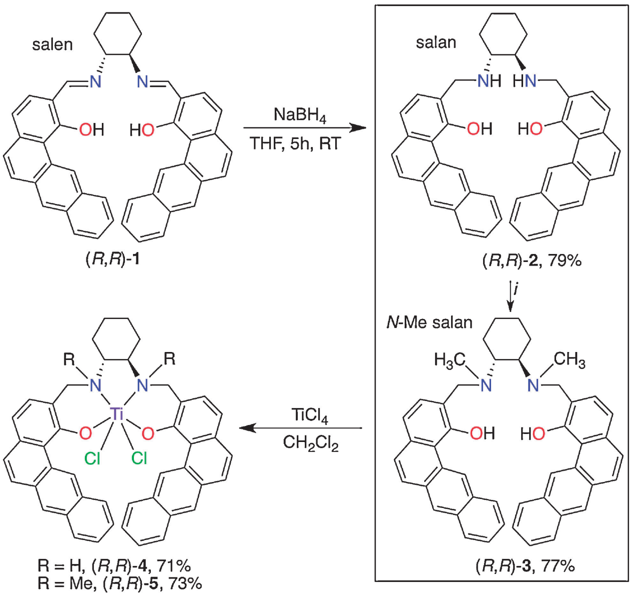
(Received May 29, 2012; CL-120457; E-mail: clevy@ksu.edu)

A new helix-directing salan ligand (*R*,*R*)-**2** with the (1*R*,2*R*)-diaminocyclohexyl backbone and benz[*a*]anthryl sidearms was synthesized by borohydride reduction of the corresponding salen ligand. Formylation and reduction of (*R*,*R*)-**2** yielded the *N*-Me counterpart, (*R*,*R*)-**3**. Complexation of these flexible ligands to $TiCl_4$ produced the $[TiCl_2(salan)]$ complexes (*R*,*R*)-**4** and (*R*,*R*)-**5**, which were characterized by NMR, IR, and HRMS techniques. The complexes were tested as catalysts for the asymmetric sulfoxidation of thioanisole with cumene hydroperoxide and hydrogen peroxide as the oxidants. Modest selectivity was observed, with the *N*-H salan complex showing somewhat better chiral induction.

Chiral sulfoxides are important chiral auxiliaries in organic synthesis and many are in direct use as pharmaceuticals.[1] Prochiral sulfides are challenging targets for catalytic asymmetric sulfoxidations and some recent progress has been achieved using metal salan complexes.[2] Salan ligands are reduced versions of salens, where the imine groups have been hydrogenated to give secondary amines. The amine nitrogens can subsequently be alkylated to give salans with tertiary amine donors.[3] When compared to salens, the absence of the C=N bond in salan ligands leads to more stable complexes that are not susceptible to hydrolysis.[4] The reduced conjugation and addition of sp^3 centers imparts added flexibility to the ligand framework and octahedral complexes can readily adopt inherently chiral α-*cis*- or β-*cis*-geometries which have stepped or twisted structures.[2] The majority of mononuclear octahedral salan complexes characterized have had the α-*cis* (*fac–fac*)-coordination mode, while bridged di- and tetranuclear complexes generally adopt the β-*cis* (*fac–mer*) mode.[5] Equilibration between α-*cis*- and β-*cis*-isomers has been observed in some cases.[6] By contrast, more rigid salen ligands normally favor the planar *trans*-coordinated octahedral complexes.[7] The helical chirality associated with twisted metal salan complexes may have an advantage in chiral induction compared to their metal salen counterparts,[1] but they have seen considerably less study as oxidation catalysts, partially due to the challenges of controlling the stereochemistry.[8] In this communication we report the synthesis of two new salan ligands with extended benz[*a*]anthryl sidearms and explore the catalytic activity of Ti(IV) complexes for the asymmetric oxidation of thioanisole.

Synthesis and characterization of the salen ligand (*R*,*R*)-**1**, which has benz[*a*]anthryl sidearms, was previously reported by our group.[9] Herein, we detail the synthesis of two versions (*N*-H and *N*-Me) of salan ligands produced from this starting compound. Reduction of (*R*,*R*)-**1** with $NaBH_4$ in THF gave (*R*,*R*)-**2** in 79% yield (Scheme 1). The *N*-Me version (*R*,*R*)-**3** was synthesized from (*R*,*R*)-**2** in 77% yield by formylation followed by reduction with $NaBH_4$ (Scheme 1). Both (*R*,*R*)-**2** and (*R*,*R*)-**3** were characterized by NMR, high-resolution ESI-MS, and IR spectroscopy. The $[M + H]^+$ ion peak with the expected isotope pattern was seen in each case. Complexes (*R*,*R*)-**4** and (*R*,*R*)-**5** were synthesized in 71% and 73% yields, respectively, as dark purple solids, by treating a solution of the ligands in methylene chloride with $TiCl_4$ at room temperature (Scheme 1).



Scheme 1. Synthesis of the ligands and Ti(IV) complexes: (*R*,*R*)-**2**–(*R*,*R*)-**5**.[13] *i*: a) 37% aq. formaldehyde, CH_3CO_2H b) $NaBH_4$; c) NaOH.

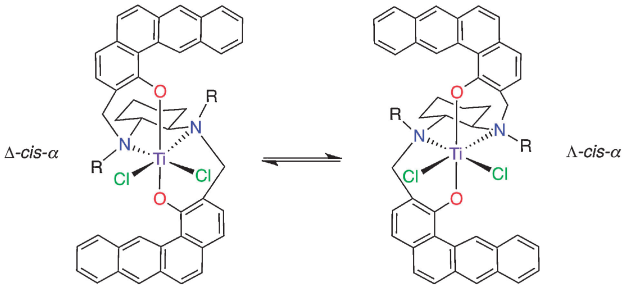
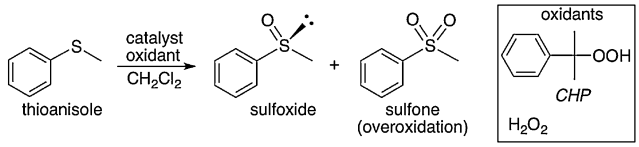


Figure 1. Exchange between diastereomeric Δ and Λ helical α-*cis*-coordinated ligands.

The two titanium complexes showed comparatively broad ^1H NMR spectra suggesting fluxional behavior, such as between diastereomeric α-*cis*-conformers (Figure 1).[10] The −30 °C spectrum (CD_2Cl_2) of complex (*R*,*R*)-**4** sharpens and is consistent with a 60:40 mixture of C_2-symmetric diastereomers based on integrations. For (*R*,*R*)-**4** the −30 °C spectrum indicates a 70:30 mixture. ESI-MS spectrometry was carried out in alcoholic solvents (MeOH and EtOH), resulting in Ti–Cl bond hydrolysis and the observance of monoalkoxo cations: $[TiL(OR)]^+$



Scheme 2. Asymmetric sulfoxidation of thioanisole with titanium catalysts (major enantiomer *R*).

(R = Me and Et). The observed isotope patterns match well with the theoretical distributions.

We have carried out preliminary studies utilizing these helical titanium salan complexes as asymmetric catalysts for the oxidation of thioanisole with hydrogen peroxide or cumene hydroperoxide (Scheme 2). Inital catalytic runs with (*R*,*R*)-**4** and 30% aqueous hydrogen peroxide indicated that the enantioselectivity was highest in methylene chloride (biphasic system), and this was selected as the solvent for subsequent reactions. Aliquots taken at different reaction times revealed more rapid conversion at the beginning of the reaction, with 70% conversion after 5 h. Conversion to sulfoxide increased up to ca. 16 h. The yield decreased at longer reaction times due to conversion of sulfoxide to sulfone and the conversion of catalyst to oxo-bridged dimers[11] with different activity/selectivity. The observed %ee of the product decreased only slightly (1–2%) over the course of the reactions, suggesting that the stereochemical course of the reactions are not affected significantly by this process. The oxidant:substrate ratio was varied, and the effect on product formation, overoxidation, and %ee was determined. There was a distinct increase in oxidation to sulfone and decrease in %ee when more than 1.5 equivalents of oxidant were used. We chose to use the more conservative 1.1 equivalents to minimize overoxidation while maintaining high conversion. The temperature of the reaction had a modest effect on enantioselectivity, with higher %ee values seen at 0 °C compared to 20 °C (43% vs. 39% with (*R*,*R*)-**4** as catalyst).

The results of the optimized catalytic runs are presented in Table 1. In all cases the major product was *R*-methyl phenyl sulfoxide, consistent with other studies that show the absolute configuration of the sulfoxide to be the same as that of the cyclohexyl backbone for titanium salan complexes.[1] Somewhat better enantioselection was seen with H_2O_2 for both catalysts, while conversions were somewhat better with cumene hydroperoxide, consistent with what has been observed in other studies with these oxidants.[4] The sulfoxide yields for (*R*,*R*)-**4** and (*R*,*R*)-**5** are quite comparable, but the enantioselection is notably higher for (*R*,*R*)-**4**. Better selectivity for titanium salan oxidation catalysts with *N*-H groups has been previously explained by Katsuki et al.[12] The key feature is hydrogen bonding between the *N*-H group and an oxygen from a peroxo ligand in a β-*cis*-intermediate. In sulfoxidation this likely assists in the transfer of a peroxo oxygen to the sulfide substrate (Figure 2).

In conclusion, we were able to synthesize and characterize helical *N*-H and *N*-Me salan ligands. The titanium complexes formed can interconvert between diastereomeric forms at room temperature. The resulting distribution is likely a primary reason for the relatively low enantioselection seen during sulfoxidations, since the asymmetric environment varies significantly with helical diastereomers. Steric interactions of the extended benz[*a*]anthryl sidearms do not appear to have been sufficient for high diastereoselection in coordination to the metal. Currently, we are working on incorporating more twisted chiral backbones that can prevent fluxionality and provide well-defined salan catalysts for asymmetric sulfoxidation.

Table 1. Sulfoxidation of thioanisole catalyzed by (*R*,*R*)-**4** and (*R*,*R*)-**5**[a]

Catalyst	Oxidant	*T*/°C	conv/%	SO/%[b]	ee/%[c]	SO_2/%[d]
4	H_2O_2	20	90	90	39	10
4	H_2O_2	0	93	85	43	15
4	CHP	0	92	95	31	5
5	H_2O_2	20	91	93	25	7
5	H_2O_2	0	93	89	30	11
5	CHP	0	91	98	20	2

[a]1% cat., 16 h in CH_2Cl_2. [b]SO: PhSOMe. [c]Enantiomeric excess measured by HPLC with DAICEL OD-H column. [d]SO_2: $PhSO_2Me$.

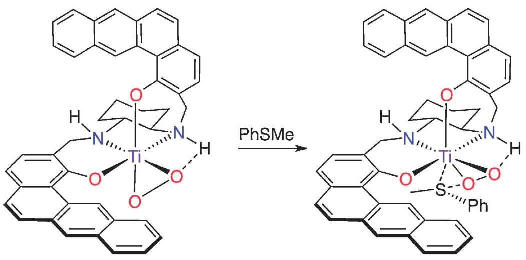


Figure 2. N–H···O hydrogen bonding in the peroxo complex in the catalytic cycle of (*R*,*R*)-**4**.

This work was supported by the National Science Foundation (No. CHE-0349258) and Kansas State University.

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13 Experimental details, NMR and IR spectra, and MS data for the complexes is provided as Supporting Information which is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.