Elucidation of the active conformation of cinchona alkaloid catalyst and chemical mechanism of alcoholysis of meso anhydrides

Hongming Li, Xiaofeng Liu, Fanghui Wu, Liang Tang, and Li Deng[1]

Department of Chemistry, Brandeis University, Waltham, MA 02454-9110

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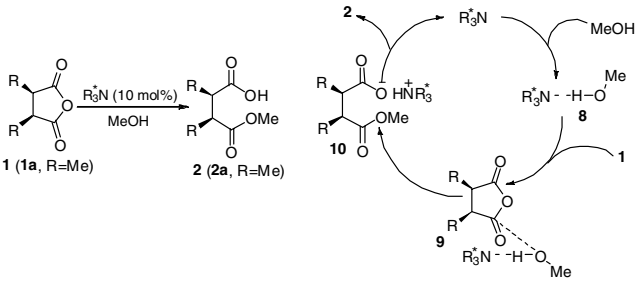
Complementary to enantioselective transformations of planar functionalities, catalytic desymmetrization of *meso* compounds is another fundamentally important strategy for asymmetric synthesis. However, experimentally established stereochemical models on how a chiral catalyst discriminates between two enantiotopic functional groups in the desymmetrization of a *meso* substrate are particularly lacking. This article describes our endeavor to elucidate the chemical mechanism and characterization of the active conformation of the cinchona alkaloid-derived catalyst for a desymmetrization of *meso* cyclic anhydrides via asymmetric alcoholysis. First, our kinetic studies indicate that the cinchona alkaloid-catalyzed alcoholysis proceeds by a general base catalysis mechanism. Furthermore, the active conformer of the cinchona alkaloid-derived catalyst DHQD-PHN was clarified by catalyst conformation studies with a designed, rigid cinchona alkaloid derivative as a probe. These key mechanistic insights enabled us to construct a stereochemical model to rationalize how DHQD-PHN differentiates the two enantiotopic carbonyl groups in the transition state of the asymmetric alcoholysis of *meso* cyclic anhydrides. This model not only is consistent with the sense of asymmetric induction of the asymmetric alcoholysis but also provides a rationale on how the catalyst tolerates a broad range of cyclic anhydrides. These mechanistic insights further guided us to develop a novel practical catalyst for the enantioselective alcoholysis of *meso* cyclic anhydrides.

cinchona alkoloid | desymmetrization | organocatalysis | general base catalysis | hydrogen bonding

Complementary to enantioselective transformations of planar functionalities, catalytic desymmetrization of *meso* compounds is another fundamentally important strategy for asymmetric synthesis (1–5). However, our understanding of how a chiral catalyst discriminates between two enantiotopic functional groups in a *meso* substrate at the molecular level is particularly lacking. Our group reported a desymmetric alcoholysis of a wide range of *meso* cyclic anhydrides with modified cinchona alkaloids to generate highly enantiomerically enriched hemiesters (5–10). Thus, we have initiated mechanistic studies to investigate how the modified cinchona alkaloids are able to efficiently differentiate the two enantiotopic carbonyl groups while tolerating variations of the substituents of the anhydrides. Herein we describe the experimental results that have enabled us to construct a transition state model to answer these mechanistic questions and to develop a practical catalyst guided by insights gained from our mechanistic studies.

Results and Discussion

In order to shed light on the origin of the catalytic activity on the enantioselective alcoholysis of *meso* cyclic anhydrides, we carried out kinetic studies on the methanolysis of *cis*-2,3-dimethyl succinic anhydride (**1a**) (*SI Appendix*). Upon treatment with the *mono* cinchona alkaloid DHQD-PHN (**3**) and the *bis* cinchona alkaloid $(DHQD)_2AQN$ (**4**) in diethyl ether at room temperature, methanolysis of anhydride **1a** furnished hemiester **2a** in 91% and 93% enantiomeric excess (ee), respectively. This enantioselective alcoholysis was found to display a first-order dependence on anhydride **1a** as well as a first-order dependence on either *mono* cinchona alkaloid DHQD-PHN (**3**) or *bis* cinchona alkaloid $(DHQD)_2AQN$ (**4**). The reaction first showed a first-order dependence on methanol, which turned to a zero-order dependence as an excess amount of methanol was employed. These kinetic results are consistent with a general base catalysis mechanism (Scheme 1) in which the cinchona alkaloid first forms an amine-alcohol hydrogen-bonding complex (**8**). The alcohol, associated with and activated by the chiral amine, reacts selectively with one of the enantiotopic carbonyl groups of **1a**. The same first-order dependence, similar reaction rate, and comparably high enantioselectivity displayed by *mono* cinchona alkaloid **3** and *bis* cinchona alkaloid **4**, respectively, indicate that one dihydroquinidyl group is sufficient to activate methanol as a nucleophile for the enantioselective alcoholysis as a hydrogen-bonding acceptor.



Scheme 1. General base catalysis mechanism

Next we turned our attention to the characterization of the active conformer of DHQD-PHN (**3**) in the transition state. This task was particularly challenging because cinchona alkaloids such as **3** possess considerable conformational flexibility resulting from rotation around both the *C*8-*C*9 and the *C*4′-*C*9 bonds. Extensive conformational studies on dihydroquinidine and its derivatives by Wynberg and coworkers identified four minimum energy conformers: **11** (*app*-closed), **12** (*app*-open), **13** (*gauche*-open), **14** (*gauche*-closed) (Fig. 2) (11–13). Our NMR studies indicate that DHQD-PHN (**3**) in toluene readily adopts all these low energy conformations (*SI Appendix*), although Sharpless and coworkers reported a solid state structure of **3** as determined by X-ray crystallography in which **3** was found to adopt a *gauche*-open conformation (14).

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To whom correspondence should be addressed. E-mail: deng@brandeis.edu.

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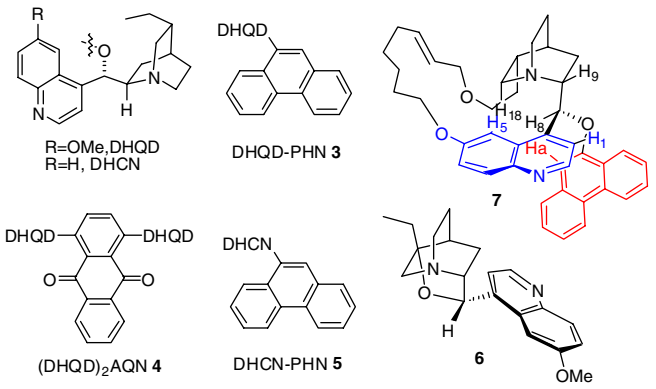


Fig. 1. Structure of cinchona alkaloids.

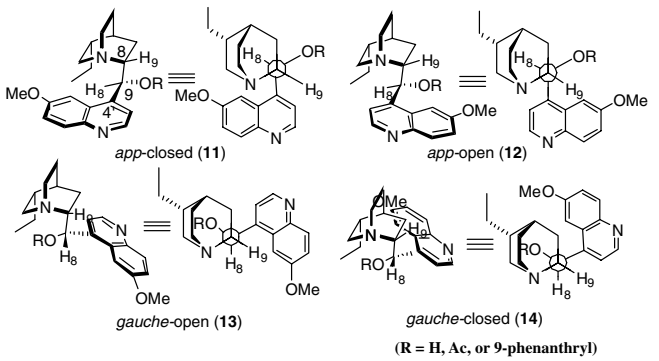
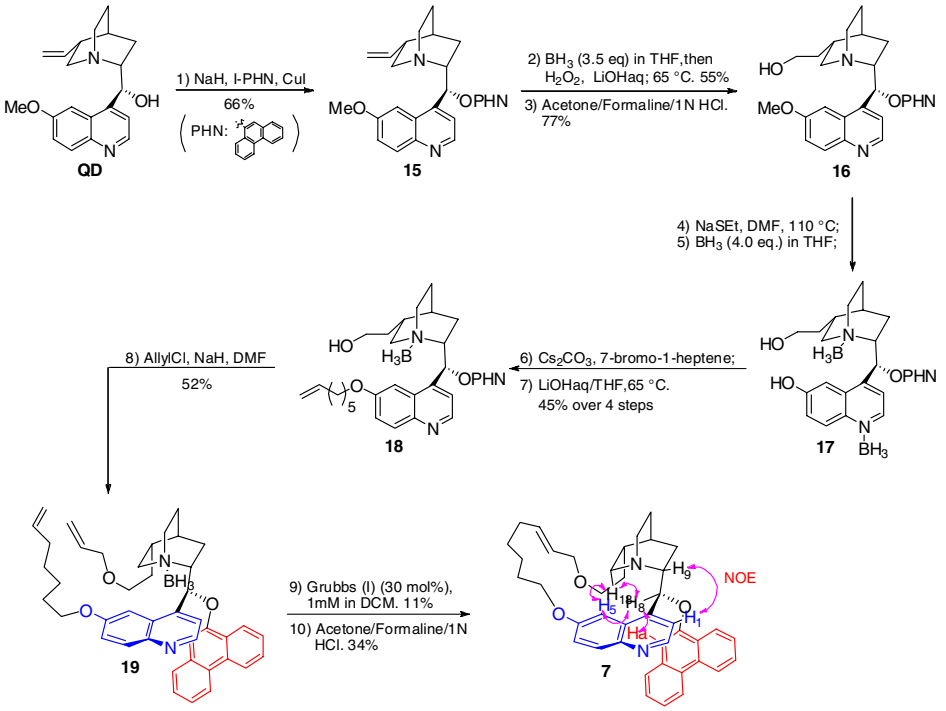


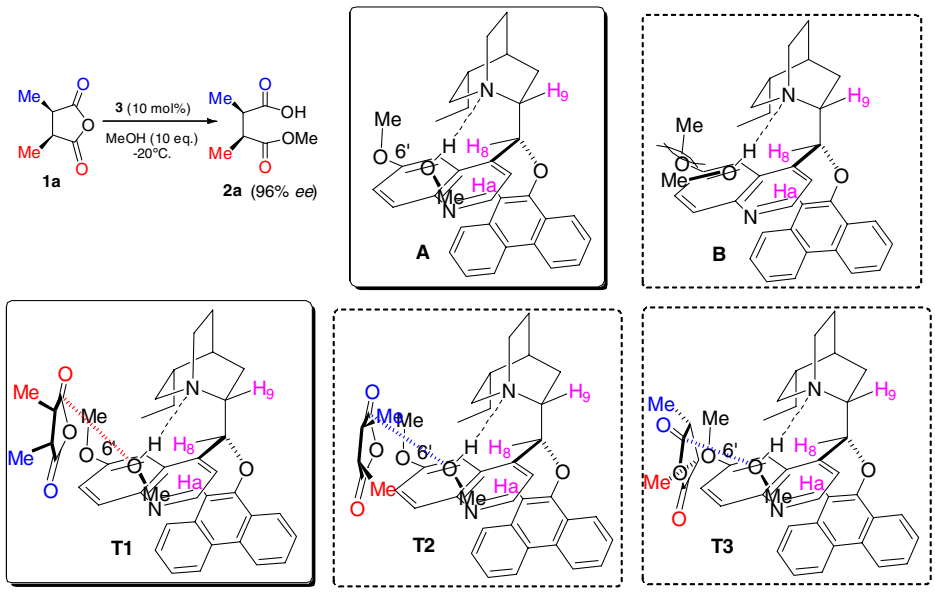
Fig. 2. Four minimum energy conformations of DHQD and its derivatives.

Conformationally rigid cinchona alkaloid derivatives were shown by Corey et al. to be powerful probes for identifying the active conformation of cinchona alkaloids as chiral ligands for the Sharpless asymmetric dihydroxylations of olefins (15–18). Recently, we have also successfully applied β-isocuperidine as a probe to elucidate the active conformation of cinchona alkaloid-derived bifunctional organic catalysts for an asymmetric conjugate addition of β-ketoesters to nitroalkenes (19). Accordingly, we examined the methanolysis of **1a** with a rigid cinchona alkaloid **6** (Fig. 1) (20), which was designed to mimic a cinchona alkaloid that is locked in a *gauche* conformation (open and closed). The **6**-catalyzed methanolysis of **1a**, compared to that catalyzed by DHQD-PHN (**3**), proceeded with a drastically reduced enantioselectivity (20% ee vs. 96% ee at −20 °C).

This result prompted us to design and synthesize a previously undescribed cinchona alkaloid derivative **7** (Fig. 1) and to investigate its ability to promote the enantioselective alcoholysis. To our knowledge, **7** represents a unique mimicry for a cinchona alkaloid derivative locked in an *app* conformation. As shown in Scheme 2 our synthesis of **7** began with the preparation of QD-PHN (**15**) from quinidine. A three-step sequence of hydroboration-oxidation-hydrolysis transformed QD-PHN (**15**) to alcohol intermediate **16** in 77% overall yield. Treatment of **16** with NaSEt furnished the corresponding 6′-OH derivative, which was converted to the cinchona alkaloid-diborane complex **17**. The complex **17** was subjected to sequential alkylation of the 6′-OH and allylation of primary alcohol to generate the diene precursor **19**. Ring-closing metathesis of diene **19** with Grubbs (I) catalyst accomplished the key task of forming the 21-membered macrocyclic ring. Hydrolysis of the bisborane complex afforded the desired rigid catalyst **7**. An extensive ^{1}H NMR analysis of **7** confirmed that it provided a mimicry of a cinchona alkaloid locked in an *app*-closed conformation (*SI Appendix*). To our delight, under identical reaction conditions, methanolysis of **1a** with **7** proceeded with similarly high enantioselectivity as that with DHQD-PHN (**3**) (93% ee for **7** vs. 96% ee for **3**). This result demonstrates unambiguously that a cinchona alkaloid in the *app*-closed conformation is able to promote a highly enantioselective alcoholysis, which provides strong experimental evidence supporting that DHQD-PHN (**3**) adopts the *app*-closed conformation as the active conformation when mediating the highly enantioselective methanolysis of meso anhydride **1a**. It is noteworthy that this conclusion emerging from our studies was implicated neither by X-ray crystallographic nor by NMR studies of



Scheme 2. Synthesis of rigid catalyst **7**



Scheme 3. Transition state model for **3** catalyzed asymmetric alcoholysis

ground state conformations of **3**.

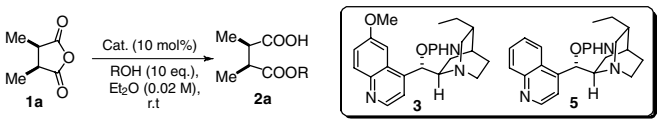
On the basis of this insight into the active conformer of DHQD-PHN (**3**) and results from our kinetic studies as described above, we were able to formulate a transition state model for **3**-catalyzed desymmetric alcoholysis of **1a**. As illustrated in Scheme 3, in the hydrogen-bonding complex between the alcohol and DHQD-PHN (**3**) adopting an *app*-closed conformation, the substituent of the alcohol is postulated to point away from the *C6′*-methoxy group of the quinoline ring of **3** in order to avoid a steric interaction between them (**A** vs. **B**). Thus, as shown in **A**, the activated alcohol is shielded on three sides by the quinoline ring, *C6′*-OMe group and the substituent (methyl) of the alcohol. When anhydride **1a** approaches the activated alcohol via the open corner, the steric repulsion between **1a** and the alcohol-amine complex is minimized when the two methyl groups of **1a** are pointing away from the alcohol-amine complex as illustrated in **T1**. In this transition state (**T1**), the activated alcohol is able to attack the top carbonyl group (pro-*S*) in **1a** via the stereoelectronically preferred Dunitz–Burgi angle (21). On the other hand, such an alignment between the activated alcohol and the bottom pro-*R* carbonyl group is not attainable. Thus the alcoholysis of **1a** occurs preferentially with the pro-*S* carbonyl group. Alternative transition state assemblies (**T2** and **T3**) could be conceived in which the anhydride **1a** is rotated in various ways to allow the pro-*R* carbonyl group to be aligned with the activated alcohol for the nucleophilic attack via the Dunitz–Burgi angle. However, compared to **T1**, they are disfavored because the substituents of anhydride **1a** engage in repulsive steric interactions with either the substituent of the alcohol (as shown in **T2**) or the *C6′*-OMe group of the cinchona alkaloid **3** (as shown in **T3**).

This stereochemical model that emerged from our mechanistic studies is consistent with the sense of asymmetric induction as determined by analysis of absolute configurations of the hemiesters obtained from the cinchona alkaloid-promoted alcoholysis (6). Moreover, the insensitivity of catalytic enantioselectivity toward variations of the substituents of the *meso* cyclic anhydrides can be easily rationalized, as in **T1** the substituents of the anhydrides are located in an open space where variations of their steric and electronic properties are well-tolerated by the cinchona alkaloid catalyst **3**.

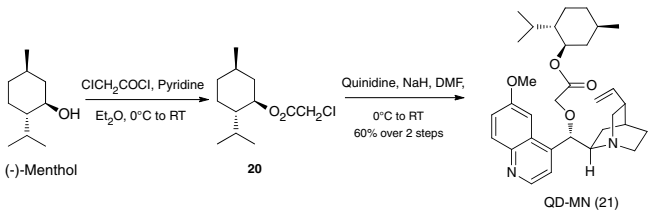
Nonintuitive predictions can also be made according to this model: (*i*) The enantioselectivity of the alcoholysis is expected to decrease significantly if the *C6′*-OMe is removed from DHQD-PHN (**3**) [i.e., using DHCN-PHN (**5**) as the catalyst]. (*ii*) Due to steric hindrance, **3**-catalyzed alcoholysis with a secondary alcohol would be dramatically slower than those with primary alcohols. Importantly, these hypotheses have been verified by experimental results (Table 1).

This model also suggests that the presence of the sterically bulky phenanthryl group in DHQD-PHN may enforce an *app* conformation for **3**; the steric interaction between the bulky *C9*-subsituent and the quinuclidinyl group is minimized when the cinchona alkaloid adopts the *app*-closed conformation (**11**), whereas it is significantly increased when the cinchona alkaloid adopts the *gauche* conformations (**13** and **14**). Following this line of analysis, we began to explore modified cinchona alkaloids bearing a bulky substituent at *C9* with the goal of developing a more practical catalyst. Subsequently, we found that cinchona alkaloid QD-MN (**21**) that could be easily prepared in multigram quantity by a two-step route in 60% overall yield

Table 1. Asymmetric alcoholysis of succinic anhydride 1a

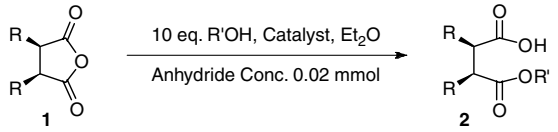


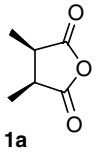
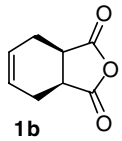
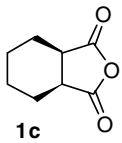
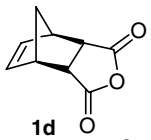
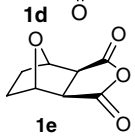
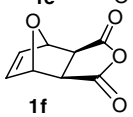
entry	cat.	ROH	*t*/*h*	conv./%	ee/%
1	DHQD-PHN(**3**)	MeOH	2	77	92
2	DHCN-PHN(**5**)	MeOH	2	49	70
3	DHQD-PHN(**3**)	Pr^{i}OH	12	<5	—



Scheme 4. Preparation of QD-MN (**21**)

Table 2. Asymmetric alcoholysis of cyclic anhydrides 1 with QD-MN and $(DHQD)_2AQN$*



Entry	Substrate	Catalyst (mol%)	Alcohol (10 eq.)	Temp (°C)	Time	Yield †	ee ‡
1	 1a	QD-MN (10%)	CF_3CH_2OH	RT	5 h	91%	94%
2		$(DHQD)_2AQN$ (5%)	CF_3CH_2OH	RT	9 h	90%	90%
3		QD-MN (10%)	MeOH	RT	9 h	90%	90%
4		$(DHQD)_2$ AQN (5%)	MeOH	RT	5 h	89%	94%
5	 1b	QD-MN (14%)	CF_3CH_2OH	RT	6 h	93%	95%
6		$(DHQD)_2AQN$ (7%)	CF_3CH_2OH	RT	5 h	96%	91%
7		QD-MN (14%)	MeOH	RT	8 h	91%	90%
8		$(DHQD)_2AQN$ (7%)	MeOH	RT	6 h	92%	94%
9	 1c	QD-MN (10%)	$CF_3CH_2OH_2$	RT	7 h	96%	94%
10		$(DHQD)_2AQN$ (5%)	CF_3CH_2OH	RT	7 h	95%	89%
11		QD-MN (10%)	MeOH	RT	8 h	94%	87%
12		$(DHQD)_2AQN$ (5%)	MeOH	RT	4 h	95%	93%
13	 1d	QD-MN (20%)	MeOH	RT	36 h	88%	90%
14		$(DHQD)_2AQN$ (10%)	MeOH	RT	12 h	90%	88%
15	 1e	QD-MN (30%)	MeOH	–20	60 h	91%	95%
16		$(DHQD)_2AQN$ (15%)	MeOH	–20	120 h	88%	96%
17	 1f	QD-MN (40%)	MeOH	–20	48 h	87%	92%
18		$(DHQD)_2AQN$ (20%)	MeOH	–20	96 h	74%	92%

*The reaction was carried out with **1** (0.02 M in diethyl ether) and R'OH [10 equivalent (eq.)] in the presence of catalyst.
†Conversion was determined by ^1H NMR.
‡See the *SI Appendix* for the determination of the ee value.

from cheap starting materials such as menthol, α-chloroacetyl chloride and quinidine (Scheme 4), matches the catalytic efficiency of DHQD-PHN (**3**) and $(DHQD)_2AQN$ (**4**) for the desymmetrization of a wide range of *meso* anhydrides (Table 2).

In summary, kinetic studies and catalyst conformational studies employing a designed rigid cinchona alkaloid derivative as a probe allowed us to determine the origin of catalytic activity and identify and the active conformer of the cinchona alkaloid catalyst for the highly enantioselective alcoholysis. These key mechanistic insights allowed us to formulate a transition state model that clarifies the molecular origin of the highly efficient recognition of enantiotopic carbonyl groups of the *meso* anhydride by the modified cinchona alkaloid. This model is consistent with the observed sense of asymmetric induction and provides a rationale for the broad scope of the asymmetric alcoholysis established from previous studies. These mechanistic insights also guided our development of a new modified cinchona alkaloid, QD-MN **21**, as a more practical catalyst for the enantioselective alcoholysis of *meso* anhydrides.

Materials and Methods

Dry methanol or 2,2,2-trifluoroethanol (3.0 mmol) was added in one portion to a stirred solution of anhydride (0.3 mmol) and QD-MN (10–40 mol%) or $(DHQD)_2AQN$ (5–7 mol%) in diethyl ether (15.0 mL) at the temperature indicated in Table 2. The reaction mixture was stirred at that temperature and the conversion of the starting material was determined by ^1H NMR analysis. The ee of each product was determined by GC analysis of the products or by HPLC analysis of a diastereoisomeric mixture of the corresponding amide-ester prepared from the hemiester.

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