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Catalytic electronic activation: indirect Sharpless asymmetric epoxidation of enals

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Abstract—The asymmetric epoxidation of allylic cyanohydrins using the Sharpless kinetic resolution (SKR) reaction was explored. The SKR methodology was extended to enals via in-situ conversion into the corresponding cyanohydrin. The prospect of achieving a dynamic Sharpless kinetic resolution was investigated and the enantioselectivity of the SKR of (*E*)-2-hydroxy-3-methyl-4-phenyl-3-butenenitrile **1** studied. Reversible hydrocyanation of α-methyl cinnamaldehyde was developed and a one-pot hydrocyanation/epoxidation process achieved.

1. Introduction

With increasing worldwide interest in domino and cascade reactions, we have recently proposed an indirect addition of nucleophiles to allylic alcohols using the concept of catalytic electronic activation.[1] In this current study we envisaged the prospect of applying transition metal-mediated epoxidation chemistry to an electron-deficient α,β-unsaturated aldehyde by temporary conversion into the electron-rich and functionally compatible allylic cyanohydrin. This had particular appeal to us because of the potential application to the Sharpless asymmetric epoxidation reaction (Scheme 1).[2]

Electron-deficient alkenes are less susceptible to electrophilic epoxidation than their electron rich analogues. Furthermore, transition-metal mediated epoxidations can benefit from neighbouring group participation by suitably placed coordinating groups. With these facts in mind, the appeal of the proposed scheme is apparent. Hydrocyanation of the electron-poor enal substrate should furnish the 'activated' racemic allylic cyanohydrin.[3] If the hydrocyanation can be made reversible and rapid with respect to the rate of epoxidation of the mismatched cyanohydrin enantiomer, one would expect to effect a dynamic kinetic resolution with respect to the cyanohydrin stereogenic centre.[4–6] Subsequent dehydrocyanation should furnish the epoxy aldehyde and potentially enable catalytic turnover of cyanide.

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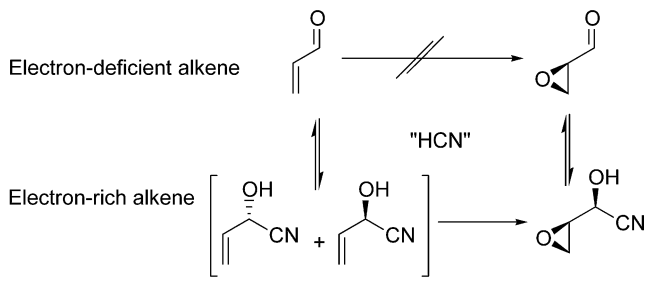
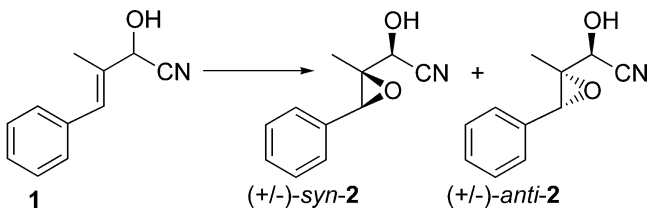
2. Results and discussion

2.1. Ti(O*i*Pr)$_4$-mediated epoxidation of the allylic cyanohydrin 1

As anticipated, cyanohydrin **1** underwent smooth epoxidation with Ti(O*i*Pr)$_4$ and *tert*-butyl hydroperoxide to give the epoxycyanohydrin **2** as a mixture of diastereomers (Scheme 2). The major diastereomer has



Scheme 1. Catalytic electronic activation: indirect Sharpless asymmetric epoxidation of enals.



Scheme 2. *Reagents and conditions*: 1 equiv. Ti(O*i*Pr)$_4$, 2 equiv. *t*BuOOH, CH_2Cl_2 (0.10 M), −16°C, 83%, 65% d.e.

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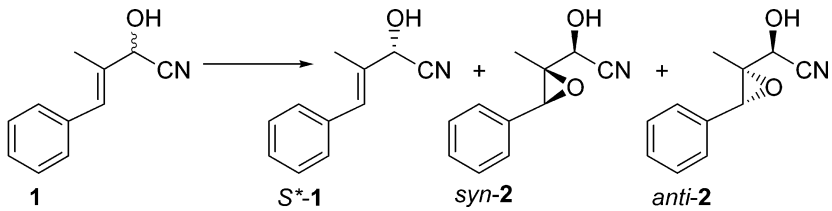
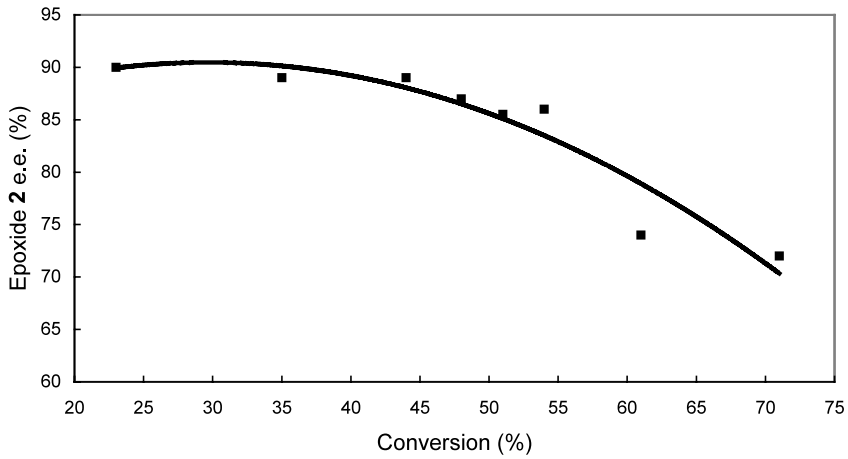
been tentatively assigned as *syn* in analogy with related epoxidation reactions of secondary allylic alcohols.

2.2. Sharpless kinetic resolution of racemic allylic cyanohydrin (±)-1

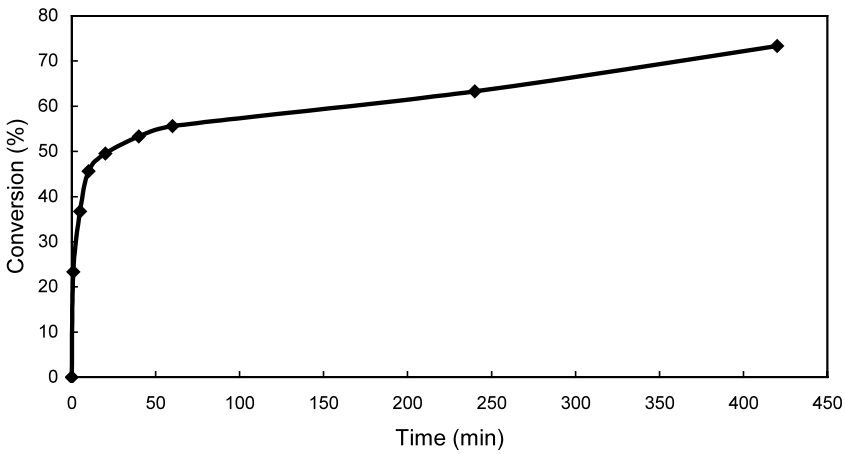
A novel Sharpless kinetic resolution[7] of cyanohydrin **1** using (+)-diethyl tartrate (DET) led to the preferential formation of the (2*R*)-epoxide (Scheme 3). The absolute stereochemistry of the cyanohydrin has been inferred using the predictive model for enantioselectivity proposed by Sharpless.[1] However, the epoxide stereocentre has been unambiguously assigned by derivatisation to the known epoxide of α-methylcinnamyl alcohol. At 48% conversion the epoxide had 87% e.e., whilst at 61% conversion the residual cyanohydrin **1** was essentially enantiomerically pure (99% e.e.). Monitoring the stereoselectivity of the reaction against time showed that initially (i.e. prior to 50% conversion), predominantly *syn*-**2** with (*R*)-epoxide configuration was formed. Allowing the reaction to proceed beyond 50% conversion resulted in reduction of enantiomeric excess **with respect to the epoxide** and dramatic slowing of the reaction rate (Scheme 3, Graphs 1 and 2).



Scheme 3. *Reagents and conditions*: 1 equiv. $Ti(OiPr)_4$, 1 equiv. (+)-DET, 2 equiv. *t*BuOOH, CH_2Cl_2 (0.1 M), –16°C.



Graph 1. Enantiomeric excess of epoxide (*syn*-**2**+*anti*-**2**) versus conversion.



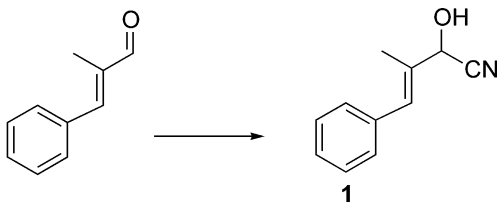
Graph 2. Conversion of cyanohydrin **1** versus time.

Table 1. Hydrocyanation of α-methyl cinnamaldehyde in the presence of titanium tetraisopropoxide

Entry	ACH (mol%)	Base (mol%)	$Ti(OiPr)_4$ (mol%)	Yield, 1 h (%)	Yield, 24 h (%)	Yield, 72 h (%)
1	100	–	100	<1	9	36
2	100	iPr_2NEt (20)	–	18	19	17
3	100	NaCN (20)	–	3	15	14
4	100	iPr_2NEt (20)	100	9	41	41
5	100	NaCN (20)	100	<1	38	39
6	100	NaCN (10)	100	9	32	31
7	500	NaCN (20)	100	32	62	63

2.3. Hydrocyanation of the enal

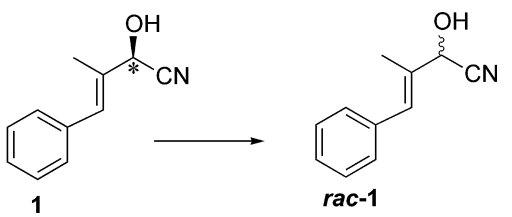
Acetone cyanohydrin (ACH) was found to be a convenient source of 'HCN' for the hydrocyanation of α-methyl cinnamaldehyde in the presence of $Ti(OiPr)_4$ (Table 1, entry 1). Furthermore, the rate of hydrocyanation was enhanced when a suitable base (e.g. R_3N or NaCN) was present. The presence of both base and $Ti(OiPr)_4$ (entries 4 and 5) appeared to have a beneficial synergistic effect over using base alone (entries 2 and 3) (Scheme 4).



Scheme 4. *Reagents and conditions*: 1 equiv. $Ti(OiPr)_4$, base, ACH, CH_2Cl_2 (0.25 M).

2.4. Racemisation and reversible hydrocyanation

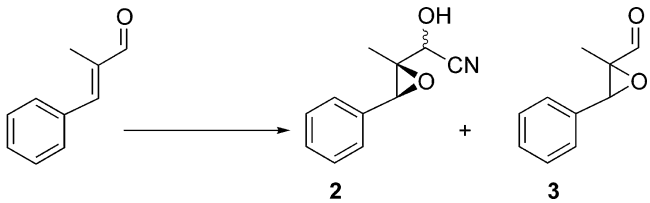
In order to realise the full potential of the proposed system we needed to ensure that hydrocyanation was reversible. We chose to investigate this through using enantiomerically enriched cyanohydrin **1**, which was prepared by asymmetric trimethylsilylcyanation of α-methyl cinnamaldehyde.[8] The absolute configuration of the major enantiomer has not been determined, but has been tentatively assigned *R* on the basis of analogy with similar examples.[8] The enantiomerically enriched cyanohydrin **1** (26% e.e.) was subjected to the optimised hydrocyanation conditions ($Ti(OiPr)_4$, ACH and base) (Scheme 5) and subsequent racemisation occurred. This confirmed that the addition of HCN was indeed a reversible exchange.[9] Racemic cyanohydrin (±)-**1** was obtained in less than 30 min using iPr_2NEt (0.2 equiv.), whilst racemisation using NaCN (0.2 equiv.) took considerably longer (22% e.e. after 4 h; racemic within 24 h).



Scheme 5. *Reagents and conditions*: 1 equiv. $Ti(OiPr)_4$, 0.2 equiv. NaCN or iPr_2NEt, 1 equiv. ACH, CH_2Cl_2 (0.25 M).

2.5. One-pot hydrocyanation/epoxidation

Attempts to effect the domino asymmetric epoxidation of α-methyl cinnamaldehyde were moderately successful and it was possible to convert α-methyl cinnamaldehyde indirectly into epoxide **2** through an SKR reaction on the hydrocyanated starting material generated in situ (Scheme 6, Table 2).



Scheme 6. One-pot hydrocyanation/epoxidation of α-methyl cinnamaldehyde.

The initial results obtained using Methods A and B were very encouraging;[10] however, the complete catalytic cycle (Scheme 1) was not realised (i.e. no epoxyaldehyde **3** observed), although the principle of substrate activation has clearly been demonstrated. More disappointing were the relatively modest enantiomeric excesses (36–38%) obtained. This is thought to reflect the lower enantioselectivity of the SKR at moderately high temperatures (7 and 22°C c.f. −16°C)[b] and may also reflect a slow rate of cyanohydrin racemisation relative to the rate of epoxidation. This could then result in a competing (less enantioselective) epoxidation of the mismatched enantiomer.

An attempted one-pot hydrocyanation/epoxidation reaction using NaCN (Method C) gave epoxycyanohydrin **2** in 66% isolated yield[11] (3:4 mixture of diastereomers). However, further analysis of this reaction revealed that after only 5 min **2** was formed as a racemic mixture (30% conversion). This suggested that the reaction is accelerated via an achiral reaction manifold and furthermore, the analysis also revealed an initial build up of cyanohydrin **1**, which subsequently reduced with concomitant formation of epoxycyanohydrin **2**. This would appear to rule out a pathway involving direct (nucleophilic) epoxidation of the enal. Additionally, no epoxidation is observed when α-methyl cinnamaldehyde is treated with NaCN (1.0 equiv.)/*t*BuOOH (2.0 equiv.) or NaCN (1.0 equiv.)/*t*BuOOH (2.0 equiv.)/$Ti(OiPr)_4$ (1.0 equiv.). However,

Table 2. Reagents and conditions for the one-pot hydrocyanation/epoxidation of α-methyl cinnamaldehyde

Method[a]	ACH (mol%)	Base (mol%)	$Ti(OiPr)_4$ (mol%)	(+)-DET (mol%)	Temp. (°C)	t (h)	Yield cyanohydrin **2**/e.e. (*R*)-epoxide
A	200	$EtNiPr_2$ (200)	100	110	7[b]	192	46% (38%, 37% d.e.)
B	200	$EtNiPr_2$ (200)	100	110	22	47	39% (36%, 40% d.e.)
C	500	NaCN (100)	100	110	22	23	66% (0%, 7% d.e.)
D	–	NaCN (100)	200	120	22	25	50%[c] (0%, 0% d.e.); 25% epoxyaldehyde **3**; 25% starting material

[a] All the experiments were carried out in CH_2Cl_2 (0.25 M) using 2 equiv. *t*BuOOH.
[b] No product was formed using these conditions at −16°C; even after 312 h.
[c] Conversion determined by ^1H NMR on the isolated mixture.

hydrocyanation/epoxidation of α-methyl cinnamaldehyde *was* achieved under the latter conditions when (+)-diethyl tartrate was present (Method D). ^1H NMR analysis of the crude product mixture revealed epoxy cyanohydrin **2** (50%) epoxy aldehyde **3** (25%) along with unreacted starting material (25%). Unfortunately the epoxide of **2** was again racemic. It is unclear why diethyl tartrate is crucial for this reaction, but it is proposed that it could function as a proton source in the absence of acetone cyanohydrin.

3. Conclusion

The first Sharpless kinetic resolution of an allylic cyanohydrin and conditions for reversible hydrocyanation of an enal that are compatible with the SKR reaction have been demonstrated. Catalytic electronic activation of the enal substrate has enabled a successful asymmetric epoxidation of an enal in a one-pot sequence. However, the poor rates of hydrocyanation at the lower temperatures, which are optimal for asymmetric epoxidation, do need to be addressed. The catalytic turnover of the nucleophile (in this case cyanide) also remains a desirable goal.

4. Experimental

4.1. General

All glassware was oven dried and cooled in a desiccator (P_2O_5 desiccant) prior to use. Dichloromethane (CH_2Cl_2) was distilled from calcium hydride and stored over 4 Å molecular sieves. Commercially supplied reagents were used as supplied. Flash column chromatography was carried out using Merck 60 silica gel (70–240 μm). In order to prevent dehydrocyanation, **all cyanohydrin products** were purified on **pre-acidified** (petroleum ether/diethyl ether/acetic acid, 20:1:1) silica gel columns. This is particularly important for cyanohydrin **1**. ^1H, ^{13}C and ^{19}F NMR spectra were recorded on either a Jeol GX270 or EX400 spectrometer. Chemical shifts are reported downfield in parts per million (ppm) from a tetramethylsilane reference. Infrared spectra were recorded on a Perkin–Elmer 1600 series FTIR spectrometer as thinly dispersed films (from CH_2Cl_2) between sodium chloride plates. Low resolution (EI+/FAB+) and accurate mass spectra were obtained using a Finnigan MAT 8340 mass spectrometer. Thin-layer chromatography was carried out using Macherey–Nagal, Polygram® SIL G/UV_{254} pre-coated plastic backed plates. The plates were visualised using ultraviolet light ($\lambda = 254$ nm) and/or $KMnO_4$ solution. High-pressure column chromatography was carried out using a Thermo Separation Products Spectraseries P200 HPLC with a UV100 detector and Chromjet integrator. Chiralcel OD (0.46 cm Diameter×25 cm) chiral stationary phase was used.

4.2. $Ti(OiPr)_4$-mediated epoxidation of (*E*)-2-hydroxy-3-methyl-4-phenyl-3-butenenitrile 1

A solution of cyanohydrin **1** (702 mg, 4.053 mmol) in CH_2Cl_2 (40 mL) with 4 Å molecular sieves (404 mg), was stirred at −5°C under a nitrogen atmosphere. Titanium tetraisopropoxide (1.20 mL, 4.065 mmol) was then added. After 5 min stirring, a solution of *tert*-butyl hydroperoxide (5 M in decane, 1.62 mL, 8.1 mmol) was added and the reaction mixture was transferred to a freezer at −16°C. The reaction was quenched after 24 h using aq. $FeSO_4$/tartaric acid solution (250 g dm^{-3}/100 g dm^{-3}, 1.0 mL) and was filtered through a pad of Celite®/Na_2SO_4. The product was purified on pre-acidified SiO_2 column using gradient elution (petroleum ether/diethyl ether, 20:1–7:3) to give **2** as a blue-grey oil (635 mg, 83%, 65% d.e. *syn*-diastereomer assumed major).

4.3. *syn*-2-Hydroxy-3-methyl-3-oxiranyl-4-phenyl butanenitrile 2

ν_{max} (liquid film): 3424, 2256, 1063 cm^{-1}; δ_H (270 MHz, $CDCl_3$): 1.28 (s, 3H, CH_3), 3.67 (s br, 1H, O*H*), 4.34 (s, 1H, PhC*H*(O)C), 4.60 (s, 1H, C*H*(OH)CN), 7.26–7.39 (m, 5H, Ph); δ_C (67.8 MHz, $CDCl_3$): 12.5 (*C*H_3), 61.0 (*C*H(OH)CN), 62.8 (PhCH(-O-)*C*(CH_3)CH), 64.7 (Ph*C*H(-O-)C(CH_3)CH), 117.2 (Ar*C*), 126.3 (2 Ar*C*H), 128.2 (*p*-Ar*C*H), 128.3 (2 Ar*C*H), 133.4 (CH(OH)*C*N); MS (70 eV): m/z (%) 189 Da ($M^{\bullet+}$, 1%), 162 ($M^{\bullet+}$–

HCN, 4%), 43 (100%): acc. mass EI+ found, 189.0790 Da, $C_{11}H_{11}NO_2$ pred., 189.07897 Da; $R_f = 0.40$ (petroleum ether/diethyl ether, 1:1).

4.4. *anti*-2-Hydroxy-3-methyl-3-oxiranyl-4-phenyl butanenitrile 2a

ν_{max} (liquid film): 3424, 2256, 1063 cm^{-1}; δ_H NMR (270 MHz, $CDCl_3$): 1.27 (s, 3H, CH_3), 3.53 (t, 1H, $J = 9.0$ Hz, CHOH), 4.29 (s, 1H, PhCH(O)C), 4.63 (d, 1H, $J = 9.0$ Hz, CH(OH)CN), 7.26–7.39 (m, 5H, Ph); δ_C (67.8 MHz, $CDCl_3$): 12.4 (CH_3), 60.0 (CH(OH)CN), 62.7 (PhCH(-O-)C(CH$_3$)CH), 64.5 (PhCH(-O-)C-(CH$_3$)CH), 117.2 (ArC), 126.4 (2 ArCH), 128.3 (p-ArCH), 128.4 (2 ArCH), 133.5 (CH(OH)CN); MS (70 eV): m/z (%) 189 Da ($M^{\bullet+}$, 1%), 162 ($M^{\bullet+}$–HCN, 4%), 43 (100%): acc. mass EI+ found, 189.0790 Da, $C_{11}H_{11}NO_2$ pred., 189.07897 Da; $R_f = 0.48$ (petroleum ether/diethyl ether, 1:1).

4.5. Sharpless kinetic resolution of (±)-(*E*)-2-hydroxy-3-methyl-4-phenyl-3-butenenitrile 1

Titanium tetraisopropoxide (1.19 mL, 4.031 mmol) was added to a cooled (−16°C) nitrogen purged solution of (+)-diethyl tartrate (0.69 mL, 4.032 mmol) in CH_2Cl_2 (32 mL) containing 4 Å molecular sieves (368 mg). After stirring the solution for 10 min a solution of cyanohydrin **1** (698 mg, 4.030 mmol) in CH_2Cl_2 (8 mL) was added dropwise. After a stirring the mixture for a further 10 min, a solution of *tert*-butyl hydroperoxide (5 M in decane, 1.61 mL, 8.05 mmol) was added.

(i) **Aliquot quench and work-up**: For the purposes of monitoring the kinetic resolution we removed aliquots (1.5 mL) of reaction mixture which were immediately quenched in vigorously stirred CH_2Cl_2 (5 mL) containing aq. $FeSO_4$/tartaric acid solution (250 g dm^{-3}/100 g dm^{-3}, five drops). After 30 min the mixture was filtered through Celite®/$MgSO_4$ with CH_2Cl_2 (2×5 mL) washings. The combined CH_2Cl_2 phase was extracted once with aq. $FeSO_4$/tartaric acid solution (250 g dm^{-3}/100 g dm^{-3}, 5 mL) and dried over $MgSO_4$. Removal of the solvent in vacuo yielded the crude product mixture, which was taken through to the next step without further purification.

(ii) **Preparation of Moshers esters**: A freshly prepared solution of dicyclohexylcarbodiimide (0.165 mmol), (*R*)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (0.165 mmol) and 4-(*N*,*N*-dimethylamino)-pyridine (0.033 mmol) in CH_2Cl_2 (2.2 mL) was added to the crude reaction mixture aliquots. After 24 h the reactions were diluted with petrol (5 mL) and filtered through a pipette containing Celite®. The crude mixture was subjected to column chromatography on pre-acidified SiO_2 (petroleum ether/diethyl ether, 20:1–15:1).[12] The enantiomeric ratio for **1** was determined by integration of the diastereomeric cyanohydrin α-methine protons ($\delta_H = 6.14$, 6.10) whilst the enantiomeric and diastereomeric ratios for **2** were determined by integration of the 4-oxyranyl methine protons ($\delta_H = 4.09$, 4.17, 4.20, 4.25). The relative conversion of **1** to **2** was determined by the sum of the integration of the cyanohydrin α-methine protons in **1** ($\delta_H = 6.14$, 6.10) relative to the sum of the cyanohydrin α-methine protons in **2** ($\delta_H = 5.42$, 5.57, 5.57, 5.60).

4.5.1. 1-(*R*)-Derived Moshers ester. δ_H (270 MHz, $CDCl_3$): 1.87 (s, 3H, C=CCH_3), 3.62 (d, 3H, $J = 1.10$ Hz, OCH_3), 6.14 (d, 1H, $J = 0.73$ Hz, C=CCH(CN)O_2C), 6.83 (s, 1H, PhCH=C), 7.23–7.53 (m, 5H, Ph); δ_F (376 MHz, $CDCl_3$): −72.09 (s, CF_3).

4.5.2. 1-(*S*)-derived Moshers ester. δ_H (270 MHz, $CDCl_3$): 1.86 (s, 3H, C=CCH_3), 3.56 (d, 3H, $J = 1.10$ Hz, OCH_3), 6.10 (d, 1H, $J = 0.74$ Hz, C=CCH(CN)O_2C), 6.88 (s, 1H, PhCH=C), 7.23–7.53 (m, 5H, Ph); δ_F (376 MHz, $CDCl_3$): −72.22 (s, CF_3).

4.5.3. 2-*syn*-(*R*)-Derived Moshers ester. δ_H (270 MHz, $CDCl_3$): 1.13 (s, 3H, CH_3), 3.60 (d, 3H, $J = 1.22$ Hz, OCH_3), 4.09 (s, 1H, PhCH(-O-)C), 5.57 (s, 1H, CCH(CN)O_2C), 7.18–7.52 (m, 5H, Ph); δ_F (376 MHz, $CDCl_3$): −72.05 (s, CF_3).

4.5.4. 2-*syn*-(*S*)-Derived Moshers ester. δ_H (270 MHz, $CDCl_3$): 1.27 (s, 3H, CH_3), 3.60 (d, 3H, $J = 1.22$ Hz, OCH_3), 4.20 (s, 1H, PhCH(-O-)C), 5.60 (s, 1H, CCH(CN)O_2C), 7.18–7.52 (m, 5H, Ph); δ_F (376 MHz, $CDCl_3$): −72.14 (s, CF_3).

4.5.5. 2-*anti*-(*R*)-Derived Moshers ester. δ_H (270 MHz, $CDCl_3$): 1.24 (s, 3H, CH_3), 3.56 (d, 3H, $J = 1.22$ Hz, OCH_3), 4.25 (s, 1H, PhCH(-O-)C), 5.42 (s, 1H, CCH(CN)O_2C), 7.18–7.52 (m, 5H, Ph); δ_F (376 MHz, $CDCl_3$): −72.26 (s, CF_3).

4.5.6. 2-*anti*-(*S*)-Derived Moshers ester. δ_H (270 MHz, $CDCl_3$): 1.26 (s, 3H, CH_3), 3.56 (d, 3H, $J = 1.22$ Hz, OCH_3), 4.17 (s, 1H, PhCH(-O-)C), 5.57 (s, 1H, CCH(CN)O_2C), 7.18–7.52 (m, 5H, Ph); δ_F (376 MHz, $CDCl_3$): −72.14 (s, CF_3).

4.6. Hydrocyanation study–monitoring the hydrocyanation of α-methyl cinnamaldehyde

4.6.1. General protocol. α-Methyl cinnamaldehyde (0.070 mL, 0.501 mmol) was added to a stirred solution/suspension of base in CH_2Cl_2 (2.0 mL). The mixture was purged with nitrogen and titanium tetraisopropoxide (0.150 mL, 0.508 mmol) was added where necessary. This was immediately followed by addition of acetone cyanohydrin. To monitor the hydrocyanation, aliquots (0.050 mL) of the reaction mixture were taken and immediately quenched in biphasic diethyl ether (1.0 mL)/aq. tartaric acid (10% w/v, 0.20 mL) which were shaken vigorously for a few seconds before being allowed to stand. A sample of ethereal phase (0.010–0.020 mL) was removed and dissolved in hexane/*i*PrOH (9:1, 1.5 mL) containing $MgSO_4$. These solutions were subjected to HPLC analysis (Chiralcel OD column with hexane/*i*PrOH (9:1) eluent, 1.00 cm^3 min^{-1} flow rate, $\lambda = 254$ nm). α-Methyl cinnamaldehyde t_R 6.9 min (signal integration multiplied by a factor of 1.145 to give relative molarity with

respect to **1**), **1**-(*S*) t_R 10.7 min, **1**-(*R*) t_R 11.6 min. See Table 1 for tabulated results.

4.6.2. (*E*)-2-Hydroxy-3-methyl-4-phenyl-3-butenenitrile 1. ν_{max} (liquid film): 3419, 2248, 1600, 1491, 1447, 1014, 700 cm^{-1}; δ_H (270 MHz, $CDCl_3$): 2.04 (d, 3H, $J=1.3$ Hz, CH_3), 3.77 (s br, 1H, O*H*), 5.03 (d, 1H, $J=4.6$ Hz, C*H*(OH)CN), 6.80 (s, 1H, PhC*H*=C), 7.26–7.41 (m, 5H, Ph); δ_C (67.8 MHz, $CDCl_3$): 14.1 (CH_3), 66.8 (*C*H(OH)CN), 118.4 (Ar*C*), 127.5 (Ar*C*H), 128.3 (2 Ar*C*H), 128.9 (2 Ar*C*H), 130.0 (Ph*C*H=C), 131.6 (C=*C*(CH_3)CH), 135.7 (CH(OH)*C*N); MS (70 eV): *m*/*z* (%) 173 Da ($M^{\bullet+}$, 11%), 145 ($M^{\bullet+}$ –HCN, 100%): acc. mass EI+ found, 173.08309 Da, $C_{11}H_{11}NO$ pred., 173.08406 Da; $R_f=0.50$ (petroleum ether/diethyl ether, 1:1).

4.7. Racemisation of (*E*)-2(*R*)-hydroxy-3-methyl-4-phenyl-3-butenenitrile 1

4.7.1. General protocol. To a nitrogen-purged vessel containing base (0.2 equiv.) and acetone cyanohydrin (1.0 equiv.) was added a solution of enantiomerically enriched **1** (0.25 M in CH_2Cl_2, 1.0 equiv.) followed by titanium tetraisopropoxide (1.0 equiv.). To monitor the racemisation, aliquots (0.050 mL) of the reaction mixture were taken and immediately quenched in biphasic diethyl ether (1.0 mL)/aq. tartaric acid (10% w/v, 0.20 mL) which were shaken vigorously for a few seconds before being allowing to stand. A sample of ethereal phase (0.010–0.020 mL) was removed and dissolved in hexane/*i*PrOH (9:1, 1.5 mL) containing $MgSO_4$. These solutions were subjected to HPLC analysis (vide supra).

4.7.2. Racemisation using *i*Pr_2NEt. As above, using *i*Pr_2NEt (0.0140 mL, 0.080 mmol) and acetone cyanohydrin (0.0370 mL, 0.405 mmol), **1** in CH_2Cl_2 (0.25 M, 1.60 mL, 0.400 mmol) and titanium tetraisopropoxide (0.120 mL, 0.406 mmol). A racemic mixture was observed within 30 min (33% α-methyl cinnamaldehyde formed).

4.7.3. Racemisation using NaCN. As above, using NaCN (5 mg, 0.102 mmol) and acetone cyanohydrin (0.0460 mL, 0.504 mmol), **1** in CH_2Cl_2 (0.25 M, 2.00 mL, 0.500 mmol) and titanium tetraisopropoxide (0.150 mL, 0.508 mmol). A racemic mixture was observed within 24 h (22% α-methyl cinnamaldehyde formed).

4.8. One-pot hydrocyanation/asymmetric epoxidation of α-methyl cinnamaldehyde

(i) To a cooled (–16°C), nitrogen purged solution of (+)-diethyl tartrate (0.096 mL, 0.561 mmol) in CH_2Cl_2 (2.0 mL) was added titanium tetraisopropoxide (0.150 mL, 0.508 mmol). After stirring for 15 min, α-methyl cinnamaldehyde (0.070 mL, 0.501 mmol) was added, followed by *i*Pr_2NEt (0.0170 mL, 0.098 mmol) and then acetone cyanohydrin (0.092 mL, 1.01 mmol). The mixture was allowed to stir at –16°C for 2 h prior to adding *tert*-butyl hydroperoxide (5 M in decane, 0.200 mL, 1.00 mmol). The reaction mixture was then transferred to a refrigerator at 7°C. The reaction was quenched after 8 days with aq. $FeSO_4$/tartaric acid solution (250 g dm^{-3}/100 g dm^{-3}, 0.3 mL) and was filtered through a pad of Celite®/Na_2SO_4. The organic phase was extracted with aq. $FeSO_4$/tartaric acid solution (250 g dm^{-3}/100 g dm^{-3}, 3×30 mL) and dried over Na_2SO_4. The product was purified on pre-acidified SiO_2 using gradient elution (petroleum/diethyl ether, 6:1–4:1). α-Methyl cinnamaldehyde was recovered (16 mg, 22%). Epoxycyanohydrin **2** was isolated as a 1:1 molar mixture with ethyl diisopropyl tartrate (94 mg mixture; calculated 43 mg **2**, 46%, 37% d.e. assumed *syn*, 38% e.e. (*R*)-epoxide determined by conversion to Moshers ester).

(ii) To a nitrogen purged flask containing NaCN (123 mg, 2.510 mmol) was added a pre-formed solution of (+)-diethyl tartrate (0.47 mL, 2.747 mmol) and titanium tetraisopropoxide (0.74 mL, 2.507 mmol) in CH_2Cl_2 (10 mL). To this stirred solution was added α-methyl cinnamaldehyde (0.35 mL, 2.507 mmol) followed by acetone cyanohydrin (1.15 mL, 12.59 mmol) and then *tert*-butyl hydroperoxide (5 M in decane, 1.00 mL, 5.00 mmol). The reaction was quenched after 24 h with aq. $FeSO_4$/tartaric acid solution (250 g dm^{-3}/100 g dm^{-3}, 1.0 mL) and filtered through a pad of Celite®/Na_2SO_4. The organic phase was extracted with aq. $FeSO_4$/tartaric acid solution (250 g dm^{-3}/100 g dm^{-3}, 3×30 mL) and dried over Na_2SO_4. The product was purified on pre-acidified SiO_2 using gradient elution (petroleum ether/diethyl ether, 20:1–7:3). Epoxycyanohydrin **2** was isolated as viscous oil (312 mg, 66%, 7% d.e. assumed *anti*, 0% e.e. epoxide determined by conversion to Moshers ester).

(iii) To a nitrogen purged suspension of NaCN (25 mg, 0.510 mmol) in CH_2Cl_2 (2.0 mL) was added titanium tetraisopropoxide (0.150 mL, 0.508 mmol) and (+)-diethyl tartrate (0.10 mL, 0.584 mmol). After stirring the solution for 10 min, α-methyl cinnamaldehyde (0.070 mL, 0.501 mmol) was added followed by *tert*-butyl hydroperoxide (5 M in decane, 0.200 mL, 1.00 mmol). The reaction was quenched after 25 h with aq. $FeSO_4$/tartaric acid solution (250 g dm^{-3}/100 g dm^{-3}, 0.2 mL) and filtered through a pad of Celite®/Na_2SO_4. The organic phase was extracted with aq. $FeSO_4$/tartaric acid solution (250 g dm^{-3}/100 g dm^{-3}, 3×30 mL) and dried over Na_2SO_4. The product was eluted through a pre-acidified (petroleum ether/diethyl ether, 7:3) SiO_2 column to yield clear oil (40 mg). ^1H NMR revealed a mixture of epoxycyanohydrin **2**/ epoxyaldehyde **3**/α-methyl cinnamaldehyde (48:26:26). This corresponds to epoxycyanohydrin **2** (21 mg, 22%, 1:1 d.r., <5% e.e. epoxide determined by conversion to Moshers ester); epoxyaldehyde **3** (10 mg, 12%, e.e. not determined); α-methyl cinnamaldehyde (9 mg, 12%). Further purification of **2** on a pre-acidified (petroleum ether/diethyl ether, 20:1–7:3) SiO_2 column gave **2** (17 mg, 18%) as a clear oil.

4.9. (*E*)-2-Methyl-3-phenyl oxiranecarbaldehyde 3[13]

ν_{max} (liquid film): 1730 (C=O), 890, 850 cm^{-1}; δ_H (270 MHz, $CDCl_3$): 1.22 (s, 3H, C*H*$_3$), 4.31 (s, 1H, PhC*H*(O)C), 7.26–7.43 (m, 5H, Ph), 9.10 (s, 1H, C*H*O); δ_C (67.8 MHz, $CDCl_3$): 9.2 (*C*H$_3$), 60.4 (Ph*C*H(-O-)C), 65.0 (CH(-O-)*C*(CH$_3$)CHO), 126.5 (2 Ar*C*H), 128.4 (2 Ar*C*H), 128.5 (*p*-Ar*C*H), 132.9 (Ar*C*), 199.1 (*C*HO); MS (70 eV): *m*/*z* (%) 162 Da ($M^{\bullet+}$, 55%), 91 ($C_7H_7^+$, 100%): acc. mass EI+ found, 162.068390 Da, $C_{10}H_{10}O_2$ pred., 162.068080 Da; $R_f = 0.65$ (petroleum ether/diethyl ether, 1:1).

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10. In this reaction, epoxycyanohydrin **2** was isolated as a 1:1 mixture with diisopropyl tartrate, a by-product from transesterification under the reaction conditions.
11. No significant transesterification was observed in this reaction; even at room temperature.
12. TLC of the crude reaction mixtures revealed a component consistent with remaining starting material but further analysis showed this to be co-running mono Moshers ester of diethyl tartrate, $R_f = 0.40$ (petroleum ether/diethyl ether, 1:1), which was easily removed by flash column chromatography. No diester was observed.
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