A Highly Enantioselective Chiral Lewis Base-Catalyzed Asymmetric Cyanation of Ketones

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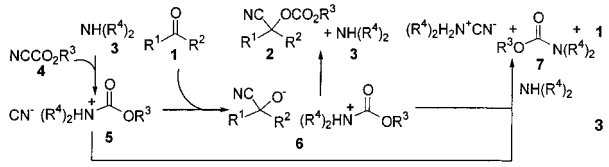
The control of absolute configuration of quaternary stereocenters represents a great challenge in asymmetric catalysis.[1−3] A conceptually direct and attractive approach is to transform prochiral ketones to chiral building blocks containing a quaternary stereocenter by a catalytic asymmetric C−C bond formation. The realization of this approach, however, has proven to be a formidable task.[1,2d,3] Achieving synthetically useful enantioselectivity with unconjugated aliphatic ketones is particularly challenging since the two alkyl substituents of the ketone closely resemble each other both electronically and sterically. We describe here the development of a highly enantioselective cyanation of dialkyl ketones catalyzed by an organic chiral Lewis base.

Guided by our recent discovery that readily available modified cinchona alkaloids are highly effective chiral Lewis base catalysts for desymmetrization of cyclic anhydrides,[4] we undertook the development of a chiral Lewis base-catalyzed asymmetric cyanation of ketones in view of its significance in asymmetric synthesis.[5] Our investigation started with the development of an efficient amine-catalyzed cyanation of ketones. Poirier reported that the treatment of unconjugated aliphatic ketones **1** with 20 equiv of diisopropylamine (**3**, R^4 = *i*-Pr) and 5−10 equiv of methyl cyanoformate (**4**, R^3 = Me) afforded tertiary cyanohydrin carbonates **2** (R^3 = Me) in good yield.[6] A large excess secondary amine **3** was used, presumably because deprotonation of **5** or **6** by a second equivalent of **3** will decompose **3** to carbamate **7** (Scheme 1). However, in principle, the reaction could be catalytic in a tertiary amine, which cannot undergo this proton transfer. Although, Poirer reported that excess Et_3N was much less effective than diisopropylamine in promoting the conversion of **1** to **2**,[6] we observed at 25 °C that cyanation of 2-heptanone with 10 mol % amine and 1.5 equiv of $NCCO_2Me$ in THF proceeded in 35−40% conversion with Et_3N, and the conversion was further improved to 84% with DABCO.

Encouraged by these results, we turned to the enantioselective conversion of **1** to **2** catalyzed by a tertiary chiral amine, such as natural and modified cinchona alkaloids (Figure 1), as shown in the proposed catalytic cycle (Scheme 2). Asymmetric cyanation of 2-heptanone (**1a**) with 1.2 equiv of methyl cyanoformate and 10 mol % of the chiral amine in $CHCl_3$ at 25 °C gave **2** (R^1 = *n*-C_5H_{11}, R^2 = R^3 = Me) in the following conversion and ee:

Scheme 1. Decomposition of Secondary Amines to Carbamates **7**



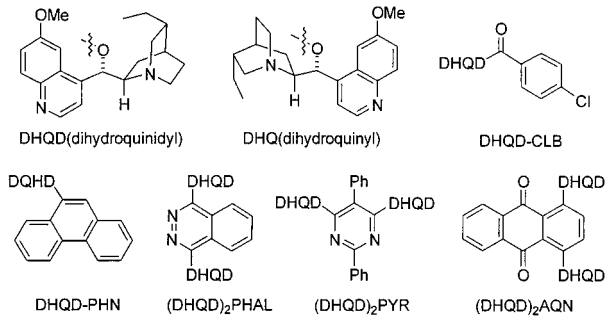
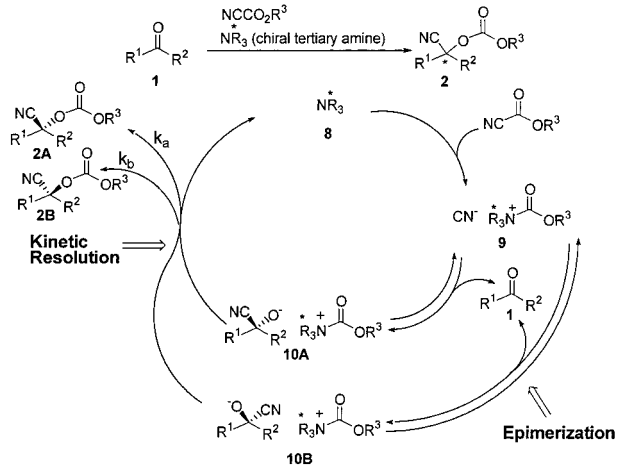


Figure 1. Structures of modified cinchona alkaloids.

Scheme 2. Proposed Catalytic Cycle for a Tertiary Chiral Amine-Catalyzed Asymmetric Cyanation of Ketones



quinidine (66%, 2.6% ee), DHQD-CLB (63%, 17% ee), QHQD-PHN (83%, 27% ee), $(DHQD)_2PYR$ (86%, 11% ee), $(DHQD)_2$-PHAL (80%, 22% ee), $(DHQD)_2AQN$ (94%, 27% ee). With $(DHQD)_2AQN$ as the catalyst, the enantioselectivity of the asymmetric cyanation can be improved from 27% ee to 40% ee by employing ethyl cyanoformate and performing the reaction at −24 °C. The substitution of ethyl cyanoformate with benzyl cyanoformate or the employment of other common organic solvents such as dichloromethane, ether, toluene, and acetonitrile resulted in deteriorated enantioselectivity for the asymmetric cyanation of 2-heptanone (see Supporting Information for details).

Most importantly, a variety of acyclic and cyclic dialkyl ketones, both α-substituted and α,α-disubstituted, are transformed to tertiary cyanohydrin carbonates in good to excellent enantioselectivity and in synthetically useful yield with either DHQD-PHN or $(DHQD)_2AQN$ as the catalyst (Table 1). Enantioselective cyanation of the sterically hindered α,α-disubstituted ketones has been reported previously only once with *tert*-butyl methyl ketone using an enzymatic method.[7,8] Particularly noteworthy is that, for the first time, a catalytic asymmetric cyanation of a cyclic ketone

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(1) For excellent reviews, see: (a) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998,** *37*, 388. (b) Fuji, K. *Chem. Rev.* **1993**, *93*, 2037.

(2) For recent examples of catalytic creation of quaternary stereocenters see: (a) Ooi, T.; Takeuchi, M.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **2000**, *122*, 5228. (b) Vachal, P.; Jacobsen, E. N. *Org. Lett.* **2000**, *2*, 867. (c) Ruble, J. C.; Fu, G. C. *J. Am. Chem. Soc.* **1998**, *120*, 11532. (d) Dosa, P. I.; Fu, G. C. *J. Am. Chem. Soc.* **1998**, *120*, 445.

(3) While this manuscript was in preparation, Shibasaki and co-workers reported the first highly enantioselective cyanosilylation of ketones catalyzed by transition metal complexes prepared via a multistep synthesis from D-glucal. See: (a) Hamashima, Y.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2000**, *122*, 7412. (b) Hamashima Y.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett.* **2001**, *42*, 691.

(4) Chen, Y.; Tian, S.-K.; Deng, L. *J. Am. Chem. Soc.* **2000**, *122*, 9542.

(5) For reviews, see: (a) Gregory, R. J. H. *Chem. Rev.* **1999**, *99*, 3649. (b) Effenberger, F. *Angew. Chem., Int. Ed.* **1994**, *33*, 1555. (c) North, M. *Synlett* **1993**, 807.

(6) (a) Poirier, D.; Berthiaume, D.; Boivin, R. P. *Synlett* **1999**, 1423. (b) Berthiaume, D.; Poirier D. *Terahedron* **2000**, *56*, 5995.

(7) Griengl, H.; Klempier, N.; Pöchlauer, P.; Schmidt, M.; Shi, N.; Zabelinskaja-Mackova, A. A. *Tetrahedron* **1998**, *54*, 14477.

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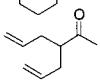
Table 1. Catalytic Asymmetric Cyanation of Unconjugated Ketones with Modified Cinchona Alkaloids[a,b]

entry	ketone		catalyst (mol%)	T (°C)	time (d)	ee[c] (%)	conv[d] (%)	yield[e,f] (%)
1		**1b**	$(DHQ)_2AQN$ (15)	-24	4	95	79	76(96)
2			$(DHQD)_2AQN$ (15)	-24	2	97[g]	68	66(97)
3		**1c**	$(DHQ)_2AQN$ (30)	-12	5	92	56	53(95)
4			$(DHQD)_2AQN$ (20)	-24	4	91[g]	65	62(95)
5		**1d**	$(DHQ)_2AQN$ (20)	-24	2	87	55	52(95)
6		**1e**	$(DHQ)_2AQN$ (20)	-24	2	81	57	54(95)
7		**1f**	$(DHQD)_2AQN$ (30)	-24	5	88	58	55(95)
8		**1g**	DHQ-PHN (30)	-24	4	95	83	80(96)
9			DHQD-PHN (20)	-24	3	93[g]	97	96(99)
10			DHQD-PHN (10)	-24	7	94	100	99(99)
11		**1h**	DHQD-PHN (35)	-12	5	96	82	78(95)
12		**1i**	DHQD-PHN (30)	-24	4	96	90	86(97)
13		**1j**	DHQD-PHN (35)	-12	4	90	68	65(96)
14		**1a**	$(DHQD)_2AQN$ (20)	-24	0.5	59[h]	56	54 (96)
15			$(DHQD)_2AQN$ (20)	-24	2.5	40	96	93 (97)

[a] The reaction was performed by treatment of the ketone (0.2 mmol) with ethyl cyanoformate (1−3 equiv) in chloroform (0.2−0.3 mL).[b] The catalyst was recovered in quantitative yield. [c] See Supporting Information for details to ee analysis. [d] Determined by GC analysis using an internal standard. [e] Isolated yields. [f] Yields in parentheses are based on the conversion of ketones. [g] The opposite enantiomer is generated. [h] The absolute configuration of the major enantiomer was determined to be *R* (see Supporting Information for detials).

is realized with excellent enantioselectivity to give the tertiary cyanohydrin derivative in greater than 90% ee (entries 1−4 and 8−11, Table 1). Since it is catalyzed by a chiral Lewis base, the reaction tolerates acid-sensitive functionality as shown by the successful cyanation of acyclic and cyclic ketones bearing either an acetal or ketal functionality that affords functionalized tertiary cyanohydrin products in excellent enantioselectivity (entries 8−13, Table 1).

The modified cinchona alkaloid-catalyzed asymmetric cyanation proceeded cleanly to consistently afford the chiral tertiary cyanohydrin carbonates in >95% yield based on converted ketone (Table 1). The reactions were usually quenched after 2−5 days when they reached a conversion between 55 and 97% to provide the desired products in 52−96% 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 cyanation of ketone **1g** (entry 9, Table 1) using 20 mol % catalyst can be also realized by using 10 mol % catalyst. 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 (entries 1,2, 3,4, and 8,9, Table 1), thus establishing themselves as the only class of synthetic catalysts to do so.[9] Furthermore, $LiAlH_4$ cleanly reduces the optically active cyanohydrin carbonates (**2b** and **2i**) to the synthetically and biologically important chiral amino alcohols[8] without any deterioration in ee.[10]

As found in the reaction with 2-heptanone (**1a**), the ee of the cyanohydrin carbonate generated from reactions involving simple dialkyl ketones started to decrease noticeably when the conversion of the reaction proceeded over 55% (entries 14−15, Table 1). However, the ee variation of the product is significantly less pronounced in reactions employing α,α-dialkoxy cyclic and acyclic ketones, which allows the generation of the corresponding cyanohydrin carbonates in excellent enantioselectivity and good to excellent isolated yield (entries 8−12). As shown in Scheme 2, the enantioselectivity of the reaction may originate from the enantioselective addition of the cyanide, as part of a chiral ion complex (**10**), to ketone **1**. Alternatively the ee of the cyanohydrin carbonates (**2**) can be determined by a dynamic kinetic resolution of cyanoalkoxides **10A** and **10B** ($k_a > k_b$ or $k_a < k_b$) via an asymmetric alkoxycarbonylation (**10** to **2**), which provides a plausible explanation for the observed ee change of cyanocarbonates **2** during the reaction course.[11,12]

In summary, we have developed a highly enantioselective cyanation of prochiral ketones promoted by a metal-free organic catalyst. The reaction is mechanistically interesting as the first efficient asymmetric cyanation of simple ketones realized with a chiral Lewis base approach. Importantly, the reaction complements known enzyme- and transition metal-based methods[3,5] in substrate scope via its unique ability to transform cyclic and sterically hindered dialkyl ketones in highly enantioselective manner. Additional notable features of the reaction are the utilization of easily accessible and fully recyclable catalysts and the employment of a simple experimental protocol. These features should render the reaction a useful catalytic entry for the asymmetric creation of quaternary stereocenters via prochiral ketones.

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Supporting Information Available: Complete experimental details (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) For a recently reported diastereoselective cyanation of sterically hindered ketones, see: Wilkinson, H. S.; Grover, P. T.; Vandenbossche, C. P.; Bakale, R. P.; Bhongle, N. N.; Wald, S. A.; Senanayake, C. H. *Org. Lett.* **2001**, *3*, 553.

(9) As reviewed in ref 5, both enantiomers of certain chiral cyanohydrins are accessible from methods based on (*R*)- or (*S*)-oxynitrilase, respectively.

(10) See Supporting Information.

(11) According to the quantitative expression described by Noyori and coworkers[12] for a dynamic kinetic resolution, the ee of the cyanohydrin carbonate is expected to decrease at high conversion if the rate of epimerization of the quaternary carbon stereocenter in intermediates **10A** and **10B**, via ketone **1**, is slower than the rate of the kinetic resolution step.

(12) (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.