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Catalytic, asymmetric synthesis of α-acetoxy amides

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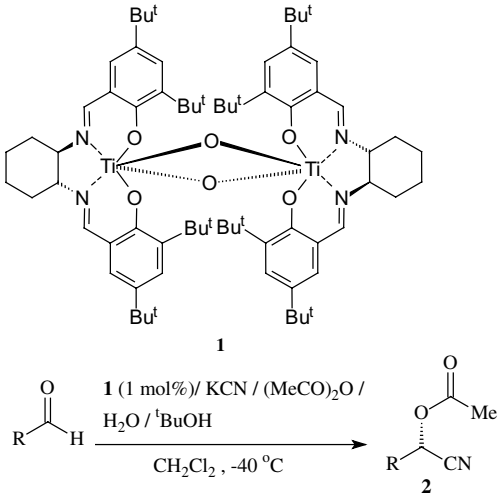
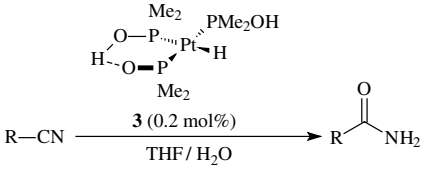
Abstract—Non-racemic cyanohydrin acetates are readily available from aldehydes and potassium cyanide/acetic anhydride by use of bimetallic titanium (salen) catalyst **1**. Treatment of the cyanohydrin acetates with a platinum(II) phosphinito catalyst **3** under neutral conditions results in chemoselective hydrolysis to the corresponding α-acetoxy amides in a racemization free process.

There is currently considerable interest in the asymmetric synthesis of cyanohydrins as these compounds are versatile intermediates for the synthesis of natural products and pharmaceuticals.[1] Virtually all asymmetric catalysts, which have been developed for this reaction in recent years, rely upon the use of trimethylsilyl cyanide as the cyanide source.[2] Unfortunately, this reagent is expensive and the resulting cyanohydrin trimethylsilyl ethers are prone to hydrolytic decomposition. In contrast, one of us has been involved in the development of bimetallic titanium based catalyst **1**, which is able to catalyze the asymmetric addition of potassium cyanide to aldehydes in the presence of acetic anhydride, leading to non-racemic cyanohydrin acetates **2** as shown in Scheme 1.[3] This methodology uses only inexpensive reagents and leads to cyanohydrin esters in good yield and with good to excellent enantioselectivity.[4]



Scheme 1.

The cyanohydrin acetates **2** contain two different functional groups, both derived from carboxylic acids, and it was of interest to develop methodology for the chemoselective manipulation of these functional groups. In particular, the hydrolysis of the nitrile group in the presence of the ester would be particularly attractive from the point of view of further manipulation. The standard conditions for the acidic or basic hydrolysis of a nitrile are quite harsh and would also hydrolyze the acetate. Racemization, especially under the conditions of basic hydrolysis would also be a concern. However, one of us has developed the platinum based catalyst **3** and shown that it would hydrolyze nitriles to amides under neutral conditions (Scheme 2) under which the acetate group should be stable.[5] In this communication, we show how the consecutive application of catalysts **1**



Scheme 2.

Keywords: Cyanohydrin; Amide; Asymmetric catalysis; Titanium; Platinum.

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Table 1. Yields and enantioselectivities of cyanohydrin acetates **2a**–**g**

Aldehyde	Catalyst (mol%)	Product	Yield (%)	ee (configuration)
PhCHO	*ent*-**1** (1)	**2a**	40	87 (*R*)
PhCHO	**1** (1)	**2b**	51	89 (*S*)
4-$MeOC_6H_4CHO$	*ent*-**1** (4)	**2c**	40	76 (*R*)
4-$F_3CC_6H_4CHO$	**1** (1)	**2d**	73	64 (*S*)
PhCH=CHCHO	*ent*-**1** (1)	**2e**	75	88 (*R*)
CyCHO	**1** (1)	**2f**	73	73 (*S*)
$C_8H_{17}CHO$	*ent*-**1** (1)	**2g**	43	79 (*R*)

Table 2. Yields and analytical data for α-acetoxy amides **4a**–**g**

Product	Time (h)	Yield (%)	$[\alpha]_D^{20}$ (*c* 1.0, $CHCl_3$)	Mp (°C)
4a	62	89 (66)[a]	−145	133–135
4b	70	40	NR	NR
4c	22	72	−115	138–140
4d	69	56	+45	73–74
4e	65	75	−89	112–114
4f	65	72	NR	128–133
4g	69	75	NR	Oil

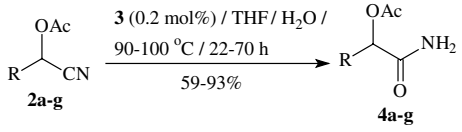
[a] Yield after recrystallization to maximum melting point.

and **3** can be used to convert aldehydes into non-racemic α-acetoxy amides.

Six aldehydes representative of aromatic, α,β-unsaturated and aliphatic systems were chosen for this study. Each was converted into its corresponding cyanohydrin acetate using either catalyst **1** (1–4 mol%) to produce the (*S*)-cyanohydrin derivative, or the enantiomer of catalyst **1** (*ent*-**1**) to form the (*R*)-cyanohydrin acetate (Table 1). These reactions were carried out on a 1–5 g scale and the products purified by bulb to bulb distillation. The enantiomeric excess of cyanohydrin acetates **2a**–**g** were determined by chiral GC and were comparable with those previously obtained from smaller scale reactions.[3]

Compounds **2a**–**g** were next treated with platinum(II) complex **3** (0.2 mol%) in a THF/water solvent mixture at 90–100 °C to produce the corresponding α-acetoxy amides **4a**–**g** (Scheme 3). The platinum phosphinito catalyst **3** is generally effective for the hydrolysis of nitriles under neutral conditions, though long reaction times can be required with sterically hindered nitriles.[6] In the case of cyanohydrin acetates **2a**–**g**, reaction times of 22–70 h were required due to the branching present at the carbon adjacent to the nitrile. Only in the case of products **4d** and **4g** was it necessary to purify the amide by flash chromatography. In all other cases, analytically pure product could be obtained by crystallization of the crude reaction product from toluene. Reaction details and selected analytical data for compounds **4a**–**g** are given in Table 2.

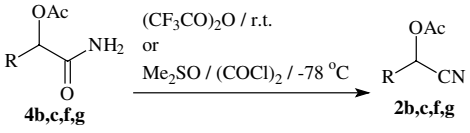
It remained to determine whether the high temperature treatment with catalyst **3** had adversely affected the enantiomeric purity of products **4a**–**g**. Only compound **4a** is a previously known compound and only the melting point of the racemate (109–110 °C) has been reported.[7] Hence, the melting point of 133–135 °C observed for product **4a** combined with its large specific rotation suggested that compound **4a** was highly enantiomerically enriched. To confirm this, and to investigate the enantiomeric purity of the other α-acetoxy amides, their conversion back into cyanohydrin acetates **2a**–**g** was investigated.



Scheme 3.

Initially, the dehydration of amide **4a** was carried out using trifluoroacetic anhydride[8] at room temperature (Scheme 4). This procedure gave the cyanohydrin acetate **2a**, but chiral GC analysis showed that the cyanohydrin acetate was completely racemic. It was not immediately apparent if the racemization had occurred during the formation of amide **4a**, or the subsequent dehydration. However, in view of the melting point and specific rotation of amide **4a**, the latter was suspected. Therefore a second method for the dehydration of amides into nitriles was investigated. It has been reported that treatment of an amide with DMSO and oxalyl chloride at −78 °C results in the formation of the corresponding nitrile without causing any racemization.[9] This methodology was applied to amides **4b**,**c**,**f**,**g**, which are representative of the aromatic and aliphatic substrates (Scheme 4) and the results are shown in Table 3.

Table 3 clearly demonstrates that amides **4c**, **4f** and **4g** had been prepared from the corresponding cyanohydrin acetates without any loss of enantiomeric purity as the enantiomeric excess of cyanohydrin acetates **2c**,**f**,**g** prepared by dehydration of the amide were identical (within the experimental error of ±3%) to the enantiomeric excess of the cyanohydrin acetate from which the amide was prepared. Interestingly, the enantiomeric excess of cyanohydrin acetate **2b** obtained from amide **4b** was significantly higher than the enantiomeric excess of the cyanohydrin **2b** from which amide **4b** was prepared. This indicates that enrichment of the enantiomeric purity of amide **4b** occurred during its purification by recrystallization from toluene.



Scheme 4.

Table 3. Conversion of amides **4b**,**c**,**f**,**g** back into cyanohydrin acetates **2b**,**c**,**f**,**g**

Substrate	ee of product cyanohydrin	ee of initial cyanohydrin
4b	97	89
4c	74	76
4f	72	73
4g	83	79

In conclusion, it has been shown that two consecutive catalytic processes can be used to convert aldehydes into non-racemic α-acetoxy amides. It is notable that both of these processes are biomimetic, mimicking oxynitrilase[10] and nitrile hydratase[11] enzymes, respectively.

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