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Asymmetric synthesis of polymer-supported cyanohydrin acetates

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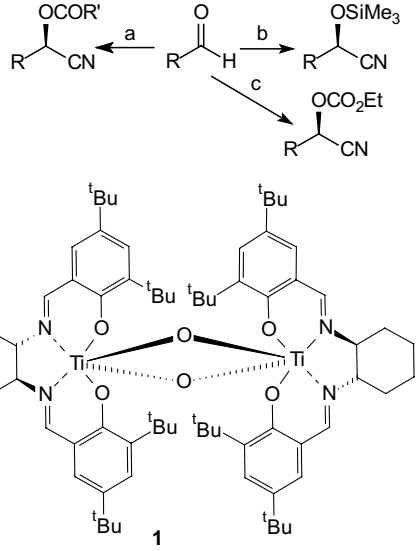
Abstract—A bimetallic titanium(salen) complex has been used to catalyze the asymmetric addition of potassium cyanide to aldehydes attached to Wang resin giving polymer supported cyanohydrin propionates with up to 91% enantiomeric excesses.

Over the last eight years, we have developed bimetallic titanium(salen) complex **1** as a highly enantioselective and remarkably versatile catalyst for the asymmetric addition of various cyanide sources to aldehydes[1] and ketones.[2] Catalyst **1** will induce the asymmetric addition of trimethylsilyl cyanide,[3] potassium cyanide/an anhydride[4] and ethyl cyanoformate[4c,5] to aldehydes, providing access to non-racemic cyanohydrin trimethylsilyl ethers, cyanohydrin esters and cyanohydrin ethyl carbonates as shown in Scheme 1. The best substrates for catalyst **1** are electron rich aromatic aldehydes, which typically give cyanohydrin derivatives with 90–99% enantiomeric excess.

In view of the significant potential of catalyst **1**, there has recently been interest in the synthesis and use of polymeric or polymer supported analogues of this catalyst.[6] Zheng and co-workers have used a linear polymeric version of catalyst **1** to catalyze the asymmetric addition of trimethylsilyl cyanide to aldehydes,[7] and a cross-linked polymeric version of catalyst **1** to catalyze the asymmetric addition of potassium cyanide and acetic anhydride to aldehydes.[8] The related vanadium(V)salen complex **2**, which we also developed[2b,4b,9] and showed to be even more enantioselective than complex **1** has also been immobilized on silica,[10,11] single walled carbon nanotubes,[11,12] or attached to an ionic liquid.[11,13] A linear polymeric version of this catalyst has also been prepared.[8] Whilst the use of a polymer supported catalyst is



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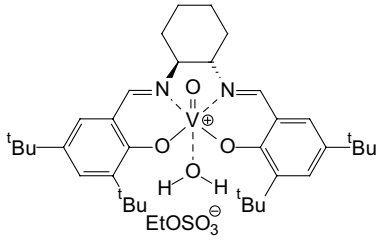

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Scheme 1. Reagents: (a) KCN/$(R'CO)_2O$/**1** (1 mol %); (b) Me_3SiCN/**1** or **2** (0.1 mol %); (c) EtOCOCN/**1** (5 mol %).

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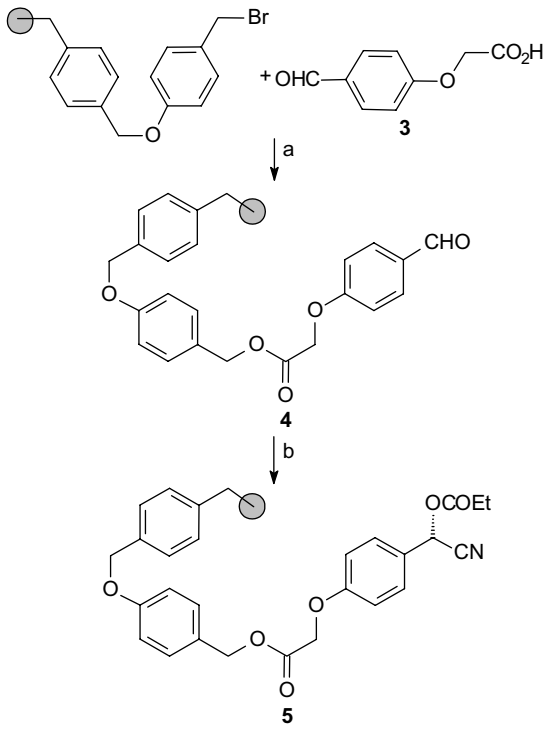
attractive, the methodology does suffer from a number of disadvantages including: the catalysts are less readily prepared than the soluble version of the catalyst; the polymer supported catalysts are often less enantioselective than their soluble analogues; and the chiral cyanohydrin derivative still requires purification to remove the other reagents and any metal that may have leached from the polymer supported catalyst. In view of these limitations, we have investigated the opposite approach that of attaching the aldehyde substrate to an insoluble polymeric support, and converting it into a polymer supported cyanohydrin ester using catalyst **1**. In this communication we report the results of this study.[14]

Of the various cyanohydrin derivatives that can be prepared using catalyst **1**, the cyanohydrin esters were felt to be the most attractive due to the hydrolytic stability of the products, the relatively small amount of catalyst (1 mol %) required, and the potential for subsequent chemoselective transformations of the functional groups.[15] However, even using a simple aldehyde, the synthesis of cyanohydrin acetates using catalyst **1** is a heterogeneous process, which is carried out in dichloromethane in the presence of solid potassium cyanide and both *tert*-butanol and water additives.[4] Hence, at the start of this work it was far from clear that this process could be applied to polymer supported aldehydes as this would effectively be a three-phase system involving two solid reagents and a solvent system in which neither of them was soluble.

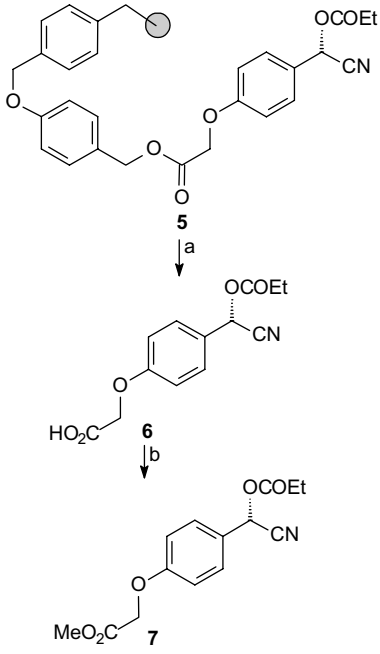
As an initial system, we selected 1% cross-linked Wang resin[16] as the polymeric support and commercially available aldehyde **3** as the substrate. This system had the advantage that products could be readily cleaved from the polymeric support by acidolysis without any danger of racemization. Attachment of aldehyde **3** to Wang resin occurred smoothly under standard conditions (Scheme 2) to give polymer supported aldehyde **4**. This reaction (and subsequent transformations) could be followed by both single bead magic angle spinning ^{1}H and ^{13}C NMR spectroscopy and diffuse reflectance FTIR spectroscopy.

When aldehyde **4** was reacted with potassium cyanide/propionic anhydride under the standard conditions (−90 to −40 °C, dichloromethane solvent with water and *tert*-butanol additives), no reaction occurred after 48 h, even using double the amount of catalyst (2 mol %) and reagents (up to 8 equiv of potassium cyanide and propionic anhydride). However, when this reaction was carried out at 0 °C, then polymer supported cyanohydrin propionate **5** was formed after just 24 h. After this time, no unreacted aldehyde **4** could be detected by ^{1}H or ^{13}C NMR spectroscopy and peaks corresponding to the cyanohydrin-CH (^{1}H NMR 6 ppm and ^{13}C NMR 65 ppm) and propionate groups of compound **5** were apparent in the spectra.

To determine the enantiomeric excess of compound **5**, a sample of the resin was treated with trifluoroacetic acid to give acid **6**, which was subsequently esterified by treatment with trimethylsilyldiazomethane[17] to give



Scheme 2. Reagents: (a) $CsCO_3$ (5 equiv)/KI (1 equiv)/DMF/80 °C then repeat coupling; (b) KCN (8 equiv)/$(EtCO)_2O$ (8 equiv)/**1** (2 mol %) ^{t}BuOH (2 equiv)/H_2O (1 equiv)/0 °C/12 h.



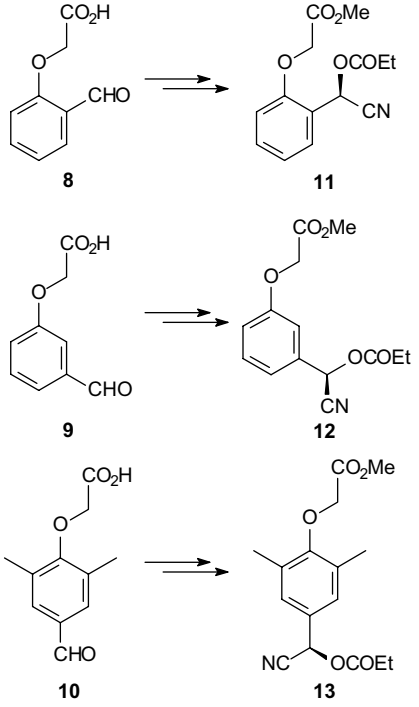
Scheme 3. Reagents: (a) CF_3CO_2H; (b) Me_3SiCHN_2/MeOH.

methyl ester **7** (Scheme 3). For comparison, racemic and non-racemic samples of ester **7** were also prepared by a solution phase synthesis. Thus, acid **3** was first esterified with trimethylsilyldiazomethane and then treated with potassium cyanide and propionic anhydride in the absence of catalyst **1** to give racemic-**7**, or in the presence of catalyst **1** (1 mol %) under standard

conditions to give a non-racemic sample of compound **7**. The enantiomeric excess of compound **7** could be determined by chiral GC, using the racemic sample to determine the retention times of the two enantiomers. The sample of ester **7** prepared under standard solution phase conditions was found to have an enantiomeric excess of 81%, whilst the sample prepared on the polymeric support had an enantiomeric excess of 54%. Although the sample of compound **7** prepared via a polymer supported synthesis had a lower enantiomeric excess than that prepared by a solution state synthesis, this result did demonstrate that polymer supported asymmetric cyanohydrin propionate synthesis using catalyst **1** was feasible.

By increasing the amount of catalyst **1** from 2 to 5 mol %, the polymer supported reaction shown in Scheme 2 was complete in 12 h[18] and gave cyanohydrin ester **5** with 91% enantiomeric excess (determined by chiral GC after conversion to compound **7**). Under these conditions, the polymer supported reaction was more enantioselective than the solution phase synthesis, though the reaction conditions were very different. In particular, the polymer supported synthesis required more catalyst, but was also conducted at a higher temperature than the solution phase synthesis.

To demonstrate the utility of this process, three other aldehydes[19] **8**–**10** were attached to Wang resin and converted into cyanohydrin propionates under the optimized conditions (Scheme 4). Aldehydes **8**–**10** were prepared from the commercially available formyl-phenols by O-alkylation with methyl bromoacetate followed by hydrolysis of the methyl ester using sodium hydroxide. Samples of each polymer supported cyanohydrin propionate were then cleaved from the resin and esterified to give the corresponding methyl esters **11**–**13**. In each case, racemic and non-racemic samples of the methyl esters were also prepared by a solution phase synthesis analogous to Scheme 3.



Scheme 4.

Table 1. Enantiomeric excesses[a] of cyanohydrin propionates obtained from aldehydes through solution and polymer supported syntheses

Cyanohydrin propionate	ee (solution)	ee (polymer supported)
7	81	91
11	nd[b]	nd[b]
12	94	75
13	80	50

[a] All enantiomeric excesses were determined by chiral GC using a γ-butyryl cyclodextrin fused silica capillary column (30 m × 0.25 mm) using hydrogen as the carrier gas (flow rate 2.3 ml/min).

[b] The enantiomeric excess could not be determined as no separation could be obtained on the chiral GC column.

Table 1 details the enantiomeric excesses observed for the various cyanohydrin esters. In the case of cyanohydrin **11**, it was not possible to separate the enantiomers by chiral GC. Cyanohydrin propionates **12** and **13** could be prepared in non-racemic form by the polymer supported synthesis, though the enantiomeric excesses were lower than those obtained by a solution phase synthesis under standard conditions. However, the reaction conditions for the polymer supported syntheses have not been optimized for each substrate.

In summary, we have shown for the first time that catalyst **1** can be used to convert polymer supported aldehydes into non-racemic cyanohydrins. Ongoing work is concerned with the subsequent transformations of the polymer supported cyanohydrins, and the synthesis of combinatorial libraries using this methodology.

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18. Typical experimental procedure: To a stirred mixture of KCN (100 mmol) and catalyst **1** (0.5 mmol) in dichloromethane (50 mL) at 0 °C were added *tert*-butanol (26 mmol), water (12.5 mmol), resin **4** (12.5 mmol) and propionic anhydride (100 mmol). The reaction was stirred at 0 °C for 12 h and was monitored by magic angle spinning ^{1}H NMR spectroscopy. The beads were then filtered and washed consecutively with CH_2Cl_2, water, MeOH, acetone, MeOH, EtOAc and CH_2Cl_2 (3×50 mL of each solvent) and dried in vacuo.
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