

Vanadium-Catalyzed Asymmetric Cyanohydrin Synthesis

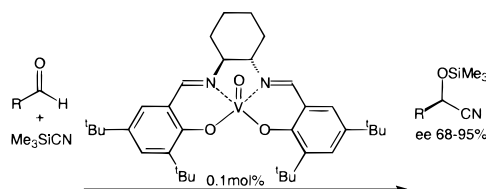
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Received April 5, 2000

ABSTRACT



Based on a mechanistic understanding of asymmetric cyanohydrin synthesis catalyzed by chiral titanium–salen complexes, a new catalyst based on vanadium(IV) has been developed. The chiral (salen)VO catalyst is more enantioselective than the titanium-based systems, 0.1 mol % of the catalyst being sufficient to convert aromatic and aliphatic aldehydes into the corresponding trimethylsilyl ethers of cyanohydrins with 68–95% enantiomeric excess at room temperature.

In recent papers, we have reported the development of chiral titanium(salen) complexes (optimally using complex **1** as the catalyst precursor) as highly active catalysts for the asymmetric addition of trimethylsilyl cyanide to both aldehydes¹ and ketones.² Detailed mechanistic studies have shown that the active species in this reaction is a bimetallic titanium–(salen) complex.³ Other workers have reported similar

catalysts,⁴ and their use to catalyze the asymmetric addition of trimethylsilyl cyanide to imines.⁵ While our titanium-based system has a number of attractive attributes including: activity at room temperature, high substrate-to-catalyst ratios, wide substrate tolerance, and good enantiomeric excesses, there is still room for improvement in the latter. In this communication, the design and development of a new catalyst for asymmetric cyanohydrin synthesis which gives products with significantly higher enantiomeric excesses than those observed with the titanium-based system is reported.

The mechanistic studies on our titanium catalyst have shown that the active species derived from complex **1** is bimetallic complex **2** which is in equilibrium with catalytically inactive monometallic complexes **3** (Scheme 1).³ Complex **2** is an extremely active catalyst since reactions employing it are complete in just a few minutes at room temperature. If the reactivity of the catalyst could be reduced, then the enantioselectivity should increase, and one way of achieving this would be to design a catalyst in which the

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A search of crystal structures of metal(salen) complexes

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1618

OH



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aldehyde	complex 4 (ee)	complex 1 (ee)
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^a All enantioselectivities were determined by chiral gas chromatography as previously reported.¹ ^b All reactions were carried out using 0.1 mol % of the catalyst in dichloromethane at ambient temperature and the catalyst derived from complex 4 gave complete conversion of aldehyde to cyanohydrin trimethylsilyl ether after 24 h. In all cases, the (*R,R*)-isomer of the catalyst gave an excess of the (*S*)-enantiomer of the cyanohydrin derivative.

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as catalysts for the asymmetric addition of trimethylsilyl cyanide to aldehydes,⁸ this is the first time that a vanadium complex has been found to form an effective catalyst. Chiral vanadium(salen) complexes have previously been used as catalysts for the asymmetric oxidation of sulfides to sulfoxides.^{7,9}

To investigate the mechanism of this vanadium-catalyzed asymmetric cyanohydrin synthesis, a kinetics study was undertaken using the methodology previously reported³ for the study of titanium complex **1**. The reaction (using benzaldehyde as substrate) was found to obey the rate equation: $\text{rate} = 76[\mathbf{4}]^{1.45}[\text{Me}_3\text{SiCN}]$, while for the same reaction using titanium complex **1**, the rate equation has previously been found to be: $\text{rate} = 634[\mathbf{1}]^{1.3}[\text{Me}_3\text{SiCN}]$. Comparison of these two rate equations shows that they have the same general form which is consistent with the reactions following the same mechanism. In particular, the concentration of benzaldehyde does not appear in either rate equation, and in both cases, the reactions are first order in trimethylsilyl cyanide concentration.

The rate constant for the vanadium-catalyzed reaction is almost a factor of 10 lower than the rate constant for the titanium-catalyzed reaction, which is consistent with the longer reaction times needed for the vanadium-catalyzed system. The order of reaction with respect to the catalyst is higher for the vanadium-catalyzed system than for the titanium-derived system. This value (which must be between one and two for a bimetallic species to be the active catalyst) is determined by the equilibrium constant between the monometallic and bimetallic species present in the reaction mixture.³ A higher value for the vanadium-containing system than for the titanium-derived system is indicative that the equilibrium between the mono- and bimetallic species favors the monometallic complexes more in the case of vanadium than titanium. Thus, the kinetics study indicates that the vanadium-catalyzed reaction probably follows the same

mechanism as the titanium-catalyzed reaction, but that the concentration of the catalytically active bimetallic species is lower for the vanadium-containing species as intended.

Also consistent with a common mechanism for the titanium- and vanadium-catalyzed reactions is the fact that both complexes derived from the (*R,R*)-salen ligand preferentially catalyze the formation of the (*S*)-enantiomer of cyanohydrin trimethylsilyl ethers, which indicates that in both cases the aldehyde is coordinated to the metal complex to allow addition of cyanide to occur preferentially on the *re*-face of the carbonyl bond. In addition, both catalyst systems display the same enantioselectivity versus substrate trend, with electron rich aromatic aldehydes giving better enantioselectivities than electron deficient aromatic, or aliphatic substrates. The formation of a vanadium complex analogous to complex **2** requires that the salen ligands adopt nonplanar coordination geometries to allow the μ -O and cyanide ligands (and μ -O and coordinated aldehyde ligands) to adopt locations *cis* to one another. There is literature precedent¹⁰ for the formation of an octahedral vanadium(IV)(salen) complex in which the salen ligand is coordinated in this way, showing that this is feasible.

In summary, the first vanadium-derived catalyst for the asymmetric addition of trimethylsilyl cyanide to aldehydes has been developed based on the previously determined mechanism of asymmetric cyanohydrin synthesis catalyzed by titanium(salen) complexes. The vanadium-catalyzed system gives higher enantioselectivities than those previously reported for the titanium-catalyzed system and the kinetics suggest that the reactions follow the same mechanism as the titanium-catalyzed reaction. Our work on the asymmetric catalysis of carbon-carbon bond forming reactions is continuing and will be reported in due course.

Acknowledgment. The authors thank the EPSRC for a studentship (to T.P.) and the EU for an INCO-COPERNICUS grant.

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