Angewandte Chemie International Edition

Enantioselective Catalysis

DOI: 10.1002/anie.201003014

A Bimetallic Titanium Catalyst for the Enantioselective Cyanation of Aldehydes Based on Cooperative Catalysis

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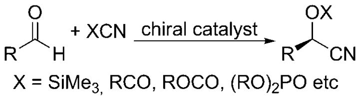
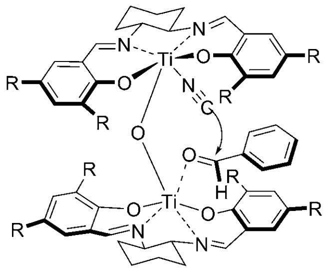
aldehydes · asymmetric catalysis · bimetallic complexes · cyanohydrin · titanium

The last 15 years have seen an explosion of interest in the asymmetric synthesis of cyanohydrins,[1] driven by the ease with which chiral cyanohydrins can be converted into other bifunctional chemicals such as α-hydroxy acids and β-amino alcohols. The asymmetric addition of cyanide to aldehydes (Scheme 1) can be catalyzed by enzymes,[2] Lewis acid based catalysts,[3] or organocatalysts[4] and can utilize many different cyanide sources to allow the synthesis of a range of protected cyanohydrin derivatives.

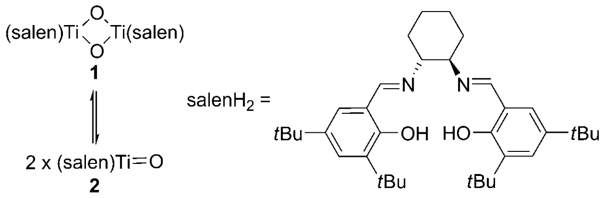


Scheme 1. Asymmetric cyanohydrin synthesis.

A feature of all of the most effective catalysts for asymmetric cyanohydrin synthesis is the need for cooperative catalysis[5] by two functional groups which activate the aldehyde and cyanide, respectively.[1,3–5] This also preorganizes the two reactants into the correct orientation to accelerate the reaction and enhance the enantioselectivity. The most active catalyst for asymmetric cyanohydrin synthesis is bimetallic titanium(salen) complex **1**, 0.1 mol % of which will catalyze the addition of trimethylsilyl cyanide (TMSCN) to aldehydes at room temperature, with reaction times of ca. 30 min and with enantioselectivities of 80–90 % for aromatic aldehydes.[6] Complex **1** also catalyzes the asymmetric addition of TMSCN to ketones[7] and the addition of other cyanide sources to aldehydes.[8,9] The mechanism of action of complex **1** has been extensively studied[9] and Scheme 2 shows the key transition state in which the bimetallic nature of the complex is critical as both titanium ions have a role in the catalysis, activating the aldehyde and cyanide, respectively. The mechanistic studies also showed that in the chlorinated solvents used for cyanohydrin synthesis, bimetallic complex **1** was in equilibrium with catalytically inactive monometallic complex **2** (Scheme 3).[9b]



Scheme 2. Stereodetermining transition state for asymmetric cyanohydrin synthesis catalyzed by complex **1** (R = *t*Bu).



Scheme 3. Equilibrium between complexes **1** and **2**.

A recent report by Ding et al.[10] built on this mechanistic knowledge to significantly enhance the catalytic activity of bimetallic titanium(salen) complexes. To maximize the amount of bimetallic complex present in solution, ligands **3a**–**f** in which the two salen ligands were covalently linked together were designed and synthesized. The ligands were then complexed to titanium and the resulting complexes (0.05 mol %) used to catalyze the asymmetric addition of TMSCN to aldehydes at 25 °C. Not surprisingly, the catalytic activity of the complexes was critically dependent on the structure of the linkage. The titanium complex of ligand **3a** displayed very low catalytic activity (29 % yield after 72 h) and enantioselectivity (51 %), presumably because the rigid, linear linkage did not allow the salen ligands to fold over one another as required to form a μ-oxo-bridged bimetallic transition state analogous to that shown in Scheme 2. Ligands **3b,c** with a flexible linker displayed much higher levels of catalytic activity (> 90 % yield after 24 h) and enantioselectivity (76–90 %), but were no

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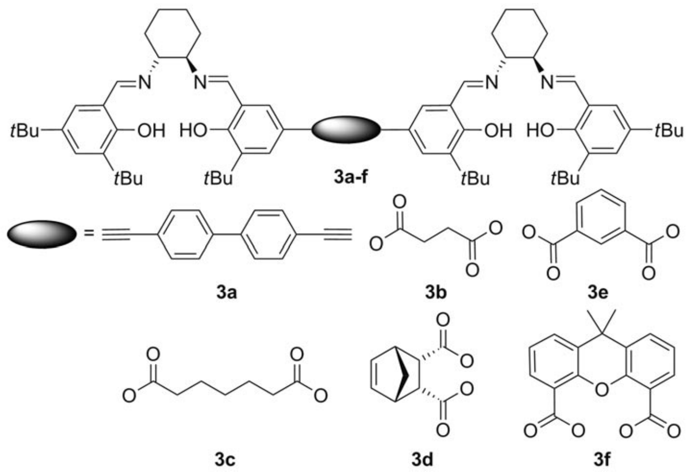

improvement over what could be achieved using complex **1**. The authors then turned their attention to linkers which were rigid but bent (**3d**–**f**) and ligand **3d** was found to have the optimal structure, giving high catalytic activity (98% yield after 5 min) and enantioselectivity (96%) from reactions using 4-methoxy-benzaldehyde as substrate. Further reduction of the catalyst loading to 0.005 mol% or even 0.0005 mol% still gave good yields (99 and 86%) and enantioselectivities (97 and 95%), though the reaction times were extended to 1 h and 72 h, respectively. A total of twenty aromatic, heteroaromatic, α,β-unsaturated, and aliphatic aldehydes were used as substrates with the catalyst derived from ligand **3d** using a catalyst loading of 0.01–0.02 mol%. In each case the reaction conditions were optimized to give yields of >87% and enantioselectivities of 64–97%, though for unfavorable substrates this did require reaction times of up to 48 h at -40°C.

In addition to catalyzing the asymmetric addition of TMSCN to aldehydes, the titanium complex of ligand **3d** also catalyzed the asymmetric addition of sodium cyanide to aldehydes in the presence of acetic anhydride, thus providing a direct synthesis of cyanohydrin acetates. When this reaction is catalyzed by complex **1**, catalyst loadings of 1 mol% and a reaction temperature of -40°C are required to achieve high yields and enantioselectivities.[8] In contrast, just 0.005 to 0.05 mol% of the titanium complex of ligand **3d** was sufficient to catalyze the synthesis of cyanohydrin acetates from nine aromatic aldehydes at 25°C with yields of 97–99% and enantioselectivities of 91–96% after reaction times of 5–48 h.

Whilst the catalytic results obtained using the titanium complex of ligand **3d** are an impressive improvement over those obtained using the parent catalyst **1**, this is offset by the significantly more difficult synthesis of ligand **3d** which contains unsymmetrically substituted salen ligands compared to the commercially available salen ligand used in complex **1**. The synthesis of ligands **3** is not described in Ding et al.'s Communication, though full characterizing data for ligands **3a**–**f** is given.[10] For this reason, probably the most significant aspect of the work is its mechanistic implications. The results using complexes of ligands **3a**–**f** (and especially those obtained using ligands **3a** and **d**) provide very strong support for the bimetallic transition state shown in Scheme 2. Further work using ligand **3d** should allow the nature of this structure to be probed in more detail. For example, the relative orientation of the two salen rings is currently unknown. The crystal structure of an analogue of complex **1** with unsubstituted aromatic rings showed that the two salen ligands were oriented at about 100° to one another,[6] though interactions between the *tert*-butyl groups in complex **1** may significantly affect the transition state structure shown in Scheme 2. Ding et al. were unable to obtain crystals of the titanium complex of ligand **3d** suitable for X-ray analysis. They did manage to crystallize the bimetallic cobalt$^{\mathrm{II}}$ complex of ligand **3d**, which confirmed the bimetallic nature of the complex and showed that the two salen ligands were oriented at 180° to one another. However, in this complex, the two salen ligands are planar (as opposed to *cis*-β in **1** and Scheme 2), there is no μ-oxo bridge between the two metal atoms and the two salen ligands are offset so that the metal ion of one ligand is located under the cyclohexyl ring of the other ligand. As a result, this is not a good model for the transition state for asymmetric cyanohydrin synthesis. However, it does provide the basis for further work involving modifying the aromatic substituents of ligand **3d** to produce more crystalline complexes, or preparing bimetallic complexes of ligand **3d** which do contain at least one μ-oxo bridge as would be formed from aluminium or iron(III) for example. In summary, this paper provides a very useful tool for future work on determining the details of asymmetric cyanohydrin synthesis and other reactions catalyzed by bimetallic salen complexes.

Received: May 18, 2010

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