Cinchona Alkaloids in Asymmetric Catalysis

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MacMillan Group Meeting
August 13, 2003

Introduction
Cinchona Alkaloids in Phase Transfer Catalysis
Cinchona Alkaloids as Nucleophiles/Bases
Sharpless Asymmetric Dihydroxylation

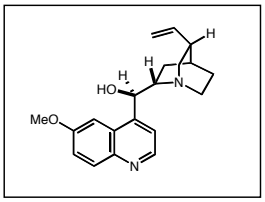
Useful Reviews

Kacprzak, K. et al. *Synthesis*, **2001**, *7*, 961-988.

Kwan, B.; MacMillan, D.W.C.; *New Strategies for Organocatalysis: Enantioselective Amine Catalysis.* **2003**, unpublished.

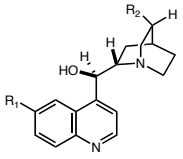
Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.

Introduction to Cinchona Alkaloids

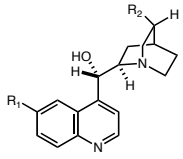


Quinine

- Quinine isolated by Pelletier in 1820.
- First used for a resolution of a racemate in 1853 by Pasteur.
- Quinine and derivatives were quickly recognized as antimalarial agents.



pseudoenantiomers



R_1 = OMe

Quinine R_2 = vinyl
Dihydroquinine R_2 = Et

R_1 = H

Cinchonidine R_2 = vinyl
Dihydrocinchonidine R_2 = Et

R_1 = OMe

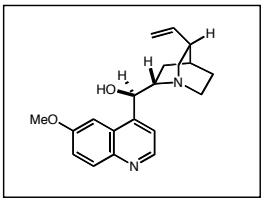
Quinine R_2 = vinyl
Dihydroquinine R_2 = Et

R_1 = H

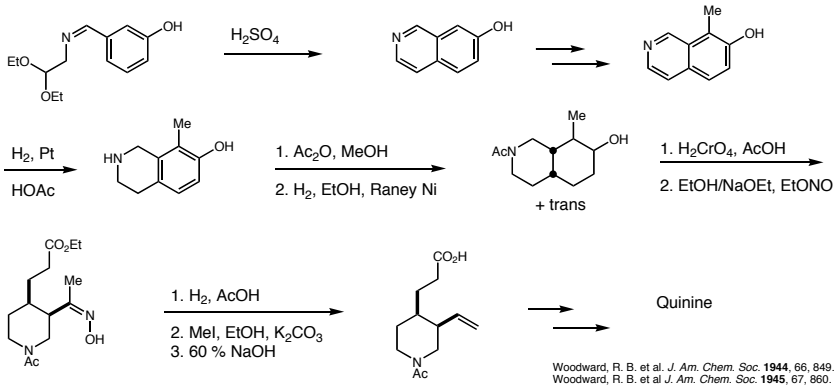
Cinchonidine R_2 = vinyl
Dihydrocinchonidine R_2 = Et

The First Total Synthesis

- Quinine was first synthesized by R.B. Woodward in 1944.



Quinine



Woodward, R. B. et al. *J. Am. Chem. Soc.* **1944**, 66, 849.
Woodward, R. B. et al *J. Am. Chem. Soc.* **1945**, 67, 860.

Cinchona Alkaloids Are Versatile Catalysts

- These are just a few of the reactions that can be performed asymmetrically.

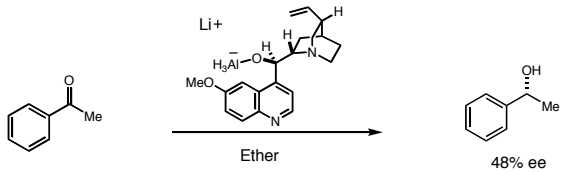
C-C Bond Forming
Alkylation
Aldol
Darzens
Michael Addition
Diels-Alder
Claisen Rearrangement

C-O Bond Forming
Epoxidation of Enones
Epoxidation of *cis*-Olefins
Asymmetric Dihydroxylation
Asymmetric Aminohydroxylation
α-Hydroxylation of Ketones

C-X Bond Forming
Aziridination
Azirination
Formation of α-Hydroxyphosphonate Esters
Addition of Thiols to Cyclic Enones

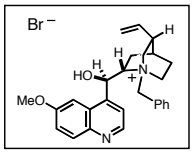
Miscellaneous Reactions
Hydrogenation
Desymmetrization
Decarboxylation

- Cinchona Alkaloids have been explored in asymmetric synthesis for the last 35 years.



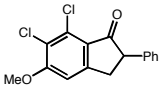
Cervinka, O.; Belovsky, O. *Coll. Czech. Chem. Commun.*, **1967**, 30, 2487.

Cinchona Alkaloids as Phase Transfer Catalysts



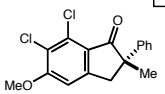
PTC

■ Alkylation of Substituted Indanones



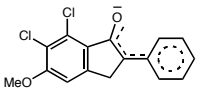
MeCl

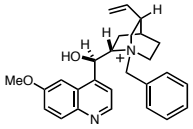
10-50 mol% PTC
Toluene, aq. NaOH, 20°C



95% yield, 92% ee

■ Ion pairing between indanone anion and PTC proposed as reason for selectivity

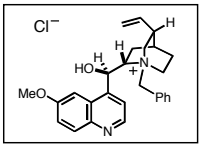




α-face blocked in rigid conformation, opens β–face to methylation

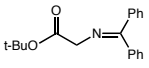
Dolling, U. -H.; Davis, P.; Grabowski, E. J. J. *J. Am. Chem. Soc.* **1984**, 106, 446.

O'Donnell: Pioneer in PTC with Cinchona Alkaloids



PTC

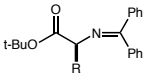
■ Efforts to synthesize chiral α–amino acids



R-Br

10 mol % PTC

50% aq. NaOH / CH_2Cl_2
RT

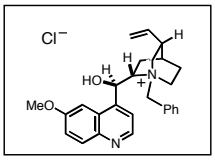


R	Time	% Yield	% ee
Allyl	5	75	66
Bn	9	75	66
Me	24	60	42
n-Bu	14	61	52
C_6H_4Cl-4	12	81	66
CH_2-2-naph	18	82	54

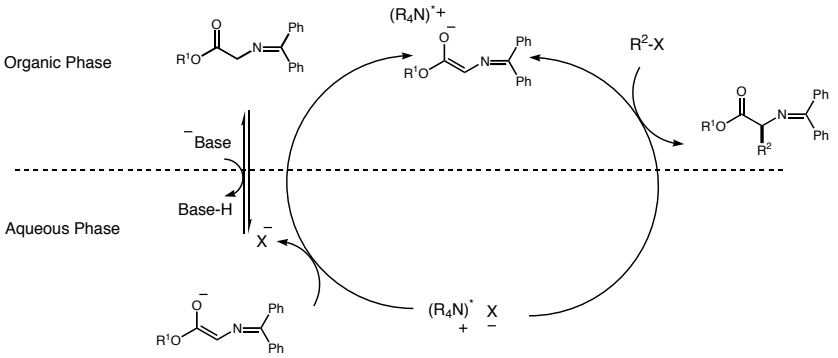
■ Recrystallization procedures were developed to obtain enantiopure compounds, but low yields indicated a need for improvement.

O'Donnell, et al. *J. Am. Chem. Soc.* **1989**, *111*, 2353.

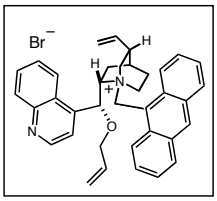
Mechanism for Phase-Transfer Alkylation



■ Proposed Mechanism for O'Donnell's PTC Alkylation



Corey Modifications to O'Donnell's Work

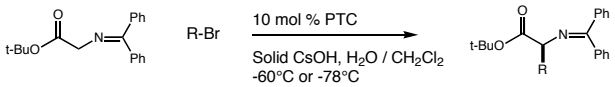


PTC

■ By using 9-(chloromethyl)anthracene to quaternize the PTC, approach from the front and right side of the catalyst is blocked.

■ Corey chose to block ion-pairing from the bottom face of the catalyst by O-allylation.

■ Therefore, the top left quadrant is now the only region open to the substrate.



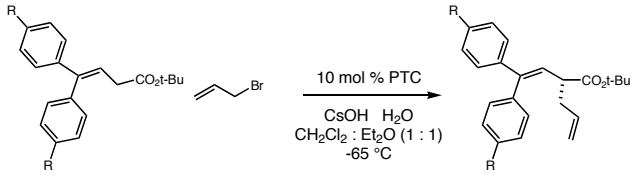
R	Time / %	Yield / %	ee / %
Me	28	71	97
Et	30	82	98
n-Hexyl	32	79	> 99
CH_2c-C_3H_5	36	75	99
Allyl	22	89	97
Methallyl	20	91	92
$CH_2C{\equiv}CTBS$	18	68	95
Bn	22	73	> 99

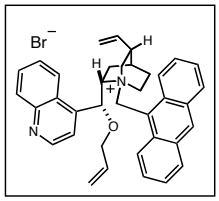
■ Enantioselectivity greatly enhanced by Corey's rational approach to catalyst design.

Corey arrived at these results while trying to understand the origin of enantioselectivity in the Sharpless Asymmetric Dihydroxylation. For relavent references, see the Kwan review.

An Interesting Sterics Versus Electronics Argument

■ Corey then tried a different experiment using diphenylalkylidene as a substrate, under the same conditions.





PTC

R	σ_p	ee / %
Ph	0.00	67
t-Bu	-0.15	81
OMe	-0.28	91
NMe_2	-0.63	96

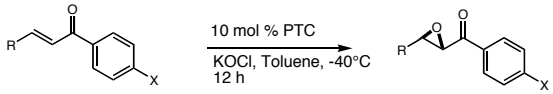
■ He found that the more electron-donating the subsituent on the phenyl ring, the more enantioselective the reaction.

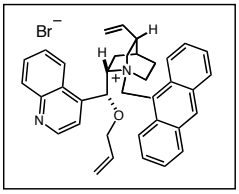
■ He then theorized that the more electron donating, the more negatively the ester oxygen is charged, and therefore the more tightly it can bind to the catalyst, thereby enhancing the selectivity.

Corey, E. J. et al. *J. Am. Chem. Soc.* **1998**, *120*, 13000.

Corey's Catalyst Applied to Epoxidation of Enones

■ Corey's catalyst modifications proved successful in the epoxidation of certain enones.





PTC

R	X	Yield / %	ee / %
C_6H_5	H	96	93
C_6H_5	F	93	98
C_6H_5	Br	92	93
$C_6H_4NO_2$-4	H	90	94
$C_6H_4NO_2$-4	F	97	95
n-C_5H_{11}	F	90	91
c-C_6H_{11}	H	85	94
c-C_6H_{11}	F	87	95
C_6H_5	OC_6H_5	89	93
2-naphthyl	H	97	93

■ Exocyclic enones were epoxidized, though with extensive erosion in enantioselectivity.

Corey, E. J.; Zhang, F. -Y. *Org. Lett.* **1999**, *1*, 1287.

Corey's Proposed Transition State for Nucleophilic Epoxidation

■ The Corey group proposed a transition state depicting the hypochlorite anion in the open quadrant around the catalyst, forming an ion-contact pair with the positively charged nitrogen.

■ The chalcone-derived substrate is believed to be oriented such that the ketone oxygen lies in contact with the quaternized nitrogen.

■ This alignment allows the oxygen to be located near the β-carbon of the enone, and also allows for electrostatic migration of the developing negative charge in the transition state.

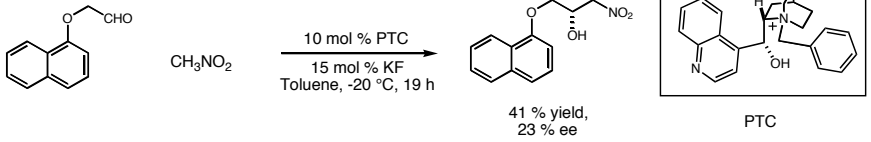
■ This model successfully predicts the sense of stereoinduction in the product epoxide.

■ This model does not, however, account for the observed need for the enone to distort its conjugation and achieve higher stereoselectivity in the reaction.

For a study demonstrating the importance of certain conditions in enantioselective epoxidations, see Lygo, B.; To, D. C. M. *Tetrahedron Lett.* **2001**, ***42***, **1343.**

Aldol Reaction with Cinchona Derivatives

■ Shibasaki was the first to report an aldol reaction using a Cinchona-derived catalyst.

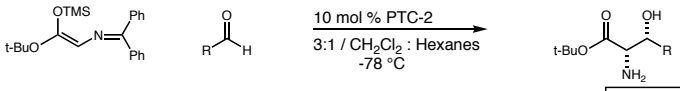


41 % yield,
23 % ee

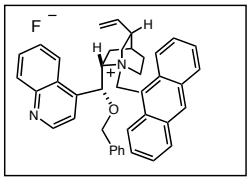
PTC

■ At the same time, Shibasaki was developing a lanthanum BINOL catalyst and was achieving better results, so he did not pursue the matter further.

■ Corey used a derivative of the epoxidation catalyst to develop this methodology for ester enolate equivalents.



R	Yield / %	syn : anti	syn ee / %
i-Pr	70	6 : 1	83
c-C_6H_{11}	81	13 : 1	46
n-C_6H_{13}	79	3 : 1	91
$(CH_2)_3Cl$	48	1 : 1	86
$(CH_2)_2Ph$	64	1 : 1	86
i-Bu	61	3 : 1	70

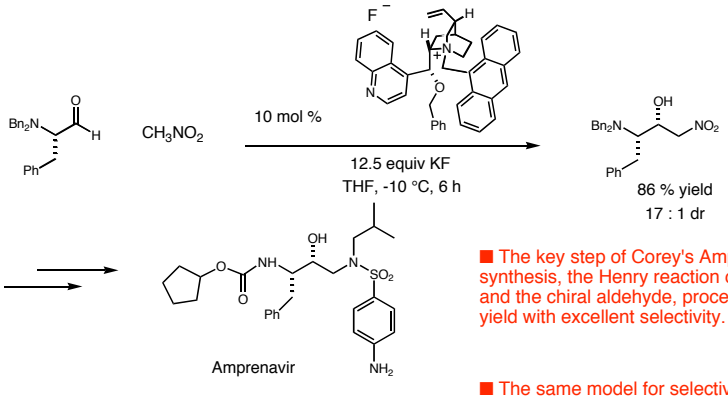


PTC-2

Corey, E. J. ... *Angew. Chem. Int. Ed.* **1999**, *38*, 1931.
Corey, E. J. ... *Tetrahedron Lett.* **1999**, *40*, 3843.
Shibasaki, M. et al. *Tetrahedron Lett.* **1993**, *34*, 855.

PTC with Cinchona Alkaloids in Total Synthesis

■ Corey extended this methodology to develop a diastereoselective Henry reaction starting with chiral aldehydes in order to synthesize Amprenavir, an HIV-protease inhibitor.



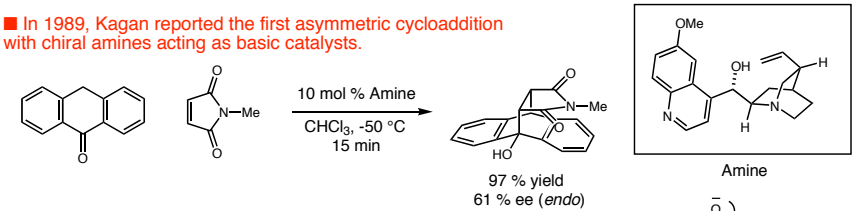
■ The key step of Corey's Amprenavir synthesis, the Henry reaction of nitroethane and the chiral aldehyde, proceeded in good yield with excellent selectivity.

■ The same model for selectivity as in the PTC-alkylation can be proposed here. The π-stacking between the aromatic aldehyde and the aromatic rings on the catalyst leave only one face of the aldehyde open to nucleophilic attack.

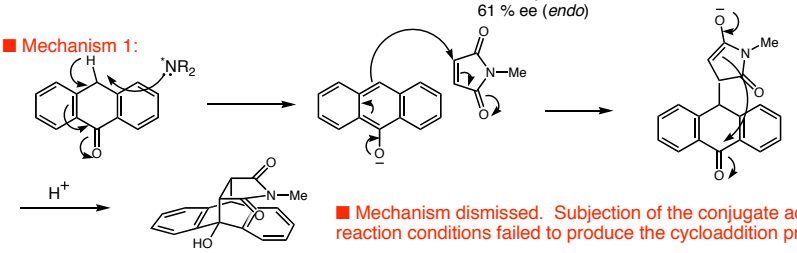
Corey, E. J. et al. *Angew. Chem. Int. Ed.* **1999**, *38*, 1931.

Cinchona Alkaloids as Nucleophilic Catalysts

■ In 1989, Kagan reported the first asymmetric cycloaddition with chiral amines acting as basic catalysts.

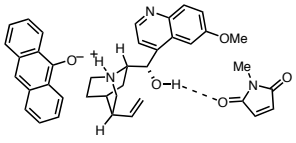


■ Mechanism 1:



■ Mechanism dismissed. Subjection of the conjugate adduct to reaction conditions failed to produce the cycloaddition product.

■ Mechanism 2:

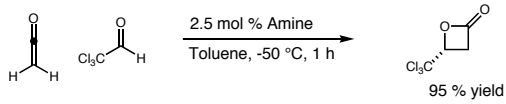


■ In this mechanism, the deprotonated anthrone forms an ion-contact pair with the quaternized nitrogen of the catalyst. Meanwhile, the dienophile is hydrogen-bonded through the hydroxyl group of the catalyst.

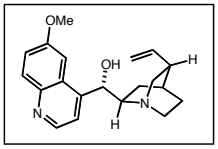
Kagan, H. B.; Riant, O. *Tetrahedron Lett.* **1989**, *52*, 7403.

Catalytic Asymmetric Synthesis of β–Lactones

■ In 1982, Wynberg published one of the first truly remarkable results in asymmetric catalysis.

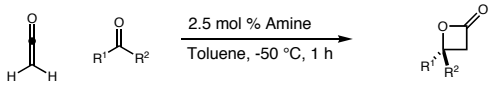


95 % yield
98 % ee



Amine

■ Based on this result, he attempted to expand substrate scope to include ketones.

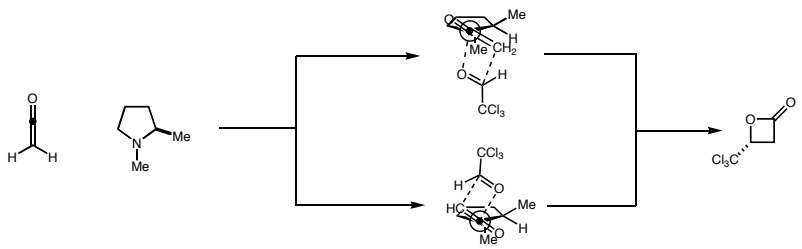


R^1	R^2	Yield / %	ee / %
CCl_3	H	89	98
$CHCl_2$	H	67	45
CCl_2Me	H	95	91
CCl_2Et	H	87	89
CCl_2Ph	H	89	90
CCl_3	Me	72	94
CCl_3	Et	1	n.d.
CCl_3	Ph	0	n.d.
CCl_3	C_6H_4Cl-4	68	90
CCl_3	$C_6H_4NO_2$-4	95	89

Wynberg, H. ... *J. Am. Chem. Soc.* **1982**, *104*, 166.
Wynberg, H. ... *J. Org. Chem.* **1985**, *50*, 1977.

Model for Stereoselectivity in Asymmetric Lactone Synthesis

■ Wynberg proposed this model to account for the observed stereoselectivity. He used 1,2-dimethylpyrrolidine as a simple model of the Cinchona catalyst.



■ Wynberg did not propose that either of these states is more likely than the other, because both lead to the observed stereochemistry in the product.

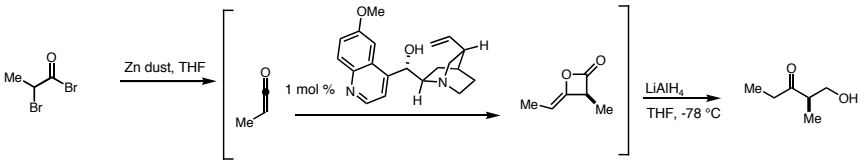
■ In the top form, the ketene oxygen faces the methylene of the catalyst ring. When chloral approaches the catalyst, it forms a complex with the trichloromethyl group facing away from the methyl group of the catalyst to avoid steric strain.

■ In the bottom form, the ring is the dominant form of stereocontrol, and the CCl_3 orients itself away from the ring methylene protons.

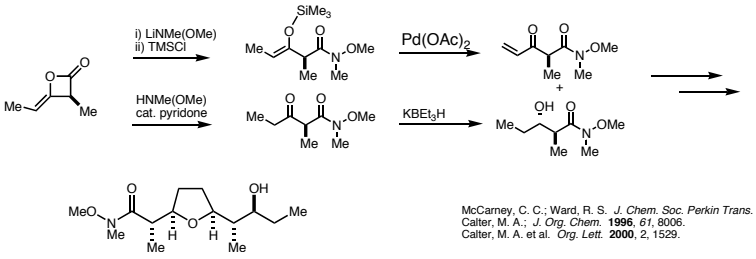
Wynberg, H. et al. *J. Am. Chem. Soc.* **1982**, *104*, 166.

Dimerization of in-situ Generated Ketenes with a Synthetic Application

■ Calter and coworkers published a ketene dimerization process in which the ketene was generated *in situ* and used as a solution in THF.



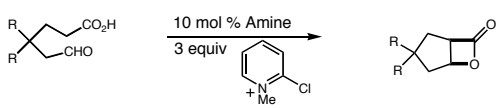
■ This methodology was applied to a convergent, stereospecific synthesis of a fragment of Pamamycin 621A.

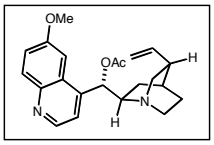


McCarney, C. C.; Ward, R. S. *J. Chem. Soc. Perkin Trans. 1* **1975, 1600.**
Calter, M. A.; *J. Org. Chem.* **1996**, *61*, 8006.
Calter, M. A. et al. *Org. Lett.* **2000**, 2, 1529.

Asymmetric Synthesis of Bicyclic Lactones

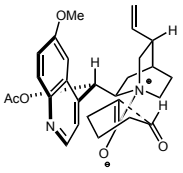
■ Romo reported a catalytic asymmetric synthesis of bicyclic lactones using a cinchona catalyst via intramolecular activation of ketene equivalents. The reaction involves both an alkaloid as well as a more simple tertiary amine base.




Amine

R	Yield / %	ee / %
H	54	92
OCH_2CH_2O	37	92
Me	45	90

■ It was observed that blocking the hydroxyl groups with different carbonyl derivatives did not affect enantioselectivity very much, and thus the following stereochemical rationale was proposed.



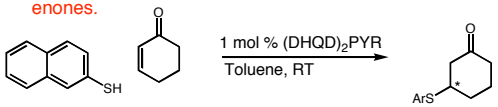
■ Once the acylammonium enolate is formed, the aldehyde approaches the enolate from the *si* face, away from the methyoxyquinoline moiety.

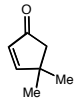
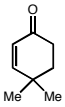
■ Per Corey's procedure of converting *gem*-trichloromethyl alcohols to amino acids, this reaction could be used to enantioselectively generate γ-substituted amino acids.

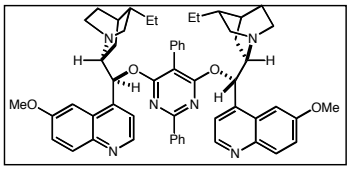
Romo, D. et al. *J. Am. Chem. Soc.* **2001**, *123*, 7945.
Romo, D. et al. *Synthesis.* **2001**, 1731.
Corey, E. J. et al. *J. Am. Chem. Soc.* **1992**, *114*, 1906.

Asymmetric Michael Addition of Thiols to Cyclic Enones

■ Recently, Li Deng developed a highly enantioselective 1,4-addition reaction of thiols to cyclic enones.



Enone		Yield / %	ee / %
	n = 0	55	41
	n = 1	77	94
	n = 2	86	97
	n = 3	82	> 99
	n = 4	91	97
		71	92
		88	95



$(DHQD)_2PYR$

■ Ordinary cinchona catalysts as well as hydroxyproline derivatives were tested, and alteration of the hydroxy group was deleterious to enantioselectivity. Therefore, a bifunctional catalytic mechanism was presumed.
■ It was believed that the cyclic enone and the thiol were simultaneously activated by the hydroxy and amino groups, respectively.

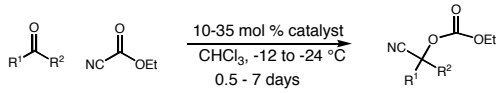
■ However, this cannot be the case for $(DHQD)_2PYR$, because it lacks a hydrogen donor. Also, $(DHQD)_2PYR$ gave the *R* isomer as the major product, while quinidine gave the *S* isomer.

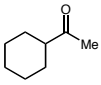
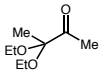
■ Therefore, the mechanism for the natural cinchona derivatives must differ significantly from that of the modified systems.

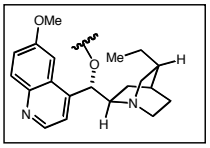
Deng, L., et al. *Angew. Chem. Int. Ed.* **2002**, *41*, 338.

Catalytic Asymmetric Cyanation of Ketones with Cinchona Alkaloid Catalysts

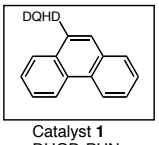
■ Deng has also recently described the asymmetric cyanation of ketones, catalyzed by cinchona Alkaloids acting as chiral Lewis bases. He used slightly modified cinchona catalysts.



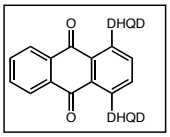
Substrate	Catalyst	Yield / %	ee / %
	2	66	97
	2	52	87
	2	55	88
	1	78	96
	1	65	90



DHQD



Catalyst **1**
DHQD-PHN

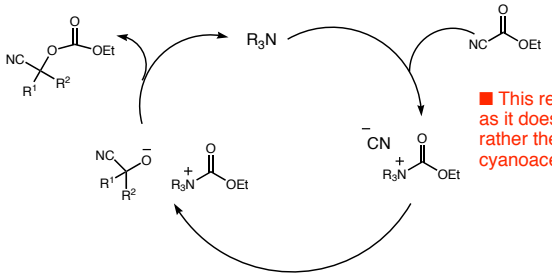


Catalyst **2**
$(DHQD)_2$-AQN

Deng, L. et al. *J. Am. Chem. Soc.* **2001**, *123*, 7475.

Mechanism of Deng's Cyanation Reaction

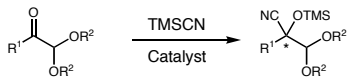
- A slightly unusual catalytic cycle.



- This reaction is synthetically favorable, as it does not require the handling of HCN; rather the CN ion comes from ethyl cyanoacetate.

- The chiral ion pair is believed to be the source of enantioselectivity. In some substrates, the group observed erosion in enantioselectivity. So, in reality, this possibility can be imagined as a dynamic kinetic resolution of sorts: This would require the following to be true:
  - Reversible cyanide addition to the ketone, and
  - The elimination of cyanide proceeding faster than esterification of the cyanoalkoxy anion.

- Within the past few months, this methodology has been applied to cyanosilation of ketones.

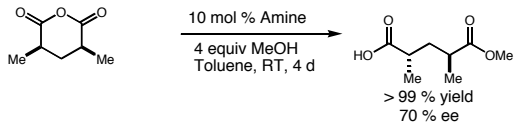


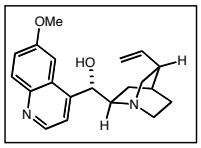
- Works with a wide range of substrates, with outstanding yields and % ee (> 90 %).

Deng, L. et al. *J. Am. Chem. Soc.* **2001**, *123*, 7475.

Desymmetrization

- Oda first demonstrated that cinchona alkaloids could be used to catalyze ring opening of a cyclic meso anyhydride with moderate enantioselectivity.



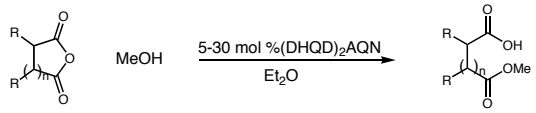


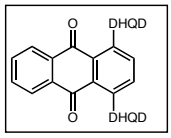
Amine

- Oda measured k_D/k_H = 2.3, indicating that general base catalysis is taking place. This value is nearly equal to that for general base catalyzed hydrolysis of acetic anhydride.

- Also, when the anhydride was subjected to quinuclidine and quinoline separately, only quinuclidine proved efficient in the reaction, suggesting that deprotonation occurred at the bridgehead nitrogen of the alkaloid.

- Deng optimized this reaction for many different substrates and found $(DHQD)_2AQN$ to be the optimal catalyst for nearly all substrates. Some catalysts proved highly effective for one substrate, but worked very poorly for others. Yields 70-99 %, % ee's 90-98 %.



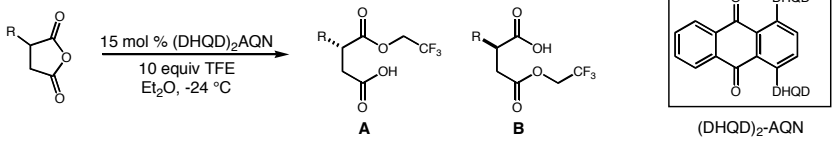


$(DHQD)_2$-AQN

Oda, J. et al. *J. Chem. Soc. Chem. Commun.* **1985**, 1717.
Deng, L. et al. *J. Am. Chem. Soc.* **2000**, *122*, 9542.

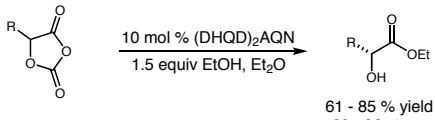
Kinetic Resolutions

■ Deng extended his anhydride opening methodology to parallel kinetic resolutions of racemic monosubstituted anhydrides.



R	**A** Yield / %	**A** ee / %	**B** Yield / %	**B** ee / %
Me	36	93	41	80
Et	38	91	50	70
n-octyl	38	98	41	66
Allyl	40	96	49	82
Ph	44	95	32	87
C_6H_4OMe-3	45	96	30	83
C_6H_4Cl-4	44	96	29	76

■ This methodology was also extended to produce α-hydroxy esters in high enantiopurity.



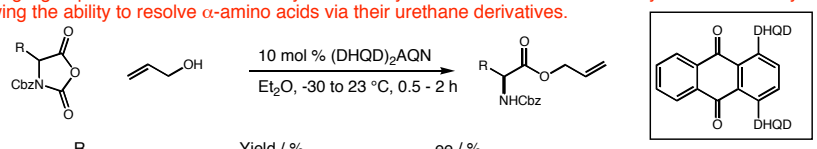
61 - 85 % yield
60 - 96 % ee

■ The aryl substituted substrates were resolved dynamically; however, the lower acidity of the α-protons of the alkyl substrates prevented dynamic resolution.

Deng, L. et al. *J. Am. Chem. Soc.* **2001**, *123*, 11302.
Deng, L. et al. *J. Am. Chem. Soc.* **2002**, *124*, 2870.

Dynamic Kinetic Resolution of α-Amino Acids

■ Deng's group also demonstrated the synthetic utility of the cinchona alkaloid catalyzed resolution by showing the ability to resolve α-amino acids via their urethane derivatives.



R	Yield / %	ee / %
Ph	97	91
C_6H_4F-4	96	90
C_6H_4Cl-4	97	92
$C_6H_4CF_3$-4	95	90
2-thiophenyl	93	92
3-thiophenyl	95	91
2-furyl	98	91
2-(5-Me-furyl)	97	93
3-(1-Tosylindolyl)	95	90

■ At lower temperatures, several of these same substrates were resolved, though not dynamically. In these cases, both enantiomers were isolated in good yields, with comparable enantiopurity.

■ Deng measured a deuterium kinetic isotope effect of 1.3. This fact, combined with the fact that both enantiomers were isolated in the same enantiopurity, suggests a general base-catalyzed mechanism for the reaction.

■ During the deallylation step, little to no racemization was observed.

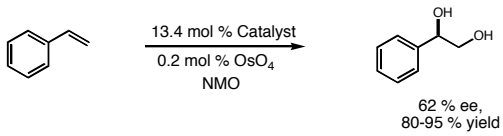
Deng, L. et al. *J. Am. Chem. Soc.* **2001**, *123*, 12696.
Deng, L. et al. *Org. Lett.* **2002**, *4*, 3321.

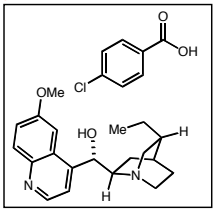
The Most Famous Cinchona-catalyzed Process - Asymmetric Dihydroxylation

■ The OsO_4 dihydroxylation of olefins is, to date, one of the most generally applicable reactions in synthetic organic chemistry. To quote Sharpless, "OsO_4 reacts with *all* olefins, and reacts *only* with olefins." (poetic license acknowledged)

■ However, stoichiometric use of the toxic and expensive osmium tetroxide is not practical, so Sharpless derived a cinchona alkaloid catalyzed asymmetric dihydroxylation, following the work by Hentges, in which acetate esters of cinchona alkaloids were used as chiral ligands.

■ In 1987, Sharpless made the cinchona-mediated process catalytic by adding NMO.





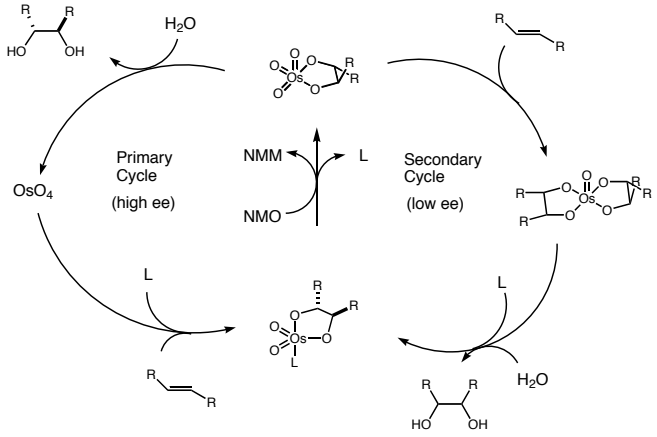
Catalyst

■ However, despite the advance that came with making the above reaction catalytic, there remained a significant problem. The enantioselectivity in the catalytic reaction was lower than the enantioselectivity in the stoichiometric reaction.

Jacobsen, E. N.; Sharpless, K. B. et al. *J. Am. Chem. Soc.* **1988**, *110*, 1968.

Why Is Enantioselectivity Lower in the Catalytic Reaction?

■ The lesser enantioselectivity was traced to a nearly racemic second catalytic cycle. The first cycle was highly enantioselective, but analysis of the mechanism shows a second cycle to be the problem.

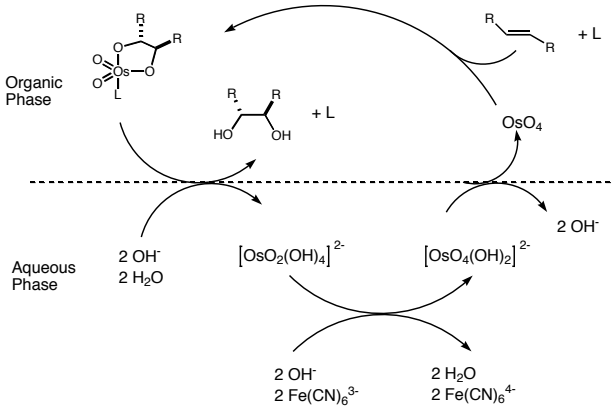


■ Performing the process in a stepwise manner produces products that support the mechanistic process outlined above. The experiments show that each cycle is equally efficient at producing diols.

Sharpless, K. B. et al. *J. Am. Chem. Soc.* **1989**, *111*, 1123.

Solution to the Problem: Use Two-Phase Conditions

■ The second catalytic cycle can be virtually eliminated by performing the reaction under two-phase conditions with $K_3Fe(CN)_6$ as the stoichiometric reoxidant instead of NMO.



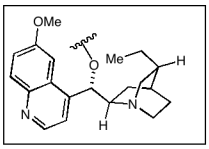
■ Using $MeSO_2NH_2$ as an additive greatly increases the reaction rate in what has become known as the "sulfonamide effect." This allows lower reaction temperatures and therefore, higher selectivity.

■ In this scenario, when the osmium (VI) monoglycolate ester is hydrolyzed, the diol and the ligand are released to the organic layer, and the Os(VI) to the aqueous layer, before reoxidation can occur, preventing entry into the second catalytic cycle.

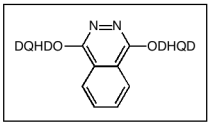
Sharpless, K. B. et al. *Tetrahedron Lett.* **1990**, *31*, 2999.

Structure-Activity Studies in the AD Reaction

■ Ligand structure-activity studies have shed light on the origin of enantioselectivity in the asymmetric dihydroxylation reaction. These studies have demonstrated the importance of a binding pocket present in the dimeric-type alkaloid ligands.



DHQD

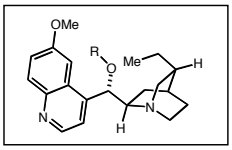


$(DHQD)_2PHAL$

■ The "dimeric" alkaloids, such as $(DHDQ)_2PHAL$, allow for the formation of an enzyme-like binding pocket, for both steric reasons and enhanced aromatic stacking interactions.

Sharpless, K. B. et al. *J. Am. Chem. Soc.* **1994**, *116*, 1278.

How the Structure of the Alkaloid Catalyst Affects Binding and Rates



Catalyst

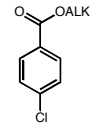
Alkaloid Moiety	Binding to Os	Rates
Quinuclidine Et group	Increases binding	Little effect
OR	Little effect	Large R drastically reduces rates
Oxygenation	Essential - carbon is too bulky	Not determined, due to lack of binding
Quinoline (Nitrogen has no influence)	Increased	Increased
Methoxy group	Increased	Increased
Configuration at C-OR	*erythro* allows higher binding	*erythro* allows higher rates

■ It is interesting to note that the binding pocket of the "dimeric" alkaloid catalysts tolerates one large substituent in the meta position of an aryl substrate, since the subsituent can easily be angled away from the quinoline ring without compromise stacking interactions. Thus, *m-tert*-butyl styrene proceeds comparably to styrene itself.

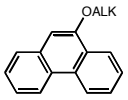
Sharpless, K. B. et al. *J. Am. Chem. Soc.* **1994**, *116*, 1278.
Sharpless, K. B. et al. *Tetrahedron Lett.* **1994**, *35*, 7315.

Other Cinchona-derived Catalysts Used in the AD Reaction

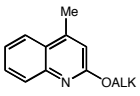
■ Over 350 cinchona-derived catalysts have been tested in the AD reaction. Some of the most effective are shown here.



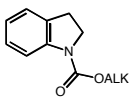
37-99 % ee



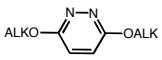
78-99 % ee

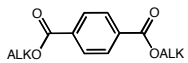


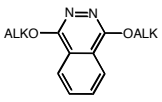
65-98 % ee



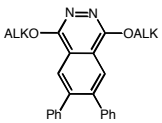
16-80 % ee



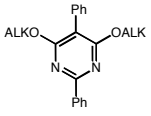




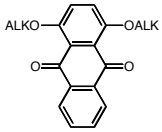
77-99.5 % ee



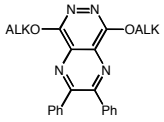
53-99 % ee



89-96 % ee



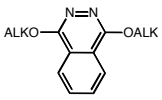
72-99 % ee



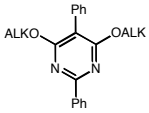
Which Ligand is Best for Asymmetric Dihydroxylation?

■ Despite several claims over the years that there is one "best" ligand for asymmetric dihydroxylation, extensive general studies have only shown that there seem to be three classes of ligands that work most effectively with certain classes of olefins.

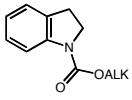
Olefin Class						
Preferred Ligand	PYR PHAL	PHAL	IND	PHAL	PHAL	PYR PHAL
ee Range	30-97 %	70-97 %	20-80 %	90-99.8 %	90-99 %	20-97 %



PHAL



PYR



IND

Conlcusion and Future Directions

■ Cinchona alkaloids can catalyze many different reaction types, with varying degrees of efficiency and enantioselectivity.

■ Cinchona-based catalysts are very desirable because they are generally recoverable, not environmentally hazardous, and readily available, either by commercial means or by synthetic methods.

■ Many of the cinchona-catalyzed reactions have been greatly enhanced by the use of "dimeric" catalysts. The Sharpless Asymmetric Dihydroxylation is the most well-known example of this, and enantioselectivities and substrate scope continue to improve as new ligands are designed and tested.

■ One problem with several cinchona catalyzed reactions is modest enantioselectivity. While all these reactions work for some substrates and with some selectivity, most are not commonly regarded as excellent methodologies. Many of these reactions, with better modeling techniques and therefore better catalyst design, could be improved.

■ There have been several reported examples of ordinary kinetic resolutions, but only very recently have any dynamic kinetic resolutions appeared in the literature. Given that cinchona derivatives can generally give either sense of stereoinduction, resolutions could reasonably be expected to provide the desired product in high purity and yield.