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Enantioselective cyanocarbonation of ketones with chiral base

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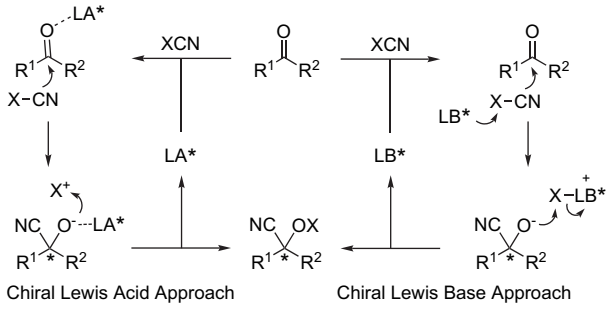
Abstract—A highly enantioselective cyanocarbonation of dialkyl ketones catalyzed by commercially available and easily recyclable cinchona alkaloid derivatives has been developed. The reaction provides a useful approach for the enantioselective construction of tetrasubstituted carbon stereocenters. Mechanistic studies have been carried out to shed light on the origin of the catalytic activity of the cinchona alkaloid and the asymmetric induction step.

1. Introduction

The asymmetric construction of molecules with tetrasubstituted carbon stereocenters is fundamentally important and represents a great challenge in organic synthesis.[1] A conceptually direct and attractive approach is to transform prochiral ketones to chiral building blocks each containing an *O*-substituted quaternary stereocenter by catalytic asymmetric C–C bond formation. The realization of this approach requires the development of chiral catalysts that are effective in promoting a C–C bond forming reaction involving a relatively weak electrophile and in discriminating the two enantiotopic faces of the sterically hindered ketone functionality. Achieving synthetically useful enantioselectivity with unconjugated aliphatic ketones is particularly challenging since the two alkyl substituents of ketone closely resemble each other both electronically and sterically.

The asymmetric cyanation of ketones, an important reaction for the creation of chiral tetrasubstituted carbon stereocenters via asymmetric C–C bond formation, produces versatile chiral cyanohydrins, which can be easily converted to many synthetically useful building blocks such as α-hydroxy acids, α-hydroxy aldehydes (or ketones), and β-aminoalcohols.[2] In principle, the catalytic asymmetric cyanation of ketones can be promoted by two fundamentally different mechanisms involving either a chiral Lewis acid that activates the electrophilic ketone or a chiral Lewis base that activates the nucleophilic cyanating agent (Scheme 1),[3] and in the recent years great breakthroughs have been made with both approaches for the highly enantioselective cyanation of various ketones.[4,5]



Scheme 1. Conceptual chemical catalyst-promoted asymmetric cyanation of ketones.

In this article we describe in detail the synthetic and mechanistic studies of the first highly enantioselective cyanation of ketones catalyzed by chiral Lewis bases.[6] We embarked on the development of a chiral amine-catalyzed cyanation of ketone for both conceptual and practical considerations. In light of the lack of a precedent, the successful development of a highly enantioselective cyanation of ketone with a chiral amine would introduce a conceptually new strategy to this area of research. As most organic functionalities are Lewis basic in nature, a chiral amine-catalyzed reaction may provide the advantage of excellent functional group tolerance. Moreover, the switch of its solubility between aqueous and organic phases corresponding to its protonated and free base form renders a chiral amine catalyst easy to be separated from most organic compounds and subsequently to be recycled. Finally, a catalytic asymmetric reaction with a chiral organic catalyst provides certain advantage in terms of environmental friendliness as well as applicability for pharmaceutical manufacturing.

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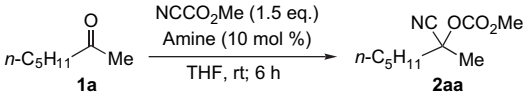
2. Results and discussion

2.1. Tertiary amine-catalyzed cyanocarbonation of ketones

The first obstacle to overcome in the development of a chiral Lewis base-catalyzed cyanation was the establishment of an efficient amine-catalyzed cyanation of ketones. In 1999, Poirier and co-workers described the synthesis of racemic tertiary cyanohydrin carbonate **2** in good yield by the addition of 5–10 equiv of methyl cyanoformate (**4**, R^3=Me) to ketone **1** in the presence of 20 equiv of diisopropylamine (**3**, R^4=^{i}Pr) (Scheme 2).[7] The use of secondary amine **3** and alkyl cyanoformate **4** in a large excess amount hinted at the existence of a decomposition reaction involving these two reagents. We postulated that the reaction proceeded through the mechanism outlined in Scheme 2, which provided a rational for the decomposition of the alkyl cyanoformate **4** and the secondary amine **3**. The acyl ammonium intermediates **5** and **6**, derived from amine **3** and alkyl cyanoformate **4**, could undergo deprotonation by another molecule of **3** to irreversibly form carbamate **7**. According to this postulation, we envisaged that these two decomposition pathways could be eliminated by employing a tertiary amine, in lieu of a secondary amine, to mediate the cyanocarbonation. Additionally, if our rationale was correct, not only a catalytic cyanocarbonation with tertiary amine could be developed, but also such a reaction should require a drastically reduced amount, if not 1 equiv, of alkyl cyanoformate **4**.

With these expectations we began to investigate the use of a tertiary amine to promote the cyanocarbonation of ketones. Although Poirier and co-workers reported that excess NEt_3 was even much less effective than diisopropylamine in promoting the conversion of ketone **1** to cyanohydrin carbonate **2**, we observed that the cyanocarbonation of 2-heptanone with 10 mol % of NEt_3 and 1.5 equiv of methyl cyanoformate in THF at 25 °C proceeded in 38% conversion (Table 1), thereby demonstrating that the cyanocarbonation of a ketone with alkyl cyanoformate **4** could be realized with a catalytic amount of a tertiary amine. It should be noted that the same reaction with 10 mol % of diisopropylamine, a secondary amine, proceeded in only 3.0% conversion. While pyridine, a weaker base, failed to catalyze this transformation, other tertiary amines, such as DABCO and DBU, were found to give significantly higher conversion than that by NEt_3 (Table 1).[8]

Table 1. Organic amine-catalyzed cyanocarbonation of 2-heptanone (**1a**)

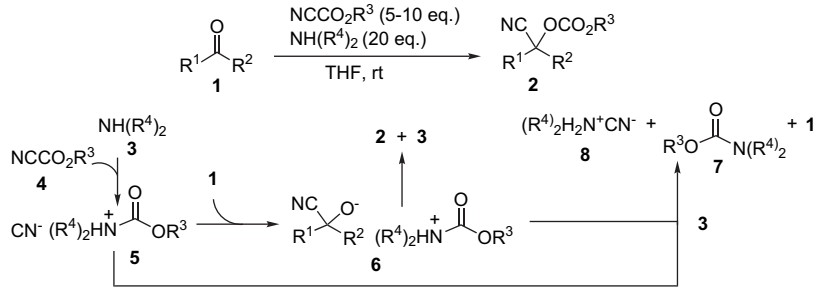


Amine	^{i}Pr$_2$NH	Pyridine	NEt_3	Quinuclidine	DABCO	DBU
Conv. (%)[a]	3.0	0.0	38	37	84	98

[a] Determined by GC using dodecane as an internal standard.

2.2. Chiral Lewis base-catalyzed asymmetric cyanocarbonation of ketones

Encouraged by our success in establishing a tertiary amine-catalyzed cyanocarbonation of ketones, we next focused on the development of an enantioselective variant with a tertiary chiral amine. The promising catalytic activity of DABCO and our discovery in 2000 that certain commercially available modified cinchona alkaloids (Fig. 1) are highly efficient



Scheme 2. Decomposition of secondary amines to carbamates **7**.

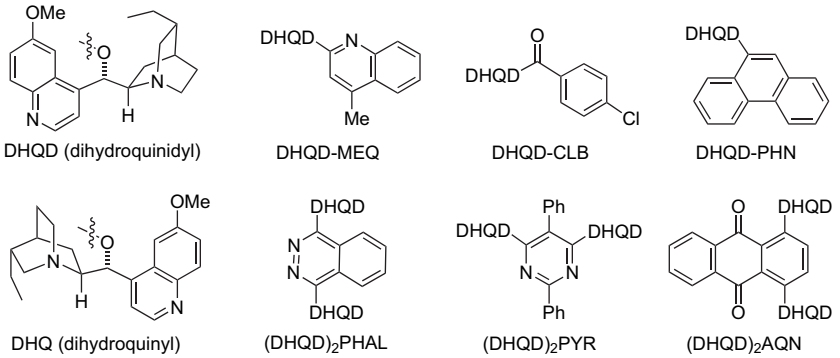


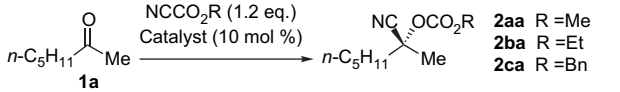
Figure 1. Structures of commercially available modified cinchona alkaloids.

catalysts for enantioselective alcoholysis of cyclic anhydrides[9] immediately attracted us to the possibility of using cinchona alkaloid to realize a highly enantioselective cyanocarbonation of ketones.

The catalyst screening studies were conducted via the asymmetric cyanocarbonation of 2-heptanone (**1a**) with 1.2 equiv of methyl cyanoformate and 10 mol % of the chiral amine catalyst in $CHCl_3$ at 25 °C. As shown in Table 2, DHQD-PHN and $(DHQD)_2AQN$ provided the highest ee (27%, entries 4 and 7), and the latter gave a higher conversion. With $(DHQD)_2AQN$ as the catalyst, the enantioselectivity of the asymmetric cyanocarbonation of 2-heptanone (**1a**) can be improved from 27 to 40% ee by employing ethyl cyanoformate and performing the reaction at −24 °C (entry 17, Table 2). The substitution of ethyl cyanoformate with benzyl cyanoformate and the employment of other common organic solvents such as dichloromethane, ether, toluene, and acetonitrile resulted in deteriorated enantioselectivity for the asymmetric cyanocarbonation of 2-heptanone (**1a**).

Under the optimized reaction condition, the $(DHQ)_2AQN$-catalyzed asymmetric cyanocarbonation of 2-heptanone (**1a**) provided the corresponding tertiary cyanohydrin carbonate in 53% yield and 64% ee (entry 3, Table 3), and the $(DHQ)_2AQN$-catalyzed reaction of 2-butanone provided the product in 51% yield and 41% ee (entry 4, Table 3). Although such enantioselectivity obtained with these α-unbranched methyl alkyl ketones was not synthetically useful, these results were very encouraging considering that these ketones are especially difficult substrates for enantioselective nucleophilic additions, as a chiral catalyst must discriminate efficiently the methyl vs ethyl or *n*-pentyl groups in order to achieve high enantioselectivity. We were pleased to observe that the enantioselectivity improved significantly with dialkyl ketones bearing two alkyl groups that are significantly different from each other in terms of steric bulk. As summarized in Table 3, a variety of acyclic and cyclic dialkyl ketones, both α-substituted and α,α-disubstituted, were transformed to the corresponding tertiary cyanohydrin carbonates in good to excellent enantioselectivity and in synthetically useful yield with DHQD-PHN and $(DHQD)_2AQN$ (Table 3). The enantioselective cyanation of the sterically hindered α,α-disubstituted ketones has been reported previously only once with pinacolone (**1g**) using an enzymatic method.[10] Particularly noteworthy is that, for the first time, a catalytic asymmetric cyanation of a cyclic ketone is realized with excellent enantioselectivity (entries 14, 15, 19, and 20, Table 3). To our knowledge, highly enantioselective cyanation of cyclic ketones remains extremely rare.[4g] The reaction, catalyzed by a chiral base catalyst, readily tolerated acid-sensitive functionality, which is illustrated by the successful enantioselective cyanocarbonation of acyclic and cyclic ketones bearing either an acetal or ketal functionality (entries 9, 11, 12, 16–18, and 21, Table 3).

Table 2. Screening studies on the catalysts, solvents, alkyl cyanoformates, and temperature[a]



Entry	R	Catalyst	Solvent	*T* (°C)	Conv. (%)[b]	ee (%)[c,d]
1	Me	Quinidine	$CHCl_3$	25	66	2.6
2	Me	DHQD-CLB	$CHCl_3$	25	63	17
3	Me	DHQD-MEQ	$CHCl_3$	25	85	17
4	Me	DHQD-PHN	$CHCl_3$	25	83	27
5	Me	$(DHQD)_2PHAL$	$CHCl_3$	25	80	22
6	Me	$(DHQD)_2PYR$	$CHCl_3$	25	86	11
7	Me	$(DHQD)_2AQN$	$CHCl_3$	25	94	27
8	Me	$(DHQD)_2AQN$	CH_2Cl_2	25	96	23
9	Me	$(DHQD)_2AQN$	CCl_4	25	98	20
10	Me	$(DHQD)_2AQN$	PhMe	25	95	14
11	Me	$(DHQD)_2AQN$	Et_2O	25	86	17
12	Me	$(DHQD)_2AQN$	THF	25	54	6.9
13	Me	$(DHQD)_2AQN$	EtOAc	25	84	11
14	Me	$(DHQD)_2AQN$	CH_3CN	25	95	22
15	Et	$(DHQD)_2AQN$	$CHCl_3$	25	97	32
16	Bn	$(DHQD)_2AQN$	$CHCl_3$	25	97	26
17	Et	$(DHQD)_2AQN$	$CHCl_3$	−24	96	40

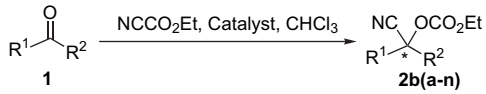
[a] The reaction was performed by treatment of 2-heptanone (0.20 mmol) with alkyl cyanoformate (1.2 equiv) and catalyst (10 mol %) in solvent (0.20 mL).
[b] Determined by GC using dodecane as an internal standard.
[c] Determined by chiral GC and HPLC analysis.
[d] The absolute configuration of the major enantiomer was determined to be *R* by acidic hydrolysis of the product (see Section 4 for the details).

The modified cinchona alkaloid-catalyzed asymmetric cyanocarbonation proceeded cleanly to consistently afford the chiral tertiary cyanohydrin carbonates in greater than 95% yield based on converted ketones (Table 3). The reactions were usually quenched after 2–7 days when they reached a conversion greater than 50% to provide the desired products in 51–99% isolated yields. It should be noted that the catalyst loading could be reduced substantially without any significant adverse effect on the enantioselectivity and yield of the reaction. For example, the nearly quantitative yield and excellent ee obtained from the cyanocarbonation of ketone **1l** (entry 17, Table 3) using 20 mol % catalyst can also be realized by using 10 mol % catalyst (entry 18, Table 3). These results have been successfully reproduced in a 10 mmol scale reaction from which the catalyst, DHQD-PHN, was recovered quantitatively using a simple extractive procedure. Although an extended reaction time was required with a reduced catalyst loading, the reaction can be carried out by simply allowing the reaction mixture in a vial to stand in a freezer without stirring and any special precaution to exclude moisture and air. Modified cinchona alkaloids derived from quinine and quinidine have been shown to furnish highly enantioselective access to both enantiomers of the tertiary cyanohydrin carbonates (Table 3).[11]

2.3. Chemical transformations of chiral tertiary cyanohydrin carbonates

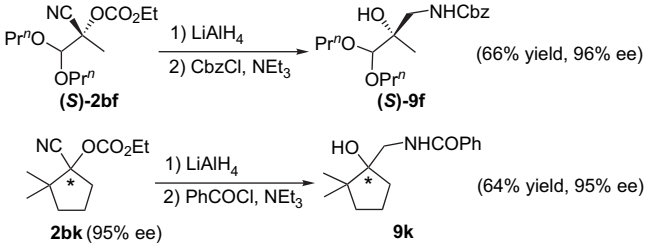
Cyanohydrin carbonates are more stable than their corresponding cyanohydrins toward acidic or basic conditions. However, the two functional groups, cyano and carbonate, of cyanohydrin carbonate can undergo useful chemical transformations under appropriate conditions. For example, $LiAlH_4$ reduces the optically active cyanohydrin carbonates (**2bf** and **2bk**) to the synthetically and biologically important chiral β-aminoalcohols without any deterioration in ee (Scheme 3).

Table 3. Catalytic asymmetric cyanocarbonation of dialkyl ketones with modified cinchona alkaloids[a,b]



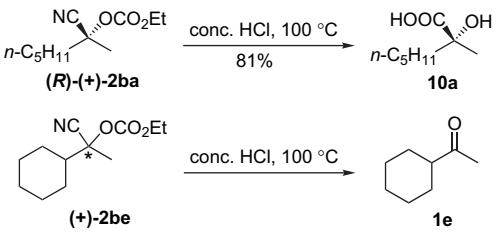
Entry	Substrate	Catalyst (mol %)	Temp (°C)	Time (days)	Conv.[c] (%)	Yield[d] (%)	ee[e](%)
1		(DHQD)$_2$AQN (20)	−24	0.5	56	54	59
2	**1a**, R=*n*-C_5H_{11}	(DHQD)$_2$AQN (20)	−24	2.5	96	93	40
3		(DHQ)$_2$AQN (15)	−24	6	55	53	64[f]
4	**1b**, R=Et	(DHQ)$_2$AQN (10)	−24	5	—	51	41
5		(DHQD)$_2$AQN (10)	−24	4	—	54	59
6	**1c**, R=Me	(DHQ)$_2$AQN (15)	−24	6	—	51	76[f]
7	**1d**, R=Allyl	(DHQ)$_2$AQN (20)	−24	2	57	54	81
8	**1e**, R=$(CH_2)_5$	(DHQ)$_2$AQN (20)	−24	2	55	52	87
9	**1f**, R=O^{n}Pr	DHQD-PHN (30)	−24	4	90	86	96[g]
10	**1g**, R=Me	(DHQD)$_2$AQN (30)	−24	5	58	55	88
11	**1h**, R=OMe	DHQD-PHN (35)	−24	4	67	63	85
12	**1i**, R=OEt	DHQD-PHN (35)	−12	4	68	65	90
13	**1j**	(DHQD)$_2$AQN (10)	25	3	—	66	74
14		(DHQ)$_2$AQN (15)	−24	4	79	76	95
15	**1k**, R=Me	(DHQD)$_2$AQN (15)	−24	2	68	66	97[f]
16		DHQ-PHN (30)	−24	4	83	80	95
17	**1l**, R=OEt	DHQD-PHN (20)	−24	3	97	96	93[f]
18		DHQD-PHN (10)	−24	7	100	99	94
19		(DHQ)$_2$AQN (30)	−12	5	56	53	92
20	**1m**, R=Me	(DHQD)$_2$AQN (20)	−24	4	65	62	91[f]
21	**1n**, R=OEt	DHQD-PHN (35)	−12	5	82	78	96

[a] The reaction was performed by treatment of the ketone (0.20 mmol) with ethyl cyanoformate (1 equiv for entries 3–6, 15; 1.5 equiv for entries 1, 2, 7, 8; 2.0 equiv for entries 9, 10, 13, 20; 3.0 equiv for the other entries) and catalyst in chloroform (0.20 mL for entries 9–21; 0.30 mL for entries 1, 2, 7, 8; 0.40 mL for entries 3–6).
[b] The catalyst was recovered in quantitative yield.
[c] Determined by GC using dodecane as an internal standard.
[d] Isolated yields.
[e] The ee of the product was determined by chiral GC and HPLC analysis.
[f] The opposite enantiomer is generated.
[g] The absolute configuration of the major enantiomer was determined to be *S* (see Section 4 for the details).



Scheme 3. Conversion of chiral tertiary cyanohydrin carbonates to β-amino-alcohol derivatives.

In the presence of a strong acid a simple cyanohydrin carbonate such as (*R*)-(+)-**2ba** was hydrolyzed to give the corresponding α-hydroxy acid (Scheme 4). However, the acidic hydrolysis of β-substituted cyanohydrin carbonate



Scheme 4. Acidic hydrolysis of cyanohydrin carbonates.

(+)-**2be** under the same condition was dominated by the decomposition of the starting material to generate the corresponding ketone **1e**.

2.4. Mechanistic considerations

While the enantioselective cyanocarbonation of unconjugated ketones was found to proceed very cleanly, the ee of the product (cyanohydrin carbonate **2**) generated from reactions with simple dialkyl ketones such as **1a** started to decrease noticeably when the conversion of the reaction proceeded over 55% (comparing entries 1 and 2 of Table 3, also see Fig. 2). This made it necessary to stop the reactions with simple dialkyl ketones well before they reached completion, resulting in the generation of the optically active cyanocarbonates **2** in modest yet still useful yield (Table 3). Interestingly, this ee variation is significantly less pronounced in a reaction employing α,α-dialkoxy cyclic and acyclic ketone such as **1f**, **1h**, **1i**, **1l**, and **1n**, and the corresponding highly enantioenriched cyanohydrin carbonates could be isolated in good to excellent yield. This ee variation of the product has to be accounted for by any proposed reaction mechanism.

Illustrated in Scheme 5 is a mechanism proposed to explain the origin of the enantioselectivity of the modified cinchona alkaloid-catalyzed cyanocarbonation. In principle, the

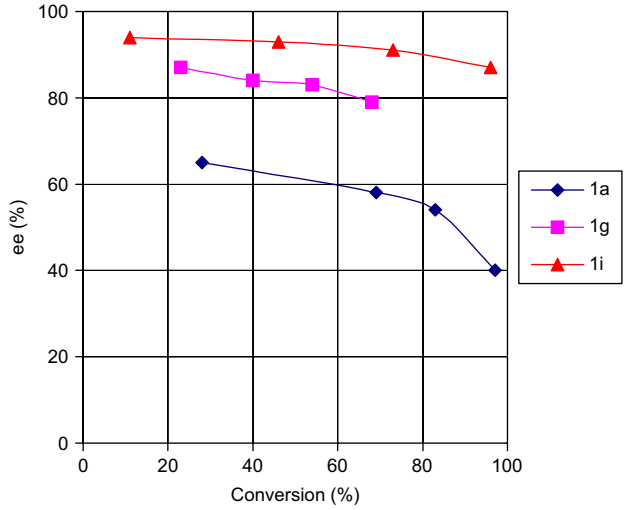
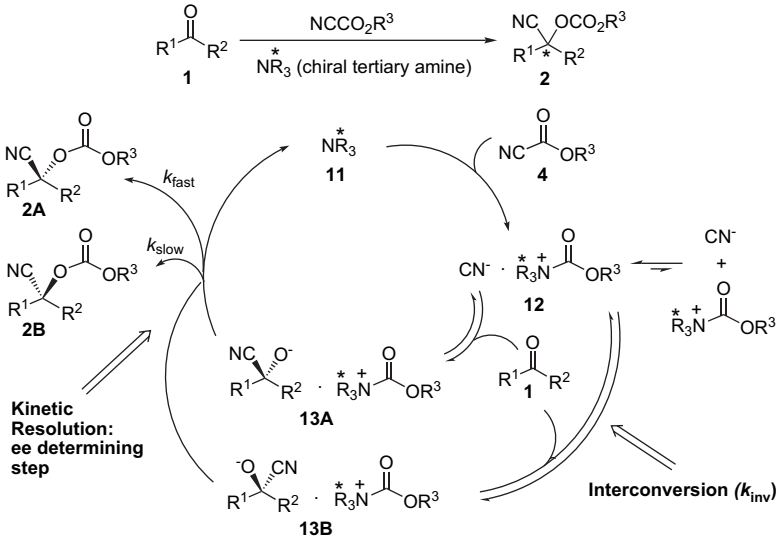


Figure 2. The ee of the product vs the conversion in the modified cinchona alkaloid-catalyzed asymmetric cyanocarbonation of ketones **1a**, **1g**, and **1i**.

asymmetric induction may arise from the enantioselective addition of the cyanide, as part of a chiral ion complex **12**, to ketone **1**. The ee deterioration of cyanocarbonate **2**, however, is difficult to be accounted for by such a mechanism, as it is highly unlikely that the ee deterioration as described above is due to either side reactions or catalyst decompositions, given that the reaction proceeded in excellent yield and the cinchona alkaloid catalysts could be recycled in nearly quantitative yield at the end of the reaction. On the other hand, the unusual ee deterioration of the cyanohydrin carbonate **2** could be explained by an alternative mode of asymmetric induction invoking a dynamic kinetic resolution[12] of intermediates **13A** and **13B**. Conceivably, the two diastereomeric complexes **13A** and **13B**, while undergoing interconversion between each other through ketone **1**, could undergo transfer of the alkoxycarbonyl group from the *N*-acyl ammonium to the alkoxide at different rate, thereby generating product **2** in optically active form via a kinetic resolution of **13A** and **13B**. According to this model, the significant drop in ee observed with simple dialkyl ketones is because the rate of the interconversion between **13A** and **13B**, involving retrocyanation of **13** and cyanation of **1**, is not significantly faster than that of the kinetic resolution step.[13] Increasing the rate of the interconversion between **13A** and **13B** should lead to a reduction in the extent of the ee drop, a phenomenon observed in the reaction with α,α-dialkoxy ketones. The electron-withdrawing dialkoxy group presumably activated the ketone toward nucleophilic attack by CN^-, thereby increasing the rate of the interconversion step. This in turn lessened the decline in the ee of the product **2** as the reaction proceeded to high conversion.

We have found that certain ketone cyanohydrin such as **14** is stable enough to be isolated. This raised the possibility of quenching the modified cinchona alkaloid-catalyzed cyanocarbonation with an alcohol to trap intermediates **13A** and **13B** by protonation of the alkoxide ions (Fig. 3). According to the proposed mechanism outlined in Scheme 5 and assuming that the protonation is much faster than the interconversion between **13A** and **13B**, the er (enantiomer ratio) of cyanohydrin **14** should reflect the dr (diastereomer ratio) of intermediates **13A** and **13B**. Consequently, if the high enantioselectivity is due to efficient kinetic resolution of **13A** and **13B**, the ee of cyanohydrin **14** should be significantly lower than that of the cyanocarbonate **2**. On the other hand, if the asymmetric induction occurred in the step of cyanation of ketone **1**, the ee values of **14** and **2** should closely match each other. In a modified cinchona alkaloid-catalyzed cyanocarbonation of pinacolone (**1g**) in chloroform, the reaction mixture was treated with methanol and the resulting mixture was then subjected to GC analysis under conditions that allowed determination of ee values of both **14** and **2bg**. As shown by the GC chromatograms in Figure 3, the ee of cyanohydrin **14** is much lower than that of the cyanocarbonation product **2bg** (21 vs 83% ee). This result provided an experimental evidence to support the mechanistic proposal that the ee determination step in the cinchona alkaloid-catalyzed cyanocarbonation of pinacolone (**1g**) is the dynamic kinetic resolution of the putative intermediates **13Ag** and **13Bg** via asymmetric transfer of the alkoxycarbonyl group.



Scheme 5. A proposed catalytic cycle for a tertiary chiral amine-catalyzed asymmetric cyanocarbonation of ketones.

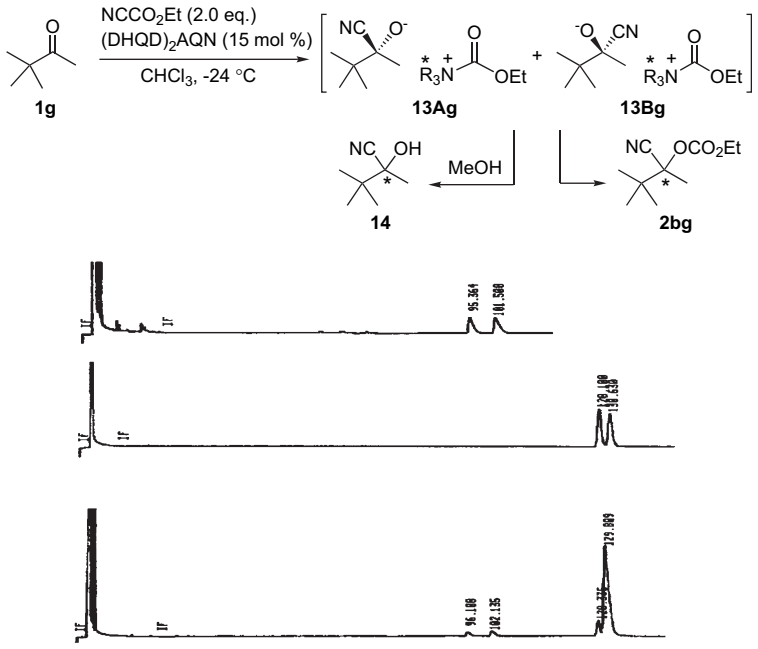


Figure 3. Chiral GC chromatograms (the retention time was expressed in minutes): top, racemic **14**; middle, racemic **2bg**; bottom, reaction mixture of the $(DHQD)_2AQN$-catalyzed asymmetric cyanocarbonation of pinacolone (**1g**) quenched at 54% conversion.

3. Conclusion

The development of the first highly enantioselective cyanocarbonation of prochiral ketones promoted by a chiral base catalyst is documented.[14] Importantly, the reaction complements known enzyme- and transition metal-based methods in substrate scope via its unique ability to promote highly enantioselective cyanocarbonation of sterically hindered simple dialkyl ketones. Additional desirable features of the reaction are the utilization of easily accessible and fully recyclable cinchona alkaloid catalysts and the employment of a simple experimental protocol that is insensitive to either air or moisture. These features should render the reaction a useful catalytic entry for the asymmetric synthesis of tertiary cyanohydrin derivatives via prochiral ketones. The reaction is conceptually interesting as the first efficient asymmetric cyanation of simple ketones realized with a chiral Lewis base approach. Mechanistic studies provided experimental evidence to shed significant light on the asymmetric induction step, in which the modified cinchona alkaloid acts as a chiral nucleophilic catalyst. These mechanistic studies in combination with those revealing cinchona alkaloids as highly efficient chiral general base catalysts underscore their remarkable ability to function as versatile yet efficient chiral organic catalysts for a wide variety of asymmetric transformations.[5b,15]

4. Experimental

4.1. General

^1H and ^{13}C NMR spectra were recorded on a Varian instrument (400 MHz and 100 MHz, respectively) and internally referenced to $SiMe_4$ signal. Low-resolution mass spectra for all the new compounds were recorded on a Hewlett–Packard 5989A GC–MS, and exact mass spectra on a VG 7070 high resolution mass spectrometer. Infrared spectra were recorded on a Perkin–Elmer FTIR Spectrometer. Specific rotations were measured on a Jasco Digital Polarimeter.

Analytical gas-liquid chromatography (GC) was performed on a Hewlett–Packard 6890 Series instrument equipped with a split mode capillary injection system, a flame ionization detector, using a HP-5 GC column or a GC column with chiral stationary phase [gamma cyclodextrin trifluoroacetyl (30 m×0.25 mm) or HP chiral (20% permethylated B-cyclodextrin, 30 m×0.25 mm)]. All the GC analyses of chiral cyanohydrin carbonates were carried out with both a crude reaction sample and a sample purified by silica gel chromatography. High pressure liquid chromatography (HPLC) analyses were performed on a Hewlett–Packard 1100 Series instrument equipped with an isostatic pump, using a Daicel Chiralpak AS (250×4.6 mm), AD (250×4.6 mm) or Hypersil SI (200×4.6 mm) column. UV detection was monitored at 254 or 220 nm.

Unless otherwise mentioned, ketones, alkyl cyanoformates, and catalysts were purchased from Aldrich (Milwaukee) and used without further purification. Ketone **1e** was prepared via oxidation of 1-cyclohexylethanol with PCC. Ketones **1d**,[16] **1f**,[17] and **1i**,[18] were prepared according to the literature. Ketones **1l** and **1n** were prepared using a modified literature procedure[19] as described below. Chloroform was distilled over K_2CO_3 before use.

4.2. Preparation of 2,2-diethoxycyclopentanone (1l)

To a solution of *p*-toluenesulfonic acid (150 mg) and cyclopentanone (16.8 g, 200 mmol) in ethanol (50 mL) was added triethyl orthoformate (32.6 g, 220 mmol). A vigorous reaction ensued which caused ebullition, after which the reaction solution was heated at reflux for 15 min. Then another

portion of *p*-toluenesulfonic acid (200 mg) was added, and the reaction mixture was fractionated to give 1-ethoxycyclopentene (68–70 °C/80 mmHg, 14.5 g, 65%) as a colorless oil.

To a solution of 1-ethoxycyclopentene (2.24 g, 20.0 mmol) in ethanol (40 mL) at 0 °C was added dropwise a solution of *m*CPBA (4.00 g, 22.0 mmol) in ethanol (40 mL) over 1 h. The mixture was allowed to warm to room temperature and stirred for 20 min. The mixture was neutralized with saturated aqueous $NaHCO_3$. Ethanol was removed under reduced pressure and the residue was extracted with ether. The organic layer was dried over $MgSO_4$ and concentrated to give crude 2,2-diethoxycyclopentanol.

To a solution of pyridine (19.0 g, 240 mmol) in dichloromethane (300 mL) at room temperature (cooled with water bath) was added CrO_3 (12.0 g, 120 mmol). The mixture was stirred for 15 min and the crude 2,2-diethoxycyclopentanol was added dropwise. After stirring for an additional 15 min at room temperature, ether (300 mL) was added and the mixture was stirred vigorously for 5 min. The mixture was filtered through a pad of silica gel and the filtrate was concentrated. The residue was purified by silica gel column chromatography (acetone/hexane 1:100) to give 2,2-diethoxycyclopentanone (**1l**) (2.53 g, 74% for two steps) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.12 (t, J=7.2 Hz, 6H), 1.79–1.88 (m, 2H), 1.98 (t, J=6.6 Hz, 2H), 2.23 (t, J=7.3 Hz, 2H), 3.42–3.56 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.3, 16.8, 34.2, 34.9, 58.3, 100.6, 210.2; IR (neat) ν 2977, 1756, 1444, 1392, 1199 cm^{-1}; MS (NH_3/CI) m/z 190 (M+NH_4^+), 173 (MH^+), 144 (M−CO), 127 (M−OEt); HRMS (NH_3/CI) calcd for $C_9H_{17}O_3$ (MH^+) 173.1178, found 173.1175.

4.3. Preparation of 2,2-diethoxycyclohexanone (1n)

This compound was prepared in 60% yield (three steps) following the same procedure employed for 2,2-diethoxycyclopentanone. Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21 (t, J=7.4 Hz, 6H), 1.71–1.82 (m, 4H), 1.92–1.96 (m, 2H), 2.47–2.51 (m, 2H), 3.37–3.45 (m, 2H), 3.48–3.56 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.5, 22.2, 27.7, 36.5, 40.3, 57.2, 101.0, 207.6; IR (neat) ν 2976, 1736, 1446, 1390, 1159 cm^{-1}; MS (NH_3/CI) m/z 204 (M+NH_4^+), 187 (MH^+), 158 (M−CO), 141 (M−OEt); HRMS (NH_3/CI) calcd for $C_{10}H_{19}O_3$ (MH^+) 187.1334, found 187.1331.

4.4. General procedure for the preparation of racemic cyanohydrin carbonates

To a stirred mixture of ketone (0.50 mmol) and alkyl cyanoformate (1.5–3.0 equiv) at room temperature (cooled with water bath) was slowly added DABCO or DBU (20 mol %). The reaction was monitored by either GC or TLC. The mixture was allowed to stand for 1.5–24 h and then diluted with ether. The resulting mixture was washed successively with 1 N HCl and brine. The organic layer was dried over $MgSO_4$ and concentrated. The residue was purified by silica gel column chromatography (acetone/hexane 1:400–1:100) to give the desired racemic cyanohydrin carbonate in good to excellent yield.

4.5. Screening studies on the catalysts

To a stirred solution of 2-heptanone (**1a**) (23 mg, 0.20 mmol) in chloroform (0.20 mL) at room temperature was added the modified cinchona alkaloid (10 mol %), dodecane (2–4 μL, as the internal standard), and methyl cyanoformate (20 mg, 0.24 mmol). The mixture was allowed to stand for 31 h, then added aqueous HCl (1 N, 2.0 mL), and extracted with ether (10 mL). The organic layer was washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by silica gel column chromatography (acetone/hexane 1:400–1:100) to give (*R*)-2-methoxycarboxy-2-methylheptanenitrile (**2aa**) as a colorless oil. The ee was determined with chiral GC [gamma cyclodextrin trifluoroacetyl, 80 °C, 4 min, 5 °C/min to 110 °C, t (major)=23.5 min, t (minor)=26.2 min]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (t, J=6.8 Hz, 3H), 1.29–1.39 (m, 4H), 1.44–1.62 (m, 2H), 1.78 (s, 3H), 1.85–1.94 (m, 1H), 1.98–2.06 (m, 1H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 22.5, 23.6, 24.6, 31.4, 39.8, 55.4, 74.5, 118.6, 153.4.

4.6. Screening studies on the solvents and alkyl cyanoformates

The procedure for the screening studies on the catalysts was used while employing a different solvent or alkyl cyanoformate. The ee of (*R*)-2-benzyloxycarboxy-2-methylheptanenitrile [(*R*)-**2ca**] was determined with chiral HPLC [Daicel Chiralpak OD, isopropanol/hexane 10:90, 0.50 mL/min, λ=220 nm; for a $(DHQD)_2AQN$-catalyzed reaction, t (major)=13.2 min, t (minor)=11.7 min]. Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (t, J=7.2 Hz, 3H), 1.27–1.39 (m, 4H), 1.41–1.61 (m, 2H), 1.76 (s, 3H), 1.86–1.96 (m, 1H), 1.98–2.08 (m, 1H), 5.18 (s, 2H), 7.31–7.40 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 22.4, 23.5, 24.5, 31.3, 39.6, 74.5, 76.9, 118.5, 128.7, 128.8, 128.9, 134.6, 152.7.

4.7. General procedure for the asymmetric catalytic cyanocarbonation of ketones

To a stirred solution of ketone (0.20 mmol) in chloroform (0.20–0.40 mL) at the temperature indicated in Table 3 was added the modified cinchona alkaloid (10–35 mol %), dodecane (2–4 μL), and ethyl cyanoformate (1.0–3.0 equiv). The resulting mixture was allowed to stand at that temperature in a freezer without stirring. When the reaction reached the conversion indicated in Table 3 as determined by GC, aqueous HCl (1 N, 2.0 mL) was added to the reaction mixture. The mixture was extracted with ether (10 mL), and the organic layer was washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by silica gel column chromatography (acetone/hexane 1:400–1:100) to give the chiral cyanohydrin carbonate.

To the aqueous layer was added K_2CO_3 to adjust the pH value of the solution to 9–11. The resulting mixture was extracted with ethyl acetate (10 mL), and the organic layer was washed with brine, dried over Na_2SO_4, and concentrated to afford the recovered catalyst, which is ^{1}H NMR ($CDCl_3$, 400 M) pure, in quantitative yield.

4.7.1. (*R*)-(+)-2-Ethoxycarboxy-2-methylheptanenitrile [(*R*)-(+)-2ba]. The ee was determined with chiral GC

[gamma cyclodextrin trifluoroacetyl, 110 °C, 4 min, 0.10 °C/min to 112 °C; for a $(DHQD)_2AQN$-catalyzed reaction, *t* (major)=19.8 min, *t* (minor)=20.5 min]. Colorless oil; 59% ee; $[\alpha]_D^{25}$ +16.2 (*c* 0.67, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.91 (t, *J*=7.0 Hz, 3H), 1.35 (t, *J*=7.2 Hz, 3H), 1.29–1.40 (m, 4H), 1.44–1.63 (m, 2H), 1.78 (s, 3H), 1.86–1.94 (m, 1H), 1.98–2.06 (m, 1H), 4.26 (q, *J*=7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 14.2, 22.4, 23.6, 24.5, 31.4, 39.7, 64.8, 74.3, 118.6, 152.7; IR (neat) ν 2950, 1759, 1468, 1371, 1265 cm^{-1}; MS (EI) *m/z* 214 (MH^+), 187 (M−CN); HRMS (EI) calcd for $C_{11}H_{20}NO_3$ (MH^+) 214.1443, found 214.1441.

4.7.2. (−)-2-Ethoxycarboxy-2-methylbutanenitrile [(−)-2bb]. The ee was determined with chiral GC [gamma cyclodextrin trifluoroacetyl, 120 °C, 4.0 min, 0.10 °C/min to 85 °C; for a $(DHQ)_2AQN$-catalyzed reaction, *t* (major)=43.4 min, *t* (minor)=42.0 min]. Colorless oil; 41% ee; $[\alpha]_D^{25}$ −8.0 (*c* 0.70, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.13 (t, *J*=7.2 Hz, 3H), 1.34 (t, *J*=7.2 Hz, 3H), 1.77 (s, 3H), 1.97 (dt, *J*=21.0, 7.2 Hz, 1H), 2.10 (dt, *J*=21.0, 7.2 Hz, 1H), 4.26 (q, *J*=7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.3, 14.2, 24.0, 35.0, 64.8, 74.8, 118.5, 152.7; IR (neat) ν 2985, 1758, 1465, 1371, 1263 cm^{-1}; MS (EI) *m/z* 172 (MH^+), 145 (M−CN); HRMS (CH_4/CI) calcd for $C_8H_{14}NO_3$ (MH^+) 172.0974, found 172.0975.

4.7.3. (−)-2-Ethoxycarboxy-2,3-dimethylbutanenitrile [(−)-2bc]. The ee was determined with chiral GC [gamma cyclodextrin trifluoroacetyl, 100 °C, 25.0 min, 1.0 °C/min to 105 °C; for a $(DHQ)_2AQN$-catalyzed reaction, *t* (major)=21.1 min, *t* (minor)=20.6 min]. Colorless oil; 76% ee; $[\alpha]_D^{25}$ −17.6 (*c* 1.50, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.10 (d, *J*=6.8 Hz, 3H), 1.14 (d, *J*=6.4 Hz, 3H), 1.34 (t, *J*=7.2 Hz, 3H), 1.75 (s, 3H), 2.19–2.29 (m, 1H), 4.25 (q, *J*=7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 16.6, 17.0, 21.1, 36.6, 64.6, 78.0, 117.8, 152.7; IR (neat) ν 2981, 1757, 1467, 1372, 1264 cm^{-1}; MS (EI) *m/z* 186 (MH^+), 159 (M−CN); HRMS (EI) calcd for $C_9H_{16}NO_3$ (MH^+) 186.1130, found 186.1126.

4.7.4. (−)-2-Ethoxycarboxy-2-methyl-3-(2-propenyl)-5-hexenenitrile [(−)-2bd]. The ee was determined with chiral GC [gamma cyclodextrin trifluoroacetyl, 110 °C, 4 min, 0.10 °C/min to 114 °C; for a $(DHQ)_2AQN$-catalyzed reaction, *t* (major)=36.8 min, *t* (minor)=38.1 min]. Colorless oil; 81% ee; $[\alpha]_D^{25}$ −25.4 (*c* 0.95, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.34 (t, *J*=7.2 Hz, 3H), 1.79 (s, 3H), 2.18–2.29 (m, 3H), 2.32–2.41 (m, 1H), 2.44–2.54 (m, 1H), 4.25 (q, *J*=7.2 Hz, 2H), 5.05–5.15 (m, 4H), 5.73–5.86 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 22.3, 33.4, 34.1, 45.5, 64.9, 77.4, 117.6, 117.7, 118.3, 135.6, 135.6, 152.6; IR (neat) ν 3080, 2983, 1759, 1642, 1444, 1371, 1260 cm^{-1}; MS (CH_4/CI) *m/z* 238 (MH^+), 211 (M−CN); HRMS (CH_4/CI) calcd for $C_{13}H_{20}NO_3$ (MH^+) 238.1443, found 238.1450.

4.7.5. (−)-2-Cyclohexyl-2-ethoxycarboxy-propionitrile [(−)-2be]. The ee was determined with chiral GC [gamma cyclodextrin trifluoroacetyl, 120 °C, 4 min, 0.10 °C/min to 124 °C; for a $(DHQ)_2AQN$-catalyzed reaction, *t* (major)=35.1 min, *t* (minor)=36.9 min]. Colorless oil; 87% ee; $[\alpha]_D^{25}$ −25.5 (*c* 0.80, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.12–1.31 (m, 5H), 1.34 (t, *J*=7.2 Hz, 3H), 1.67–1.74 (m, 1H), 1.75 (s, 3H), 1.82–1.92 (m, 4H), 1.99–2.06 (m, 1H), 4.25 (q, *J*=7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 21.6, 25.9, 26.0, 27.0, 27.3, 46.0, 64.8, 77.8, 118.2, 152.8; IR (neat) ν 2936, 1757, 1454, 1371, 1267 cm^{-1}; MS (EI) *m/z* 226 (MH^+); HRMS (EI) calcd for $C_{12}H_{20}NO_3$ (MH^+) 226.1443, found 226.1450.

4.7.6. (*S*)-(+)-2-Ethoxycarboxy-2-methyl-3,3-dipropoxypropionitrile [(*S*)-(+)-2bf]. The ee and absolute configuration were determined after transforming this compound to its corresponding β-aminoalcohol derivative **9f** (vide infra). Colorless oil; 96% ee (DHQD-PHN-catalyzed reaction); $[\alpha]_D^{25}$ +14.6 (*c* 1.25, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.94 (t, *J*=7.2 Hz, 3H), 0.97 (t, *J*=7.2 Hz, 3H), 1.34 (t, *J*=7.0 Hz, 3H), 1.58–1.72 (m, 4H), 1.76 (s, 3H), 3.48–3.55 (m, 1H), 3.61–3.66 (m, 1H), 3.70–3.82 (m, 2H), 4.26 (q, *J*=7.2 Hz, 2H), 4.90 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.6, 14.3, 18.5, 23.1, 23.2, 65.1, 72.4, 72.9, 75.7, 102.0, 117.5, 152.7; IR (neat) ν 2968, 1760, 1466, 1372, 1267 cm^{-1}; MS (CH_4/CI) *m/z* 274 (MH^+); HRMS (CH_4/CI) calcd for $C_{13}H_{24}NO_5$ (MH^+) 274.1654, found 274.1659.

4.7.7. (+)-2-Ethoxycarboxy-2,3,3-trimethylbutyronitrile [(+)-2bg]. The ee was determined with chiral GC [20% permethylated B-cyclodextrin, 60 °C, 4 min, 0.10 °C/min to 75 °C; for a $(DHQD)_2AQN$-catalyzed reaction, *t* (major)=124.3 min, *t* (minor)=126.6 min]. Colorless oil; 88% ee; $[\alpha]_D^{25}$ +36.0 (*c* 0.90, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.15 (s, 9H), 1.34 (t, *J*=7.2 Hz, 3H), 1.76 (s, 3H), 4.25 (q, *J*=7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 19.1, 24.8, 38.8, 64.8, 80.5, 118.2, 153.0; IR (neat) ν 2981, 1760, 1469, 1372, 1266 cm^{-1}; MS (EI) *m/z* 200 (MH^+), 173 (M−CN); HRMS (EI) calcd for $C_{10}H_{18}NO_3$ (MH^+) 200.1287, found 200.1287.

4.7.8. (+)-3,3-Dimethoxy-2-ethoxycarboxy-2-methylbutyronitrile [(+)-2bh]. The ee was determined with chiral GC [gamma cyclodextrin trifluoroacetyl, 120 °C, 10.0 min, 0.1 °C/min to 123 °C; for a DHQD-PHN-catalyzed reaction, *t* (major)=26.0 min, *t* (minor)=25.3 min]. Colorless oil; $[\alpha]_D^{25}$ +41.8 (*c* 2.25, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.34 (t, *J*=7.2 Hz, 3H), 1.53 (s, 3H), 1.83 (s, 3H), 3.42 (s, 3H), 3.44 (s, 3H), 4.26 (q, *J*=7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 16.9, 19.8, 51.4, 65.1, 78.9, 102.0, 117.8, 152.5; IR (neat) ν 2984, 1760, 1454, 1372, 1265 cm^{-1}; MS (EI) *m/z* 232 (MH^+), 200 (M−OMe); HRMS (CH_4/CI) calcd for $C_{10}H_{18}NO_5$ (MH^+) 232.1185, found 232.1174.

4.7.9. (+)-3,3-Diethoxy-2-ethoxycarboxy-2-methylbutyronitrile [(+)-2bi]. The ee was determined with chiral GC [gamma cyclodextrin trifluoroacetyl, 100 °C, 4 min, 0.10 °C/min to 106 °C; for a DHQD-PHN-catalyzed reaction, *t* (major)=48.3 min, *t* (minor)=46.7 min]. Colorless oil; 90% ee; $[\alpha]_D^{25}$ +34.5 (*c* 2.35, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.20–1.24 (m, 6H), 1.34 (t, *J*=7.0 Hz, 3H), 1.54 (s, 3H), 1.83 (s, 3H), 3.63–3.72 (m, 4H), 4.25 (q, *J*=7.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 15.6, 17.9, 19.7, 59.0, 59.1, 64.9, 79.2, 101.6, 118.0, 152.6; IR (neat) ν 2982, 1759, 1446, 1372, 1263 cm^{-1}; MS (CH_4/CI) *m/z* 260 (MH^+), 214 (M−OEt);

HRMS (CH_4/CI) calcd for $C_{12}H_{22}NO_5$ (MH^+) 260.1498, found 260.1502.

4.7.10. 2-Ethoxycarboxy-2-(adamantan-1-yl)propionitrile (2bj). The ee was determined after transforming this compound to its corresponding β-aminoalcohol derivative **9j** (vide infra). White solid; 74% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34 (t, J=7.0 Hz, 3H), 1.66–1.84 (m, 15H), 2.08–2.11 (m, 3H), 4.24 (q, J=7.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 17.7, 28.2, 36.0, 36.6, 39.9, 64.7, 80.9, 117.8, 153.1.

4.7.11. (−)-1-Ethoxycarboxy-2,2-dimethylcyclopentanecarbonitrile [(−)-2bk]. The ee was determined with chiral GC [gamma cyclodextrin trifluoroacetyl, 90 °C, 4 min, 0.10 °C/min to 100 °C; for a $(DHQ)_2AQN$-catalyzed reaction, t (major)=87.5 min, t (minor)=91.7 min]. Colorless oil; 95% ee; $[\alpha]_D^{25}$ −15.8 (c 1.90, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.16 (s, 3H), 1.21 (s, 3H), 1.34 (t, J=7.2 Hz, 3H), 1.63–1.92 (m, 4H), 2.33–2.42 (m, 1H), 2.51–2.60 (m, 1H), 4.19–4.31 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 19.6, 21.5, 25.1, 35.3, 36.7, 47.6, 65.0, 84.8, 117.7, 153.3; IR (neat) ν 2974, 1760, 1470, 1372, 1276 cm^{-1}; MS (EI) m/z 212 (MH^+); HRMS (EI) calcd for $C_{11}H_{18}NO_3$ (MH^+) 212.1287, found 212.1297.

4.7.12. (−)-2,2-Diethoxy-1-ethoxycarboxycyclopentanecarbonitrile [(−)-2bl]. The ee was determined with chiral GC [gamma cyclodextrin trifluoroacetyl, 95 °C, 4 min, 0.05 °C/min to 104 °C; for a DHQ-PHN-catalyzed reaction, t (major)=150.6 min, t (minor)=158.3 min]. White solid, mp 74–75 °C; 95% ee; $[\alpha]_D^{25}$ −32.1 (c 2.70, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20 (t, J=7.0 Hz, 3H), 1.24 (t, J=7.0 Hz, 3H), 1.33 (t, J=7.1 Hz, 3H), 1.68–1.75 (m, 2H), 1.82–1.90 (m, 1H), 2.08–2.15 (m, 1H), 2.39–2.57 (m, 2H), 3.54–3.62 (m, 2H), 3.71–3.86 (m, 2H), 4.25 (q, J=7.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 15.3, 18.1, 30.5, 35.9, 57.5, 58.8, 65.1, 79.2, 109.3, 117.1, 152.7; IR ($CHCl_3$) ν 3019, 1757, 1423, 1221 cm^{-1}; MS (CH_4/CI) m/z 271 (M^+); HRMS (CH_4/CI) calcd for $C_{13}H_{21}NO_5$ (M^+) 271.1420, found 271.1424.

4.7.13. (−)-1-Ethoxycarboxy-2,2-dimethylcyclohexanecarbonitrile [(−)-2bm]. The ee was determined by chiral GC [gamma cyclodextrin trifluoroacetyl, 115 °C, 4 min, 0.10 °C/min to 121 °C; for a $(DHQ)_2AQN$-catalyzed reaction, t (major)=51.1 min, t (minor)=54.0 min]. Colorless oil; 92% ee; $[\alpha]_D^{25}$ −15.5 (c 2.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.13 (s, 3H), 1.22 (s, 3H), 1.34 (t, J=7.2 Hz, 3H), 1.48–1.68 (m, 6H), 2.11–2.21 (m, 1H), 2.30–2.40 (m, 1H), 4.25 (q, J=7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 20.4, 21.6, 22.7, 25.2, 29.1, 35.7, 38.2, 64.7, 81.2, 117.7, 152.8; IR (neat) ν 2939, 1755, 1458, 1371, 1261 cm^{-1}; MS (EI) m/z 226 (MH^+); HRMS (EI) calcd for $C_{12}H_{20}NO_3$ (MH^+) 226.1443, found 226.1448.

4.7.14. (+)-2,2-Diethoxy-1-ethoxycarboxycyclohexanecarbonitrile [(+)-2bn]. The ee was determined with chiral GC [gamma cyclodextrin trifluoroacetyl, 105 °C, 4 min, 0.05 °C/min to 113 °C; for a DHQD-PHN-catalyzed reaction, t (major)=145.9 min, t (minor)=143.6 min]. Colorless oil; 96% ee; $[\alpha]_D^{25}$ +26.0 (c 2.50, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21 (t, J=7.0 Hz, 3H), 1.25 (t, J=7.0 Hz, 3H), 1.34 (t, J=7.2 Hz, 3H), 1.44–1.62 (m, 4H), 1.78–1.96 (m, 2H), 2.24–2.34 (m, 1H), 2.42–2.52 (m, 1H), 3.62 (q, J=7.0 Hz, 2H), 3.72–3.82 (m, 2H), 4.26 (q, J=7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 15.4, 15.6, 20.4, 21.4, 30.2, 32.2, 57.3, 57.9, 64.9, 99.5, 117.4, 152.4; IR (neat) ν 2979, 1758, 1447, 1371, 1258 cm^{-1}; MS (CH_4/CI) m/z 286 (MH^+), 285 (M^+), 240 (M−OEt); HRMS (CH_4/CI) calcd for $C_{14}H_{23}NO_5$ (M^+) 285.1576, found 285.1564.

4.8. A 10 mmol-scale synthesis of (+)-2,2-diethoxy-1-ethoxycarboxycyclopentanecarbonitrile [(+)-2bl]

To a stirred solution of 2,2-diethoxycyclopentanone (1.72 g, 10.0 mmol) and DHQD-PHN (502 mg, 1.00 mmol) in chloroform (10 mL) at −24 °C was added dropwise ethyl cyanoformate (2.97 g, 30.0 mmol). After the mixture was allowed to stand at −24 °C in a freezer for 7 days, aqueous HCl (1 N, 20 mL) was added. The resulting mixture was stirred vigorously for 2 min and then extracted with ether (50 mL), and the organic layer was washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by silica gel column chromatography (acetone/hexane 1:100) to give the cyanohydrin carbonate (2.69 g, 99%, 94% ee) as a white solid. This compound was also obtained in 87% yield and 97% ee simply by recrystallizing the residue in hexane.

To the aqueous layer was added K_2CO_3 to adjust the pH value of the solution to 9–11. The resulting mixture was extracted with ethyl acetate (50 mL), and the organic layer was washed with brine, dried over Na_2SO_4, and concentrated to afford the recovered catalyst DHQD-PHN, which is ^{1}H NMR ($CDCl_3$, 400 M) pure, in quantitative yield.

4.9. Transformation of cyanohydrin carbonate (−)-2bk to β-aminoalcohol derivative 9k

To a solution of (−)-**2bk** (95% ee, 20 mg, 0.095 mmol) in ether (0.50 mL) at room temperature was added $LiAlH_4$ (18 mg, 0.47 mmol). The mixture was stirred for 2 h, and then added water (three drops) and ether (5.0 mL). The resulting mixture was dried over Na_2SO_4, filtered, and to the filtrate was added benzoyl chloride (25 mg, 0.18 mmol) and triethylamine (36 mg, 0.36 mmol). After being stirred at room temperature for 2 h, the mixture was filtered and concentrated. The residue was purified by silica gel column chromatography (acetone/hexane 1:20–1:10) to give amide **9k** (13 mg, 63%) as a white solid. The ee of **9k** was determined to be 95% with chiral HPLC [Daicel Chiralpak AS, isopropanol/hexane 5:95, 1.0 mL/min, t (major)=33.9 min, t (minor)=43.2 min]. Mp 98–100 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97 (s, 3H), 1.06 (s, 3H), 1.45–1.53 (m, 1H), 1.60–1.84 (m, 4H), 1.91–2.00 (m, 1H), 2.22 (br s, 1H), 3.44 (dd, J=13.8, 4.4 Hz, 1H), 3.68 (dd, J=13.8, 7.0 Hz, 1H), 6.69 (br s, 1H), 7.39–7.44 (m, 2H), 7.49 (t, J=7.2 Hz, 1H), 7.78 (d, J=7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.0, 22.3, 24.7, 36.1, 39.5, 44.8, 45.2, 84.1, 127.1, 128.7, 131.6, 134.8, 168.4; MS (NH_3/CI) m/z 248 (MH^+), 230 (M−OH); HRMS (NH_3/CI) calcd for $C_{15}H_{22}NO_2$ (MH^+) 248.1651, found 248.1660.

4.10. Transformation of cyanohydrin carbonate (*S*)-(+)-2bf to β-aminoalcohol derivative (*S*)-9f

Cyanohydrin carbonate (*S*)-(+)-**2bf** (prepared from a DHQD-PHN-catalyzed reaction, 14 mg, 0.050 mmol) was reduced to its corresponding β-aminoalcohol with $LiAlH_4$ using the same procedure as described above. To the solution of crude β-aminoalcohol in ether (5 mL) was added benzyl chloroformate (17 mg, 0.10 mmol) and triethylamine (20 mg, 0.20 mmol). The mixture was stirred at room temperature for 1 h, and then concentrated. The residue was purified by silica gel column chromatography (acetone/hexane 1:40) to give carbamate (*S*)-**9f** (12 mg, 66%) as a colorless oil. The ee of (*S*)-**9f** was determined to be 96% [HPLC conditions: Daicel Chiralpak AD+Hypersil SI, isopropanol/hexane 1:99, 0.5 mL/min, *t* (major)=91.7 min, *t* (minor)=103.3 min]. (*S*)-**9f** can also be obtained from (*S*)-(+)-2-trimethylsiloxy-2-methyl-3,3-dipropoxypropionitrile[5b] employing the same sequences, so the absolute configuration was determined to be *S*. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94 (t, *J*=7.4 Hz, 6H), 1.17 (s, 3H), 1.58–1.68 (m, 4H), 2.45 (s, 1H), 3.30–3.36 (m, 2H), 3.43–3.50 (m, 2H), 3.71–3.79 (m, 2H), 4.24 (s, 1H), 5.11 (s, 2H), 5.25–5.30 (m, 1H), 7.39–7.39 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.8, 20.7, 23.4, 46.7, 65.6, 66.9, 72.8, 72.8, 74.1, 107.8, 127.2, 128.2, 128.7, 136.9, 157.2.

4.11. Transformation of cyanohydrin carbonate 2bj to β-aminoalcohol derivative 9j

This transformation was accomplished by employing the above sequences. The ee was determined to be 74% with chiral HPLC [Daicel Chiralpak OD, isopropanol/hexane 20:80, 0.50 mL/min, λ=254 nm; *t* (major)=13.4 min, *t* (minor)=12.0 min]. White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.14 (s, 3H), 1.62–1.76 (m, 12H), 2.01–2.07 (m, 3H), 3.45 (dd, *J*=13.4, 3.0 Hz, 1H), 3.67 (dd, *J*=13.4, 8.0 Hz, 1H), 6.58–6.62 (m, 1H), 7.41–7.52 (m, 3H), 7.78–7.81 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.6, 28.7, 34.6, 36.4, 37.2, 39.1, 44.7, 76.8, 127.1, 128.8, 131.6, 134.9, 168.6.

4.12. Acidic hydrolysis of (*R*)-(+)-2ba

To a concentrated aqueous hydrochloric acid (5 mL) was added (*R*)-(+)-**2ba** (59% ee, 82 mg, 0.38 mmol). The mixture was stirred at room temperature overnight and then heated under reflux for 5 h. After being cooled down to room temperature, the mixture was extracted with ethyl acetate (3×5 mL). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by flash chromatography (ether/hexane 1:1) to give (*R*)-(−)-2-hydroxy-2-methylheptanoic acid (**10a**) (50 mg, 81%). The absolute configuration of (+)-**2ba** was determined to be *R* by comparing the specific rotation {$[\alpha]_D^{25}$ −5.4 (*c* 1.60, $CHCl_3$)} with that reported in literature {$[\alpha]_D^{25}$ −9.4 (*c* 0.35, $CHCl_3$), 98% ee}.[20] ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, *J*=7.2 Hz, 3H), 1.15–1.36 (m, 5H), 1.42–1.53 (m, 1H), 1.47 (s, 3H), 1.62–1.72 (m, 1H), 1.75–1.84 (m, 1H), 6.60 (br s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 22.6, 23.4, 26.0, 32.0, 40.1, 75.0, 181.7.

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References and notes

1. (a) For reviews, see: Christoffers, J.; Mann, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4591; (b) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388; (c) Fuji, K. *Chem. Rev.* **1993**, *93*, 2037.
2. For reviews on the preparation and application of chiral cyanohydrins in organic synthesis, see: (a) Brunel, J.-M.; Holmes, I. P. *Angew. Chem., Int. Ed.* **2004**, *43*, 2752; (b) North, M. *Tetrahedron: Asymmetry* **2003**, *14*, 147; (c) Gregory, R. J. H. *Chem. Rev.* **1999**, *99*, 3649. For a recent application of chiral ketone cyanohydrin in the total synthesis of complex natural products, see: Hong, R.; Chen, Y.; Deng, L. *Angew. Chem., Int. Ed.* **2005**, *44*, 3478.
3. Tian, S.-K.; Chen, Y.; Hang, J.; Tang, L.; MaDaid, P.; Deng, L. *Acc. Chem. Res.* **2004**, *37*, 621.
4. For chiral Lewis acid approach, see: (a) Hamashima, Y.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2000**, *122*, 7412; (b) Yabu, K.; Masumoto, S.; Yamasaki, S.; Hamashima, Y.; Kanai, M.; Du, W.; Curran, D. P.; Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 9908; (c) Deng, H.; Isler, M. P.; Snapper, M. L.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2002**, *41*, 1009; (d) Belokon, Y. N.; Green, B.; Ikonnikov, N. S.; North, M.; Parsons, T.; Tararov, V. I. *Tetrahedron* **2001**, *57*, 771; (e) Chen, F.; Feng, X.; Bo, Z.; Zhang, G.; Jiang, Y. *Org. Lett.* **2003**, *5*, 949; (f) Chen, F. X.; Zhou, H.; Liu, X. H.; Qin, B.; Feng, X. M. *Chem.—Eur. J.* **2004**, *10*, 4790; (g) Fuerst, D. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2005**, *127*, 8964; (h) Ryu, D. H.; Corey, E. J. *J. Am. Chem. Soc.* **2005**, *127*, 5384.
5. For chiral Lewis base approach, see: (a) Tian, S.-K.; Deng, L. *J. Am. Chem. Soc.* **2001**, *123*, 6195; (b) Tian, S.-K.; Hong, R.; Deng, L. *J. Am. Chem. Soc.* **2003**, *125*, 9900; (c) Liu, X.; Qin, B.; Zhou, X.; He, B.; Feng, X. *J. Am. Chem. Soc.* **2005**, *127*, 12224.
6. For a preliminary communication, see Ref. 5a.
7. (a) Poirier, D.; Berthiaume, D.; Boivin, R. P. *Synlett* **1999**, 1423; (b) Berthiaume, D.; Poirier, D. *Tetrahedron* **2000**, *56*, 5995.
8. The cyanocarbonation of aldehydes catalyzed by DABCO was reported almost at the same time as we published our preliminary results, see: Deardorff, D. R.; Taniguchi, C. M.; Tafti, S. A.; Kim, H. Y.; Choi, S. Y.; Downey, K. J.; Nguyen, T. V. *J. Org. Chem.* **2001**, *66*, 7191.
9. Chen, Y.; Tian, S.-K.; Deng, L. *J. Am. Chem. Soc.* **2000**, *122*, 9542.
10. Griengl, H.; Klempier, N.; Pöchlauer, P.; Schmidt, M.; Shi, N.; Zabelinskaja-Mackova, A. A. *Tetrahedron* **1998**, *54*, 14477.
11. As reviewed in Ref. 2, both enantiomers of certain chiral cyanohydrins are accessible from methods based on (*R*)- or (*S*)-oxynitrilase, respectively.
12. For a recent review, see: Pellisser, H. *Tetrahedron* **2003**, *59*, 8291.
13. For the quantitative expression of the relationship between ee of the product, conversion and relative rate of the epimerization vs the kinetic resolution of the racemic starting material

in a dynamic kinetic resolution, see: (a) Kitamura, M.; Tokunaga, M.; Noyori, R. *J. Am. Chem. Soc.* **1993**, *115*, 144; (b) Noyori, R.; Tokunaga, M.; Kitamura, M. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 36.

14. For examples on the chiral metal complex-catalyzed enantioselective cyanation of aldehydes using an alkyl cyanoformate as the cyanating agent, see: (a) Yamagiwa, N.; Tian, J.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc*. **2005**, *127*, 3413; (b) Tian, J.; Yamagiwa, N.; Matsunaga, S.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 3636; (c) Belokon, Y. N.; Blacker, A. J.; Clutterbuck, L. A.; North, M. *Org. Lett.* **2003**, *5*, 4505; (d) Casas, J.; Baeza, A.; Sansano, J. M.; Nájera, C.; Saá, J. M. *Tetrahedron: Asymmetry* **2003**, *14*, 197.
15. For reviews, see: (a) Chen, Y.; McDaid, P.; Deng, L. *Chem. Rev.* **2003**, *103*, 2965; (b) France, S.; Guerin, D. J.; Miller, S. J.; Lectka, T. *Chem. Rev.* **2003**, *103*, 2985; (c) Kacprzak, K.; Gawronski, J. *Synthesis* **2001**, 961. For the first experimental evidence of a modified cinchona alkaloid as a highly efficient chiral general base catalyst, see: (d) Hang, J.; Tian, S.-K.; Tang, L. *J. Am. Chem. Soc*. **2001**, *123*, 12696. For recent examples, see: (e) Song, J.; Wang, Y.; Deng, L. *J. Am. Chem. Soc*. **2006**, *128*, 6048; (f) Li, H.; Wang, B.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 732; (g) Wu, F.; Li, H.; Hong, R.; Deng, L. *Angew. Chem., Int. Ed.* **2006**, *44*, 947; (h) Li, H.; Song, J.; Liu, X.; Deng, L. *J. Am. Chem. Soc.* **2005**, *127*, 8948; (i) Li, H.; Wang, Y.; Tang, L.; Wu, F.; Liu, X.; Guo, C.; Foxman, B. M.; Deng, L. *Angew. Chem., Int. Ed.* **2005**, *44*, 105; (j) Li, H.; Wang, Y.; Tang, L.; Deng, L. *J. Am. Chem. Soc.* **2004**, *126*, 9906.
16. Cho, S. Y.; Shibasaki, M. *Tetrahedron: Asymmetry* **1998**, *9*, 3751.
17. Gupta, S. K. *J. Org. Chem.* **1976**, *41*, 2642.
18. Berens, U.; Leckel, D.; Oepen, S. C. *J. Org. Chem.* **1995**, *60*, 8204.
19. (a) Heut, F.; Pellet, M.; Lechevallier, A.; Conia, J.-M. *J. Chem. Res., Synop.* **1982**, 246; (b) Frimer, A. A. *Synthesis* **1977**, 578; (c) Lindsay, D. G.; Reese, C. B. *Tetrahedron* **1965**, *21*, 1673.
20. Effenberger, F.; Hörsch, B.; weingart, F.; Ziegler, T.; Kühner, S. *Tetrahedron Lett.* **1991**, *32*, 2605.