Enantioselective Synthesis of Aliphatic Cyanohydrin Acetates

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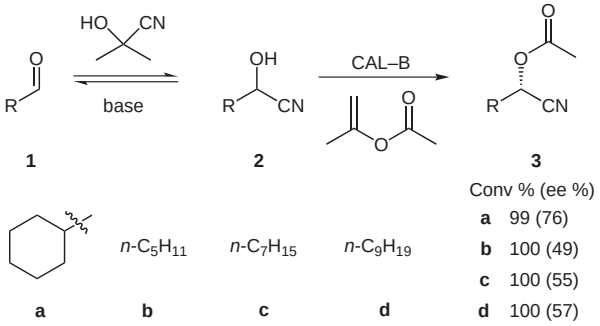
Abstract: When the standard conditions for the enantioselective synthesis of cyanohydrin acetates via dynamic kinetic resolution are applied to aliphatic substrates, only a kinetic resolution is observed. However, by exchanging the base (Amberlite) against NaCN, quantitative conversions and good enantioselectivities are obtained.

Key words: cyanohydrins, asymmetric synthesis, *Candida antarctica* lipase B, enzyme catalysis, dynamic kinetic resolution

Enantiopure cyanohydrins are highly versatile building blocks in organic synthesis.[1] A variety of chemical and enzymatic approaches to prepare them have been described, the dynamic kinetic resolution (DKR) being particularly attractive.[2] It combines a base-catalysed equilibrium between an aldehyde, acetone cyanohydrin and the resulting racemic cyanohydrin of the aldehyde, with a lipase-catalysed acylation of one enantiomer of this cyanohydrin. As the remaining enantiomer of the cyanohydrin is racemised by the base, yields of up to 100% can be obtained (Scheme 1).



Scheme 1 The dynamic kinetic resolution of aliphatic cyanohydrins

In spite of its elegance and successful use,[3] this method has gained only moderate attention compared with the hydroxynitrile lyase (HNL)-catalysed addition of HCN to aldehydes and ketones.[4] In the case of aliphatic substrates, this could be due to the poor results which were communicated in the first description of the reaction.[5] There, **1b** and isobutyraldehyde gave 63% and 85% conversion to the corresponding cyanohydrin acetates with 51% and 15% ee, respectively. This is comparable to what can be obtained from a poor kinetic resolution (KR), indicating that the base (Amberlite IRA-904 in OH^--form) fails to racemise the cyanohydrin.

Previously, we succeeded in significantly improving the DKR of aromatic cyanohydrins,[6] and we therefore set out to apply our findings to aliphatic aldehydes. The latter compounds have not only proven to be troublesome substrates for DKR, but from among the chemical routes that have been explored, there are only a few examples which gave high enantioselectivities.[7]

In our previous work on the optimisation of the enantioselective synthesis of aromatic cyanohydrin esters, we found that cyanide salts were capable of catalysing the DKR starting from aromatic aldehydes, however, with unsatisfactory results. Some salts, e.g. NaCN, were too basic and catalysed mainly the chemical acylation, resulting in a racemic product, while CuCN gave nearly no conversion at all.[6b] In contrast to the aromatic cyanohydrins, stronger bases are needed to racemise the aliphatic cyanohydrins, making the solid cyanide salts potential bases for this reaction. To confirm this, we used NaCN, KCN and $Zn(CN)_2$ as bases/salts and compared them with Amberlite OH^- and NaOAc in the synthesis of **3a** and **3b**.[8] Since it has earlier been demonstrated that the carrier of the enzyme can have a significant influence on the reaction, two different immobilisates of *Candida antarctica* lipase B (CAL-B), an enzyme that has been shown to be particularly selective both in the KR and the DKR of cyanohydrins,[9] were employed (Table 1).

For the reactions reported in Table 1, entry 1, we also monitored the ee of **2a** during the reaction,[10] and after six days we found 71%, 81%, and 80% ee for the reactions using $Zn(CN)_2$, NaOAc and Amberlite, respectively. This is a good evidence that the racemisation of **2** is too slow for a successful DKR. The results in entry 2, 3 and 4 also indicate that these three bases are too weak and only give a KR without any racemisation of the intermediate cyanohydrin **2**.

In the case of NaCN and KCN, no ee for **2a** could be observed, demonstrating that these bases are indeed strong enough to efficiently racemise the cyanohydrin. However, the ee in the reactions using these two salts are lower than those that can be observed when using $Zn(CN)_2$, NaOAc and Amberlite. One reason for this could be the base-catalysed racemisation of **3b**, but this is unlikely since no decrease in ee could be observed for a reaction that was stirred for another four days after its completion. As that was the case for the aromatic aldehydes, some degree of base-catalysed acylation of **2b** might cause this lower ee of **3b**.[6]

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Table 1 The Use of Cyanide Salts as Bases in the DKR Using 380 U/mmol of *Candida antarctica* Lipase B[a]

Substrate	Enzyme	NaCN[b,c]	KCN[b,c]	$Zn(CN)_2$[b,c]	NaOAc[b,c]	Amberlite[b,d]
1a	Novozyme 435	99 (76)	78 (58)	47 (82)	54 (74)	70 (74)
1a	CAL-B on Celite	100 (42)	86 (29)	32 (92)	31 (89)	46 (90)
1b	Novozyme 435	100 (49)[e]	–	79 (62)	68 (27)	73 (28)
1b	CAL-B on Celite	97 (46)[e]	93 (29)	60 (68)	51 (56)	68 (52)

[a] Reaction time: 6 d.
[b] Conversion into **3a** and **3b** [% and ee (%)].
[c] 1 Equiv.
[d] 0.3 Equiv.
[e] Reaction time: 2 d.

$Zn(CN)_2$, NaOAc and Amberlite gave the highest ee for **3** when they were used in combination with the Celite R-633 immobilised enzyme (Table 1). NaCN and KCN gave the best results in combination with Novozyme 435. Probably Celite R-633 has a higher affinity to water and binds it, while the methacrylate polymer carrier of CAL-B in Novozyme 435 more readily releases the water bound to the carrier into the reaction media.[6b] Since NaCN and KCN will neutralise any acetic acid formed by hydrolysis of the acylating agent, it is less critical for the reaction to use Celite R-633 as the carrier for CAL-B. The formed HCN will add to the aldehyde to form **2**, and the metal acetate, which acts as a mild base.

On the other hand when NaOAc and Amberlite are used, it is more important to use a carrier that does not release any water into the reaction mixture. Amberlite will neutralise the acid but at the same time form a new molecule of water. NaOAc will form a buffer with the acetic acid but the capacity of this buffer might be exceeded.

As expected, $Zn(CN)_2$ seems to follow the trend of NaOAc and Amberlite, rather than that of the two other cyanide salts. This shows that the $Zn(CN)_2$ is a weaker base than KCN or NaCN and therefore less efficient in the neutralisation of the acid.

In order to probe whether a higher ee could be obtained with an aldehyde containing a longer chain than **1b**, we also tested **1c** and **1d** as substrates for the reaction, but neither the reaction rate nor the enantioselectivity of the reaction changed significantly.[11]

When the reaction was scaled up[12] using Novozyme 435 in combination with NaCN, **3a** and **3b** were isolated with a yield of 92% and 74%, and an ee of 78%[13] and 50%,[14] respectively. This is a significant improvement of the first DKR of aliphatic cyanohydrins.

In conclusion, by exchanging the Amberlite OH^-, which is commonly used as a base in the DKR of cyanohydrins against NaCN, a true DKR of the aliphatic cyanohydrins could be developed. In addition, by using NaCN, the reaction also became less sensitive towards water that is present in the reaction mixture. However, the ee of the products were lower than what could be expected, most likely due to a small degree of base-catalysed chemical acylation.

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(10) All conversion and enantiomeric purity was determined by chiral GC using a β-cyclodextrin column (CP-Chirasil-Dex CB 25m × 0.25 mm) using He with a linear gas velocity of 75 cm/s.
(11) Racemic **3c**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 7.0 Hz, 3 H, C*H*$_3$–CH$_2$), 1.25–1.40 (m, 8 H, CH$_3$–C*H*$_2$–C*H*$_2$–C*H*$_2$–C*H*$_2$), 1.50 (m, 2 H, C*H*$_2$–CH$_2$–CH), 1.90 (m, 2 H, C*H*$_2$–CH), 2.13 (s, 3 H, C*H*$_3$–C=O), 5.31 (t, *J* = 6.8 Hz, 1 H, C*H*–CN). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0 (C8), 20.4 (*C*H$_3$–C=O), 22.6 (C7), 24.6 (C6), 28.8 (C5), 29.0 (C4), 31.6 (C3), 32.3 (C2), 61.2 (C-O), 117.0 (CN), 169.2 (C=O). Racemic **3d**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 6.8 Hz, 3 H, C*H*$_3$–CH$_2$), 1.20–1.40 (m, 10 H, CH$_3$–C*H*$_2$–C*H*$_2$–C*H*$_2$–C*H*$_2$–C*H*$_2$), 1.50 (m, 2 H, C*H*$_2$–CH$_2$–CH), 1.90 (m, 2 H, C*H*$_2$–CH), 2.12 (s, 3 H, C*H*$_3$–CO), 5.30 (t, *J* = 6.8 Hz, 1 H, C*H*–CN). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1 (C10), 20.4 (*C*H$_3$–C=O), 22.7 (C9), 24.6 (C8), 28.9 (C7), 29.3 (C6), 29.3 (C5), 29.4 (C4), 31.9 (C3), 32.3 (C2), 61.2 (C-O), 117.0 (CN), 169.2 (C=O).
(12) For the procedure, see the preparative scale experiment in ref. 6b.
(13) Compound (*S*)-**3a**: $[\alpha]_D^{25}$ –47,7 (*c* 1, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.10–1.40 (m, 5 H, ring CH and CH$_2$), 1.70–1.90 (m, 6 H, ring CH$_2$), 2.14 (s, 3 H, C*H*$_3$), 5.17 (d, *J* = 6.0 Hz, 1 H, C*H*–CN). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.3 (CH$_3$), 25.3, 25.4, 25.8, 28.0, 28.1 and 40.5 (ring C), 65.6 (CH–O), 116.2 (CN), 169.3 (C=O).
(14) Compound (*S*)-**3b**: $[\alpha]_D^{25}$ –36.9 (*c* 1, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.90 (m, 3 H, C*H*$_3$–CH$_2$), 1.33 (m, 4 H, CH$_3$–C*H*$_2$–C*H*$_2$), 1.50 (m, 2 H, C*H*$_2$–CH$_2$–CH), 1.90 (m, 2 H, C*H*$_2$–CH), 2.14 (s, 3 H, C*H*$_3$–CO), 5.31 (t, *J* = 6.8 Hz, 1 H, C*H*–CN). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9 (C6), 20.4 (*C*H$_3$–C=O), 22.3 (C5), 24.2 (C4), 30.9 (C3), 32.3 (C2), 61.2 (CH), 117.0 (CN), 169.2 (C=O).