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Chiral Lewis Base Catalyzed Enantioselective Acetylcyanation of α-Oxo Esters

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Dedicated to Professor Karl Hult on the occasion of his 65th birthday

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Acetyl cyanide adds to alkyl benzoylformates and to 2-oxoalkanoates to yield enantioenriched acylated cyanohydrins in one step in the presence of a catalytic amount of a chiral base. The reaction is accelerated by Lewis acids and by the addition of a catalytic amount of methanol. Under optimized conditions, 94 % of a 94:6 mixture of the *O*-acetylated and non-protected cyanohydrins was formed from methyl benzoylformate in the presence of cinchonidine; from this mixture the acylated compound with 66 % *ee* was isolated in 77 % yield. Ethyl pyruvate and *tert*-butyl 2-oxobutanoate were more reactive, and essentially full conversion to the products with 69 and 82 % *ee*, respectively, was achieved. The reaction proceeds by a non-selective addition of cyanide ion to give the non-protected cyanohydrin followed by a dynamic kinetic resolution to provide the enantioenriched acetylated product.

Introduction

The addition of cyanide to the carbonyl function of aldehydes and ketones is currently receiving considerable attention due to the usefulness of the products obtained as intermediates in organic synthesis.[1] A variety of enantioselective catalytic systems based on Lewis acids and/or Lewis bases have been employed for the additions, in many cases providing highly enantioenriched products.[2]

Reactions with ketones as substrates are particularly challenging as they require control of the stereochemistry of a quaternary center. However, several successful examples of such additions have been reported. Trimethylsilyl cyanide has most commonly been employed as cyanide source in additions to ketones, thus providing direct access to *O*-protected cyanohydrins. Lewis base[3] or bifunctional activation incorporating a metal-centered Lewis acid[4] or a hydrogen-bond donor[5] has been employed for this purpose. Cyanoformates have also been added to ketones, affording enantioenriched carbonates by using chiral Lewis bases as catalysts.[6] We have recently found that, in the presence of a catalyst consisting of a chiral Lewis acid and an achiral Lewis base, acylcyanation of aldehydes proceeds in one step, yielding *O*-acylated cyanohydrins from a variety of acyl cyanides with excellent yields and enantioselectivities and perfect atom economy.[7] Cyano esters obtained by this procedure have useful applications[8] at the same time as they serve as versatile synthetic intermediates.[9]

So far, no examples of direct cyano ester formation from ketones have been reported. We decided to attempt the same conditions as those used for aldehydes for the addition of acetyl cyanide to prochiral ketones. We have now found that activated α-oxo esters serve as substrates for the addition, although under slightly different conditions, probably as a result of a different reaction mechanism.

Results and Discussion

First the same conditions as those used for additions to aldehydes were attempted for the reaction of methyl benzoylformate (**1a**) with acetyl cyanide (Scheme 1). Thus, subjecting **1a** to 2 equiv. of acetyl cyanide in the presence of a catalyst composed of 5% Ti(salen) dimer **2**, introduced and used by Belokon, North and co-workers for silylcyanation of both aldehydes[10] and ketones[11] and 10% triethylamine in dichloromethane, resulted after 5 h at room temperature in 50% conversion to a 84:16 mixture of *O*-acetylated cyanohydrin **3a** and nonprotected cyanohydrin **4a** (Table 1, Entry 1). The ratio of the two compounds increased slightly over time (88:12 after 30 h) although the total yield of the two products remained essentially constant. To our disap-

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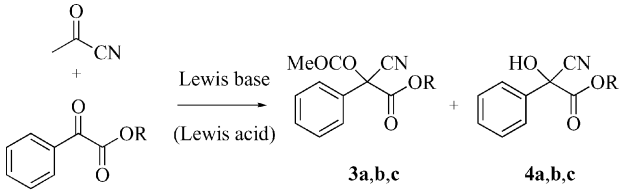
pointment, the desired cyano ester was obtained as a racemate. The reaction also occurred in the absence of the Ti catalyst, but at a lower rate (30% conversion after 16 h, Entry 2). Even a reaction performed at –40 °C, in the presence of **2**, did not lead to any selectivity (Entry 3). The addition of 1.2 equiv. of methanol resulted in a more rapid reaction, providing 72% conversion to a 74:26 **3a**/**4a** mixture after 16 h at room temperature (Entry 4). Similar catalytic activity was observed in the absence of triethylamine, although a product mixture consisting mainly of the alcohol **4a** was obtained (13:87, Entry 5). The formation of nonprotected cyanohydrin was suppressed when acetyl cyanide was added slowly over 30 min. Thus, in a reaction performed without methanol at room temperature under



Scheme 1. Acetylcyanation of alkyl benzoylformates.

conditions of slow addition, some alcohol **4a** was observed in the initial part of the reaction, but after 16 h 97% conversion to **3a**, still as a racemate, was observed (Entry 6). A more active catalytic system also resulted when triethylamine was replaced by DMAP, with 96% conversion to a 98:2 ratio of **4a** and **3a** observed in the presence of Ti complex **2** after 6 h at room temperature (Entries 7 and 8, to be compared to Entries 1 and 2).

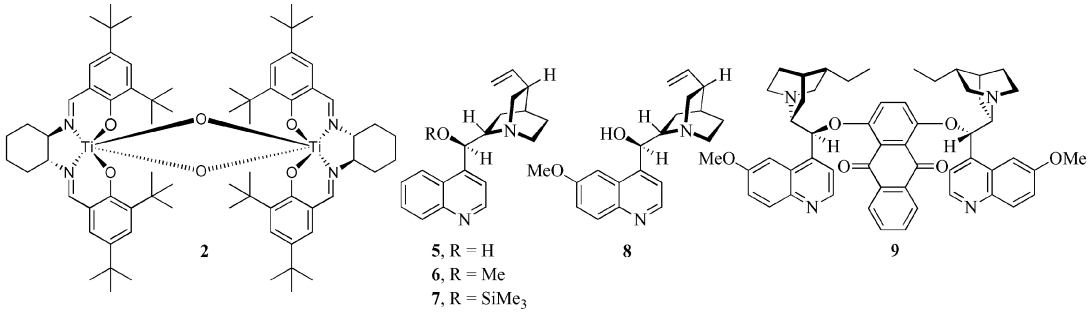
We were pleased to find that the use of the chiral base cinchonidine (**5**) in place of triethylamine resulted in the formation of enantioenriched cyano ester. Thus, a catalyst composed of cinchonidine and (*R*,*R*)-salen dimer gave 48% of a 52:48 mixture of **3a** and **4a**, the former with 29% *ee*, after 4 h at 0 °C followed by 13 h at room temperature (Entry 9). The same enantiomer of **3a**, with the same selectivity (30 vs. 29% *ee*) was obtained when the (*R*,*R*)-salen dimer was replaced by its enantiomer (Entry 10), demonstrating again that chirality transfer from the titanium complex is inefficient.

Higher conversions and higher enantioselectivities were achieved at lower temperature by omitting the Lewis acid. After 6 h at –40 °C, 99:1 mixtures of **3a** and **4a** were obtained, the former with 66% *ee* (Entries 11 and 12), with slightly higher conversions observed in the presence of MeOH (77 compared to 69%). Slow addition of acetyl cya-

Table 1. Lewis acid/Lewis base catalyzed additions of acetyl cyanide to keto esters **1a**–**c**.

Entry[a]	Oxo ester	Lewis acid	Lewis base	MeOH [mol-%]	Time [h]	Temperature [°C]	Conversion (%)[b] **3**/**4**	*ee* (%)[c] **3**
1	**1a**	**2**	Et_3N	–	5	room temp.	50, 84:16	0
					30	room temp.	51, 88:12	0
2	**1a**	–	Et_3N	–	16	room temp.	30, 67:33	–
3	**1a**	**2**	Et_3N	–	16	–40	30, 57:43	0
4	**1a**	**2**	Et_3N	120	16	room temp.	72, 74:26	0
5	**1a**	**2**	–	120	16	room temp.	70, 13:87	0
6	**1a**	**2**	Et_3N	–	16[d]	room temp.	97, 100:0	0
7	**1a**	**2**	DMAP	–	3	room temp.	76, 86:14	0
					6	room temp.	96, 98:2	0
8	**1a**	–	DMAP	–	3	room temp.	48, 76:24	–
					6	room temp.	65, 88:12	–
9	**1a**	**2**	**5**	–	4+13	0 to room temp.	48, 52:48	29
10	**1a**	*ent*-**2**	**5**	–	4+14	0 to room temp.	53, 66:34	30
11	**1a**	–	**5**	–	6	–40	69, 99:1	66
12	**1a**	–	**5**	10	6	–40	77, 99:1	66
13	**1a**	–	**5**	10	6[e]	–40	91, 93:7	66
14	**1a**	–	**6**	10	6	–40	20, 51:49	6
15	**1a**	–	**7**	10	6	–40	n.d.	16[f]
16	**1a**	–	**8**	–	48	–40	7, 71:29	42
17	**1a**	–	**8**	10	21	–40	21, 63:37	34
18	**1a**	–	**9**	–	6	–40	41, 96:4	44
19	**1a**	–	**9**	10	6	–40	53, 99:1	34
20	**1b**	–	**5**	10	6+12	–40 to room temp.	67, 99:1	64
21	**1b**	–	**6**	10	6	–40	40	8
22	**1c**	–	DMAP	–	3	room temp.	96, 100:0	–
23	**1c**	–	**5**	10	6	0	40, 68:32	49
24	**1c**	–	**5**	10	16	0	82, 99:1	53
25	**1c**	–	**6**	10	6	0	30, 50:50	0
26	**1c**	–	**7**	10	6	0	30, 50:50	6[f]
27	**1c**	–	**9**	10	6	0	34, 67:33	45

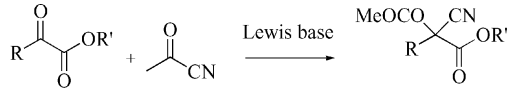
[a] Reaction conditions: 10 mol-% Lewis acid (when relevant), 10 mol-% Lewis base (5 mol-% **9**), the indicated mol-% MeOH, 0.12 mmol of oxo ester and 0.24 mmol of acetyl cyanide in 0.5 mL of CH_2Cl_2. [b] Determined by ^1H NMR spectroscopy. [c] Determined by chiral HPLC. [d] Acetyl cyanide was added over 30 min. [e] Acetyl cyanide was added over 3 h. [f] Opposite enantiomer.



nide, over 3 h, improved the conversion to 91% (Entry 13). From a reaction run under these conditions **3a**, with 66% *ee*, was isolated in 77% yield. Replacement of cinchonidine by *O*-methylated (**6**) or *O*-silylated (**7**) cinchonidine or by quinine (**8**) or $(DHQD)_2AQN$ [hydroquinidine (anthraquinone-1,4-diyl) diether, **9**] resulted in inferior enantioselectivities and lower conversions, both in the presence and absence of methanol (Entries 14–19). The reaction using *O*-silylated cinchonidine **7** gave the opposite enantiomer as the major product (Entry 15); similar inversion of stereochemistry was previously observed in hydrogenations using cinchonidine derivatives.[12]

Ethyl benzoylformate (**1b**) reacted with acetyl cyanide in the presence of **5** in the same way as **1a** to provide, under the optimized conditions, acylated cyanohydrin **3b** in 67% isolated yield and 64% *ee* (Table 1, Entry 20), whereas the same reaction run in the presence of *O*-methylated cinchonidine **6** resulted in poor selectivity (Entry 21). Sterically crowded *tert*-butyl ester **1c** reacted smoothly with acetyl cyanide in the presence of DMAP at room temperature (Entry 22). However, use of chiral bases **5**, **6**, **7**, and **9** resulted in lower or no selectivity (Entries 23–27) than observed with **1a** and **b**.

Ethyl pyruvate (**1d**) proved to be considerably more reactive than the aromatic oxo esters. Essentially full conversion to product **3d** was achieved within 4 h at –40 °C in the presence of **5**, without Lewis acid (Table 2, Entry 1). Under these conditions, the enantioselectivity was low, however (41% *ee*). Somewhat higher selectivity was observed at –78 °C (47–53% *ee*), but conversions were lower, in particular in reactions without MeOH (Entries 2 and 3). In contrast to the situation with **1a**, highest enantioselectivities were achieved by using $(DHQD)_2AQN$ (**9**) as a Lewis base (Entries 4–6); at –78 °C essentially full conversion to **3d** with 68% *ee* was observed in the presence of MeOH (Entry 6). Sterically hindered *tert*-butyl ester **1e** also reacted smoothly with acetyl cyanide in the presence of triethylamine (98% conversion after 3 h at room temperature, Entry 7), and this substrate resulted in higher enantioselectivity than **1d** when chinchonidine was used as base (82% *ee*, Entry 8). Use of other chiral bases (**6**, **7**, **9**) provided the product with lower selectivity (Entries 9–11).



1d, R = Me, R' = Et
1e, R = Et, R' = *t*Bu

3d,**e**

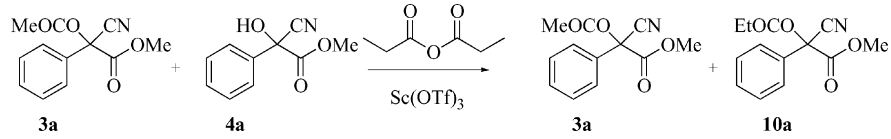
Mechanistic Aspects

Our results demonstrate that the Lewis base is responsible for the chirality transfer to the product because racemic

Table 2. Lewis acid/Lewis base catalyzed additions of acetyl cyanide to oxo ester **1d**,**e**.

Entry[a]	Oxo ester	Lewis base	MeOH [mol-%]	Time [h]	Temperature [°C]	Conversion (%)[b] **3**c	*ee* (%)[c] **3**
1	**1d**	**5**	10	4	–40	98	41
2	**1d**	**5**	10	1	–78	63	47
				3	–78	60	47
3	**1d**	**5**	–	3	–78	53	53
4	**1d**	**9**	10	1	–40	89	64
				3	–40	99	64
5	**1d**	**9**	–	1	–40	54	69
				3	–40	58	69
6	**1d**	**9**	10	1	–78	71	68
				3	–78	96	69
				6	–78	99	68
7	**1e**	Et_3N	–	3	room temp.	98	–
8	**1e**	**5**	10	3	–78	98	82
9	**1e**	**6**	10	3	–78	98	16
10	**1e**	**7**	10	3	–78	98	0
11	**1e**	**9**	10	3	–78	98	65

[a] Reaction conditions: 10 mol-% Lewis base (5 mol-% **7**), the indicated amount of MeOH, 0.36 mmol of oxo ester and 0.72 mmol of acetyl cyanide (added over 30 min) in 1.5 mL of CH_2Cl_2. [b] Determined by ^1H NMR spectroscopy. [c] Determined by chiral GC.



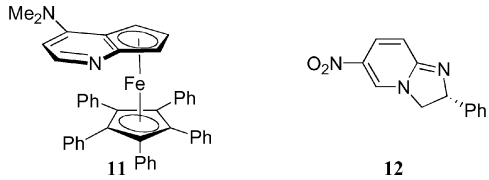
Scheme 2. Acylation of **4a** in the presence of **3a**.

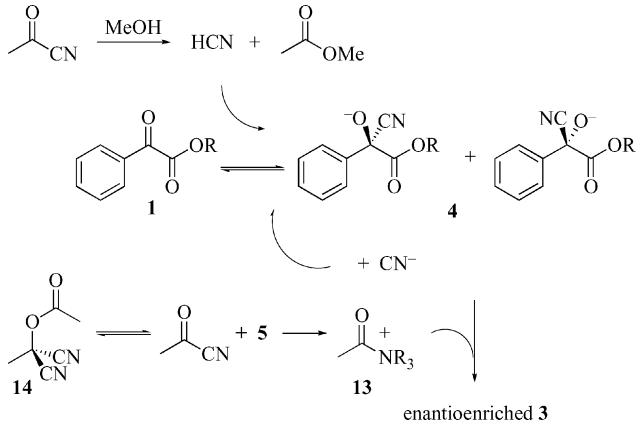
product is obtained in the presence of **2** and an achiral Lewis base, and because the same enantiomer, with the same selectivity, is obtained when **2** is replaced with *ent*-**2** in the presence of cinchonidine (**5**). A further observation comes from Entries 1, 7 and 8 of Table 1, which show that the ratio **3a**/**4a** increases during the catalytic reaction, suggesting that the cyanohydrin **4a** may be an intermediate in the formation of product **3a**. This was indeed verified by monitoring a reaction performed in the presence of in situ prepared Ti(salen) complex **5** and MeOH in toluene at room temperature over time. Under these conditions 91% conversion to a 3.1:1 mixture of **3a** and **4a** was achieved after 5 h. The total amount of the two products remained constant, but the **3a**/**4a** ratio changed to 7.3:1 and 14.1:1 after 20 and 48 h, respectively.

In principle, the enantioselection can take place either in the addition of cyanide to the prochiral oxo ester or in the acylation of the initially formed cyanohydrin. In order to elucidate which step is responsible for the selectivity, the *ee* of the cyanohydrin **4a** was determined. Under the conditions used for the analysis of the cyano ester (chiral HPLC), the enantiomers of **4a** did not separate. Therefore, a reaction mixture containing **3a** and **4a** was treated with propionic anhydride in the presence of $Sc(OTf)_3$,[13] thus affording a mixture of the original acetates **3a** (Scheme 2) and propionates **10a**, formed from **4a**. This allowed the *ee* values of both cyano ester **3a** and the ester derived from **4a** to be determined by HPLC from a single experiment. It was found that whereas the *ee* of **3a** obtained from a reaction run with 0.5 equiv. of MeOH at –40 °C for 4 h was 53%, the ethyl ester **10a**, and thus **4a**, were found to be essentially racemic (2% *ee*). The catalytic reaction therefore most probably proceeds by a non-selective cyanation followed by a dynamic kinetic resolution to form the enantioenriched *O*-acetylated product. This is similar to what was found by Tian and Deng[6] in the cyanocarbonation of ketones and is consistent with the observation that in a few cases the enantioselectivity decreased slightly as the reaction proceeded.

Recognizing that acylation of **4a** is the enantioselective step, use of known chiral acyl transfer reagents was considerred to be of interest. We are not aware of any examples of enantioselective acylations of tertiary cyanohydrins. Therefore chiral DMAP analogue **11**[14] and reagent **12**,[15] exhibiting high selectivity in acylations of secondary alcohols, were tested in the acetylcyanation of **1a**. However, with both reagents, poor conversions, even at room temperature, and poor enantioselectivities were observed.

Our results are consistent with the mechanism shown in Scheme 3. The reaction is supposed to be initiated by HCN, produced from acetyl cyanide and methanol,[16] or by cyanide present as an impurity in the acylating agent. Racemic **4**, resulting from reaction of **1** with cyanide, is acylated by **13**, obtained from the chiral base and acetyl cyanide, which is known to be in equilibrium with dimer **14**.[17] This process is a dynamic kinetic resolution, which requires a rapid equilibrium between **1** and **4**. The acylated amine **13** is expected to be a more efficient acyl transfer reagent than acetyl cyanide, in accordance with the high ratio of **4a** to **3a** observed in the absence of tertiary amine (compare, e.g., Table 1, Entries 4 and 5). Acylation liberates cyanide, which enables catalytic turnover.





Scheme 3. Plausible mechanism for enantioselective acetylcyanation of α-oxo esters.

Compounds of the type prepared through the catalytic method presented here have found some applications. The ethyl ester **3b** has previously been prepared in racemic form and used for the preparation of β-lactons acting on the central nervous system,[18] and racemic naphthyl analogues have been prepared by radical reaction.[19] Our new procedure thus offers a convenient route to enantioenriched **3b**.

Conclusions

Acetylcyanation of alkyl benzoylformates and 2-oxoalkanoates is catalyzed by Lewis bases and proceeds by initial addition of cyanide to the oxo group of the substrate followed by acyl transfer from the reagent obtained from acetyl cyanide and chiral amine. The chiral induction origi-

nates from a dynamic kinetic resolution during acylation of the initially formed racemic cyanohydrin. This mechanism is different from that of acylcyanations of prochiral aldehydes.[7] The latter type of reactions requires dual Lewis acid/Lewis base activation and proceeds by Lewis acid promoted enantioselective addition of cyanide to the carbonyl function. Chiral Lewis bases have minor influence on the enantioselectivity, and no intermediate non-protected cyanohydrin is observed in the latter type of reactions.

Experimental Section

General: CH_2Cl_2 was distilled from CaH_2. oxo esters **1a**, **1b** and **1d** were commercial and used without further purification. Acetyl cyanide[7c,20] was prepared from acetyl bromide and CuCN, and **1c**[21] and **1e** were prepared by reaction of benzoylformic acid and propionylformic acid, respectively, with methansulfonyl chloride and *tert*-butyl alcohol.[22] *O*-Methylcinchonidine (**6**) and *O*-(trimethylsilyl)cinchonidine (**7**) were prepared by *O*-functionalization of cinchonidine.[12] Conversions were determined by ^{1}H NMR spectroscopy, and enantiomeric excesses were determined by chiral HPLC (Daicel Chiralcel OD-H, 250 × 4.6 mm) or by GC/MS using a chiral column [Chiraldex, G-TA (gamma cyclodextrin trifluoroacetyl), 30 m × 0.25 mm]. ^{1}H NMR spectra were recorded at 500 or 400 MHz, ^{13}C NMR spectra at 125 or 100 MHz. The ^{1}H and ^{13}C chemical shifts are reported in ppm relative to the solvent as internal standard.

Procedure for Optimization of Reaction Conditions: The Lewis acid (0.012 mmol, 10 mol-% based on Ti), Lewis base (0.012 mmol, 10 mol-%) and the indicated amount of methanol in CH_2Cl_2 (0.2 mL) were added to a CH_2Cl_2 solution (0.3 mL) of methyl benzoylformate (**1a**, 17 μL, 0.12 mmol, 1 equiv.). The reaction started by addition of acetyl cyanide (17 μL, 0.24 mmol, 2 equiv.) by a syringe (in the cases of slow addition, the acetyl cyanide was dissolved in 30 μL of CH_2Cl_2) at the indicated temperature. The reaction was monitored by ^{1}H NMR spectra of samples taken from the reaction mixture, and the products were analyzed by chiral HPLC.

Methyl 2-Acetoxy-2-cyano-2-phenylacetate (3a): α-Oxo ester **1a** (85 μL, 0.6 mmol, 1 equiv.) and methanol (60 mM in CH_2Cl_2, 1 mL, 10 mol-%) were added to a solution of cinchonidine (17.7 mg, 10 mol-%) in CH_2Cl_2 (1.5 mL). After the solution was cooled to –40 °C, acetyl cyanide (86 μL, 1.2 mmol, 2 equiv.) was added in portions of about 2 μL during 3 h. The reaction mixture was stirred at –40 °C for 6 h, then moved to a freezer and stirred for another 12 h. The final reaction solution was concentrated in vacuo, and the residue was purified by silica gel chromatography using diethyl ether/hexane (1:8) as eluent to give **3a** (107 mg) as a white powder in 77% isolated yield and 66% *ee*. HPLC (Daicel Chiralcel OD-H, 250 × 4.6 mm, 2-propanol/hexane, 1:99, flow 0.5 mL/min, detection at 220 nm): t_R (minor) = 26.4 min, t_R (major) = 34.6 min. M.p. 47–49 °C. $[\alpha]_D^{20}$ = –56.8 (*c* = 1.0, in $CHCl_3$, sample with 66% *ee*). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.72–7.73 (m, 2 H), 7.45–7.49 (m, 3 H), 3.84 (s, 3 H), 2.30 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 169.1, 164.4, 130.9, 130.7, 129.2, 126.1, 114.8, 74.4, 54.5, 20.3 ppm.

Ethyl 2-Acetoxy-2-cyano-2-phenylacetate (3b): α-Oxo ester **1b** (95 μL, 0.6 mmol, 1 equiv.) and methanol (60 mM in CH_2Cl_2, 1 mL, 10 mol-%) were added to a solution of cinchonidine (17.7 mg, 10 mol-%) in CH_2Cl_2 (0.5 mL). After the solution was cooled to –40 °C, acetyl cyanide (86 μL, 1.2 mmol, 2 equiv.) was added in portions of about 2 μL during 3 h. The reaction mixture was stirred at –40 °C for 6 h, then moved to a freezer and stirred for another 12 h. Workup as described above gave **3b** (99 mg) as a colorless oil, which slowly solidified in 67% isolated yield and 64% *ee*. HPLC (Daicel Chiralcel OD-H, 250 × 4.6 mm, 2-propanol/hexane, 1:99, flow 0.5 mL/min, detection at 220 nm): t_R (minor) = 20.0 min, t_R (major) = 29.2 min. M.p. 58–60 °C. $[\alpha]_D^{20}$ = –68.4 (*c* = 1.6, in $CHCl_3$, sample with 64% *ee*). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.72–7.74 (m, 2 H), 7.46–7.48 (m, 3 H), 4.22–4.34 (m, 2 H), 2.30 (s, 3 H), 1.26–1.29 (t, *J* = 7.3 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 169.0, 163.8, 131.0, 130.6, 129.1, 126.1, 114.9, 74.5, 64.0, 20.3, 13.7 ppm. $C_{13}H_{13}NO_4$ (247.25): calcd. C 63.15, H 5.30, N 5.67; found C 63.18, H 5.35, N 5.38.

***tert*-Butyl 2-Acetoxy-2-cyano-2-phenylacetate (3c):** α-Oxo ester **1c** (0.6 mmol, 124 mg, 1 equiv.) and methanol (60 mM in CH_2Cl_2, 1 mL, 10 mol-%) were added to a solution of cinchonidine (17.7 mg, 10 mol-%) in CH_2Cl_2 (1.5 mL). After the solution was cooled to 0 °C, acetyl cyanide (86 μL, 1.2 mmol, 2 equiv.) was added slowly over 30 min. The reaction mixture was stirred at 0 °C for 16 h. The reaction solution was concentrated in vacuo, and the residue was purified by silica gel chromatography using diethyl ether/hexane (1:8) as eluent to give the product (130 mg), as colorless oil in 79% isolated yield and 53% *ee*. HPLC (Daicel Chiralcel QD-H, 250 × 4.6 mm, 2-propanol/hexane, 0.1:99.9, flow 0.5 mL/min, detection at 220 nm): t_R (major) = 24.9 min]: t_R (minor) = 26.9 min. $[\alpha]_D^{20}$ = –49.0 (*c* = 1.0, in $CHCl_3$, sample with 53% *ee*). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.68–7.74 (m, 2 H), 7.43–7.48 (m, 3 H), 2.29 (s, 3 H), 1.46 (s, 9 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 169.4, 162.8, 131.9, 130.8, 129.4, 126.4, 115.7, 86.3, 75.4, 29.9, 20.8 ppm. $C_{15}H_{17}NO_4$ (275.3): calcd. C 65.44, H 6.22, N 5.09; found C 65.37, H 6.33, N 5.02.

Ethyl 2-Acetoxy-2-cyanopropanoate (3d): Ethyl pyruvate (**1d**, 174 μL, 1.5 mmol) and methanol (6.1 μL, 0.15 mmol) were added to a solution of $(DHQD)_2AQN$ (64.3 mg, 0.075 mmol) in dry CH_2Cl_2 (6.25 mL). After the solution was cooled to –78 °C, acetyl cyanide (213 μL, 3 mmol) was added slowly over 30 min. The reaction mixture was stirred at –78 °C for 4 h, diluted with Et_2O and filtered through silica, and the solvent was evaporated under vacuum. The residue was purified by bulb-to-bulb distillation followed by silica gel chromatography using diethyl ether/hexane (1:1) as eluent to give a sample of the pure product (30%) as a colorless oil. GC [Chiraldex, G-TA (gamma cyclodextrin trifluoroacetyl), 30 m × 0.25 mm, GC parameters: 70 °C (hold 1 min), 4 °C/min up to 95 °C and then 15 °C/min up to 120 °C (hold 43 min)]: t_R (minor) = 15.9 min, t_R (major) = 17.7 min. $[\alpha]_D^{20}$ = –48.0 (*c* = 1.7, in $CDCl_3$, sample with 57% *ee*). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 4.29–4.35 (m, 2 H), 2.18 (s, 3 H), 1.87 (s, 3 H), 1.33 (t, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 168.8, 165.3, 115.7, 69.3, 63.7, 23.6, 20.1, 13.8 ppm.

***tert*-Butyl 2-Acetoxy-2-cyanobutanoate (3e):** *tert*-Butyl 2-oxobutanoate (**1e**, 9.5 μL, mmol) and methanol (60 mM in CH_2Cl_2, 0.1 mL, 10 mol-%) were added to a solution of cinchonidine (1.75 mg, 10 mol-%) in dry CH_2Cl_2 (0.25 mL). After the solution was cooled to –78 °C, acetyl cyanide (8.6 μL, 0.12 mmol) was added slowly over 30 min. The reaction mixture was stirred at –78 °C for 3 h, diluted with Et_2O and filtered through silica, and the solvent was evaporated under vacuum. GC [Chiraldex, G-TA (gamma cyclodextrin trifluoroacetyl), 30 m × 0.25 mm, GC parameters: 95 °C (hold 4 min), 15 °C/min up to 120 °C (hold 25 min)]: t_R (minor) = 16.1 min, t_R (major) = 16.4 min. $[\alpha]_D^{20}$ = –60.0 (*c* = 1.0, in $CDCl_3$, sample with 82% *ee*). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.18 (s, 3 H), 2.08–2.12 (m, 2 H), 1.52 (s, 3 H), 1.16 (t, *J* = 7.2 Hz, 3 H) ppm.

***ee* Determination of 3a and 4a:** α-Oxo ester **1a** (85 μL, 0.6 μmol, 1 equiv.) and methanol (12 μL, 0.5 equiv.) were added to a solution of cinchonidine (17.7 mg, 10 mol-%) in CH_2Cl_2 (2.5 mL). After the solution was cooled to –40 °C, acetyl cyanide (86 μL, 1.2 mmol, 2 equiv.) was added in one portion. The reaction mixture was stirred at –40 °C for 4 h and then concentrated at low pressure. The residue was passed through a pad of silica and eluted with diethyl ether. The collected solution containing a mixture of unreacted substrate and products was dried with Na_2SO_4, the solvent was removed at low pressure, and the residue dried under vacuum for a short time (^{1}H NMR spectroscopy showed that about 0.15 mmol of alcohol **4a** was present in the residue). The above mixture was re-dissolved in CH_2Cl_2 (5 mL), to which was added propionic anhydride (38 μL, 0.3 mmol, 2 equiv. based on **4a**) and $Sc(OTf)_3$ (5.0 mg). The resulting solution was stirred at room temperature for 2 h, by which time **4a** was completely converted to its ethyl ester **10a**. A sample was taken from the reaction mixture and analyzed by chiral HPLC (2-propanol/hexane, 0.5:99.5, flow 0.5 mL/min, detection at 220 nm).

Supporting Information (see footnote on the first page of this article): ^{1}H NMR and ^{13}C NMR spectra of compounds **3a**–**e**, HPLC of **3a**–**c** and of a mixture of **3a** and **8a**, and GC of **3d**–**e**.

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[1] a) F. Effenberger, *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1555–1564; b) R. J. H. Gregory, *Chem. Rev.* **1999**, *99*, 3649–3682.

[2] a) M. North, *Tetrahedron: Asymmetry* **2003**, *14*, 147–176; b) J.-M. Brunel, I. P. Holmes, *Angew. Chem. Int. Ed.* **2004**, *43*, 2752–2778; c) N. H. Khan, R. I. Kureshy, S. H. R. Abdi, S. Agrawal, R. V. Jasra, *Coord. Chem. Rev.* **2008**, *252*, 593–623; d) M. North, D. L. Usanov, C. Young, *Chem. Rev.* **2008**, *108*, 5146–5226.

[3] a) S.-K. Tian, R. Hong, L. Deng, *J. Am. Chem. Soc.* **2003**, *125*, 9900–9901; b) X. Liu, B. Qin, X. Zhou, B. He, X. Feng, *J. Am. Chem. Soc.* **2005**, *127*, 12224–12225.

[4] a) Y. Hamashima, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2000**, *122*, 7412–7413; b) Y. Hamashima, M. Kanai, M. Shibasaki, *Tetrahedron Lett.* **2001**, *42*, 691–694; c) K. Yabu, S. Masumoto, S. Yamasaki, Y. Hamashima, M. Kanai, W. Du, D. P. Curran, M. Shibasaki, *J. Am. Chem. Soc.* **2001**, *123*, 9908–9909; d) H. Deng, M. P. Isler, M. L. Snapper, A. H. Hoveyda, *Angew. Chem. Int. Ed.* **2002**, *41*, 1009–1012; e) Y. Shen, X. Feng, G. Zhang, Y. Jiang, *Synlett* **2002**, 1353–1355; f) F. Chen, X. Feng, B. Qin, G. Zhang, Y. Jiang, *Org. Lett.* **2003**, *5*, 949–952; g) Y. Shen, X. Feng, Y. Li, G. Zhang, Y. Jiang, *Eur. J. Org. Chem.* **2004**, 129–137; h) B. He, F.-X. Chen, Y. Li, X. Feng, G. Zhang, *Tetrahedron Lett.* **2004**, *45*, 5465–5467; i) F.-X. Chen, B. Qin, X. Feng, G. Zhang, Y. Jiang, *Tetrahedron* **2004**, *60*, 10449–10460; j) B. He, F.-X. Chen, Y. Li, X. Feng, G. Zhang, *Eur. J. Org. Chem.* **2004**, 4657–4666; k) F.-X. Chen, H. Zhou, X. Liu, B. Qin, X. Feng, G. Zhang, Y. Jiang, *Chem. Eur. J.* **2004**, *10*, 4790–4797; l) Y. Xiong, X. Huang, S. Gou, J. Huang, Y. Wen, X. Feng, *Adv. Synth. Catal.* **2006**, *348*, 538–544; m) Q. Li, X. Liu, J. Wang, K. Shen, X. Feng, *Tetrahedron Lett.* **2006**, *47*, 4011–4014; n) S. S. Kim, J. M. Kwak, *Tetrahedron* **2006**, *62*, 49–53; o) S. S. Kim, S. H. Lee, J. M. Kwak, *Tetrahedron: Asymmetry* **2006**, *17*, 1165–1169; p) M. Shibasaki, M. Kanai, *Org. Biomol. Chem.* **2007**, *5*, 2027–2039; q) K. Shen, X. Liu, Q. Li, X. Feng, *Tetrahedron* **2008**, *64*, 147–153.

[5] a) D. E. Fuerst, E. N. Jacobsen, *J. Am. Chem. Soc.* **2005**, *127*, 8964–8965; b) S. J. Zuend, E. N. Jacobsen, *J. Am. Chem. Soc.* **2007**, *129*, 15872–15883; c) B. Qin, X. Liu, J. Shi, K. Zheng, H. Zhao, X. Feng, *J. Org. Chem.* **2007**, *72*, 2374–2378; d) S. J. Zuend, E. N. Jacobsen, *J. Am. Chem. Soc.* **2007**, *129*, 15872–15883.

[6] a) S.-K. Tian, L. Deng, *J. Am. Chem. Soc.* **2001**, *123*, 6195–6196; b) S.-K. Tian, L. Deng, *Tetrahedron* **2006**, *62*, 11320–11330.

[7] a) S. Lundgren, E. Wingstrand, M. Penhoat, C. Moberg, *J. Am. Chem. Soc.* **2005**, *127*, 11592–11593; b) E. Wingstrand, S. Lundgren, M. Penhoat, C. Moberg, *Pure Appl. Chem.* **2006**, *78*, 409–414; c) S. Lundgren, E. Wingstrand, C. Moberg, *Adv. Synth. Catal.* **2007**, *349*, 364–372.

[8] a) H. Huang, J. E. Stok, D. W. Stoutamire, S. J. Gee, B. D. Hammock, *Chem. Res. Toxicol.* **2005**, *18*, 516–527; b) G. Shan, B. D. Hammock, *Anal. Biochem.* **2001**, *299*, 54–62; c) C. E. Wheelock, A. M. Wheelock, R. Zhang, J. E. Stok, C. Morisseau, S. E. Le Valley, C. E. Green, B. D. Hammock, *Anal. Biochem.* **2003**, *315*, 208–222; d) C. J. Peterson, R. Tsao, A. L. Eggler, J. R. Coats, *Molecules* **2000**, *5*, 648–654; e) E. Wingstrand, F. Li, S. Lundgren, M. Penhoat, C. Moberg, *Chim. Oggi* **2007**, supplement to vol. 25, no. 5, p. 14–15.

[9] a) M. North, A. W. Parkins, A. N. Shariff, *Tetrahedron Lett.* **2004**, *45*, 7625–7627; b) H. Abe, H. Nitta, A. Mori, S. Inoue, *Chem. Lett.* **1992**, 2443–2446; c) L. Veum, S. R. M. Pereira, J. C. van der Waal, U. Hanefeld, *Eur. J. Org. Chem.* **2006**, 1664–1671.

[10] Y. N. Belokon, S. Caveda-Cepas, B. Green, N. S. Ikonnikov, V. N. Khrustalev, V. S. Larichev, M. A. Moscalenko, M. North, C. Orizu, V. I. Tararov, M. Tasinazzo, G. I. Timofeeva, L. V. Yashkina, *J. Am. Chem. Soc.* **1999**, *121*, 3968–3973.

[11] Y. N. Belokon, B. Green, N. S. Ikonnikov, M. North, V. I. Tararov, *Tetrahedron Lett.* **1999**, *40*, 8147–8150.

[12] S. Diezi, A. Szabo, T. Mallat, A. Baiker, *Tetrahedron: Asymmetry* **2003**, *14*, 2573–2577.

[13] K. Ishihara, M. Kubota, H. Kurihara, H. Yamamoto, *J. Am. Chem. Soc.* **1995**, *117*, 4413–4414.

[14] J. C. Ruble, H. A. Lathan, G. C. Fu, *J. Am. Chem. Soc.* **1997**, *119*, 1492–1493.

[15] V. B. Birman, E. W. Uffman, H. Jiang, X. Li, C. J. Kilbane, *J. Am. Chem. Soc.* **2004**, *126*, 12226–12227.

[16] S. Hünig, R. Schaller, *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 36–49.

[17] B. E. Tate, P. D. Bartlett, *J. Am. Chem. Soc.* **1956**, *78*, 5575–5580.

[18] E. Testa, L. Fontanella, G. F. Cristiani, L. Mariani, *Justus Liebigs Ann. Chem.* **1961**, *639*, 166–180.

[19] A. Citterio, D. Fancelli, R. Santi, A. Pagani, S. Bonsignore, *Gazz. Chim. Ital.* **1988**, *118*, 405–408.

[20] P. Roth, A. Hädener, C. Tamm, *Helv. Chim. Acta* **1990**, *73*, 476–482.

[21] J. W. Yang, B. List, *Org. Lett.* **2006**, *8*, 5653–5655.

[22] A. F. Hegarty, P. O'Neill, *Synthesis* **1993**, 606–610.

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