

Catalytic Asymmetric Synthesis with Cinchona Alkaloids

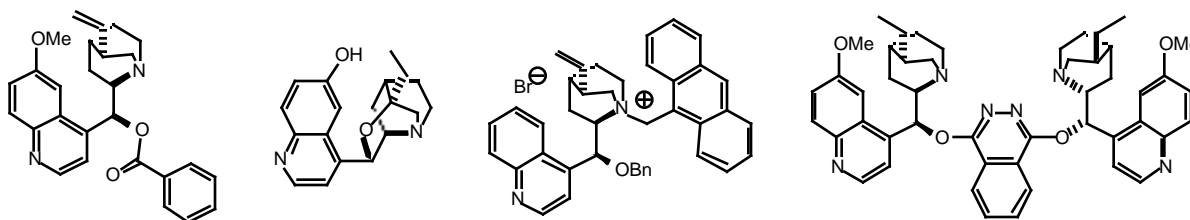
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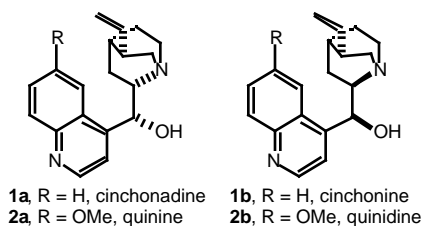
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ABSTRACT



This article reviews the advances in catalytic asymmetric synthesis using cinchona alkaloids, as the basis for the chiral induction, in a wide range of reactions.

The field of catalytic asymmetric synthesis is providing synthetic chemists with new and powerful tools for the efficient asymmetric synthesis of complex organic molecules. A majority of the more notable catalysts use transition metals to promote a reaction in the presence of a chiral ligand.¹ While it is true that most of the popular catalytic systems are inorganic in nature, one must not forget the use of purely organic catalysts like (S)-proline,² simple peptides,³ and easily the most popular choice, the cinchona alkaloids.



The overall utility of asymmetric catalysts can be compared by examining three main criteria: 1) the variety of reactions that the catalyst can promote, 2) the availability of both enantiomeric antipodes of the catalyst at a reasonable price, and 3) the stability of the catalyst. Cinchona alkaloids fulfill all of these criteria making them one of the most useful catalysts to date.

The family of cinchona alkaloids consists of two pseudoenantiomeric pairs, including cinchonine, cinchonidine, quinine and quinidine.⁴ They are isolated by extracting the bark of the cinchona tree; a native of tropical regions. Outside of chemistry, the cinchona alkaloids have found wide use in everything from food flavorings to the treatment of malaria. Due to their widespread use, all four members are readily available in large quantities from most chemical suppliers. The cinchona alkaloids and their derivatives are also benchtop stable, unlike many of the inorganic catalysts, withstanding oxygen, water and moderate amounts of light.

One of the earliest uses of cinchona alkaloids in asymmetric catalysis was demonstrated by Pracejus in the

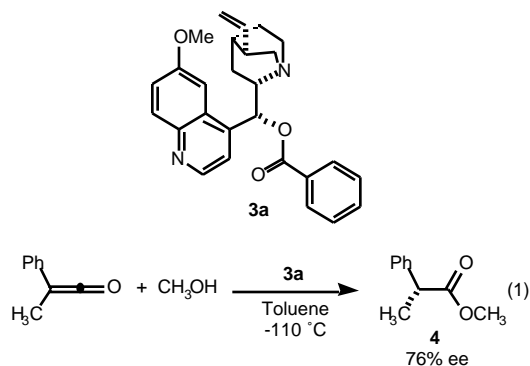
¹ Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; John Wiley & Sons, Inc.: New York, 1994.

² Gröger, H.; Wilken, J. *Angew. Chem. Int. Ed.* **2001**, *40*, 529-532.

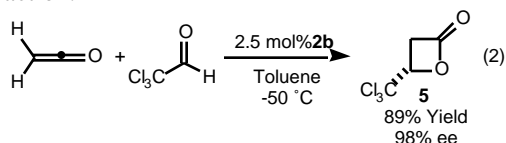
³ (a) Jarvo, E. R.; Vasbinder, M. M.; Miller S. J. *Tetrahedron* **2000**, *56*, 9773-9779. (b) Horstmann, T. E.; Guerin, D. J.; Miller, S. J. *Angew. Chem. Int. Ed.* **2000**, *39*, 3635-3638.

⁴ The term pseudoenantiomeric is used because although the molecules are not enantiomers, their properties are enantiomeric in nature.

1960's to catalyze the asymmetric alcoholysis of ketenes (eq 1).⁵ One proposed mechanism is that the alcohol is activated via a hydrogen bond with the tertiary amine of benzoylquinine. Addition of the alcohol to the ketene is followed by quenching of the resultant enolate by the chiral ammonium salt. The resultant esters are isolated in up to 76% enantiomeric excess (ee). Ideally, the enantioselectivities could be higher. A reason for the depreciated values is likely due to the high background rate of the reaction. While attempts were made to suppress the background rate by reducing the temperature to -110 °C, the steric hindrance of a tertiary alcohol would probably also help.

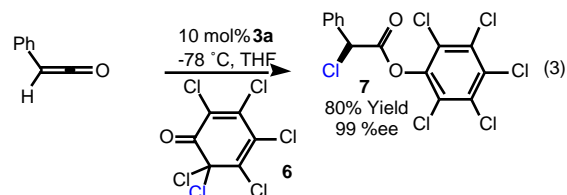


Building on these initial studies, Wynberg later discovered the [2 + 2] addition of ketene to polychlorinated aldehydes to yield α -lactones (eq 2) in high enantioselectivity (98% ee) and yield (89%). It is proposed that the ketene reacts with the quinuclidine ring of quinidine to form a zwitterionic intermediate which then proceeds in a stepwise addition to the aldehyde. Unprotected quinidine is used, but surely it catalyzes its own acylation very rapidly. Supporting this hypothesis, reactions using preacylated alkaloid give similar enantioselectivities. This methodology has recently been updated to include the use of *in situ* generated ketenes, which adds much versatility to the reaction.⁶

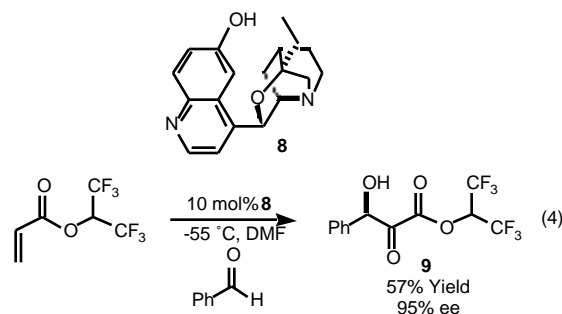


Recently, there have been many additional publications using cinchona-ketene systems for asymmetric synthesis.⁷ One of the most impressive of these recent works is Lectka's α -halogenation of acid chlorides.⁸ The previously known benzoylquinine-ketene system reacts with quinone

based electrophilic halogenating reagents (6) to yield activated α -halogenated esters with enantioselectivities as high as 99%, and with good yields (eq 3). This system could be applied to the extremely important unsolved problem of catalytic asymmetric fluorination, where cinchona derivatives have already been used, though only stoichiometrically.⁹



The first catalytic asymmetric Baylis-Hillman reaction has been developed using derivatives of quinidine to effect the reaction of activated alkenes with aldehydes (eq 4).¹⁰ Until this report, although there had been many attempts, there still was not an efficient and selective catalytic asymmetric version of this important reaction. In the presence of 10 mol% catalyst 8 a wide variety of aromatic and aliphatic aldehydes were converted into α -hydroxy esters in low to moderate yields, but with enantioselectivities as high as 99% ee. The reaction time seems highly substrate dependent, varying between one and 72 h. The key to the use of 8 was the conversion of the quinoline methoxy group to a phenol. Without this modification, there is virtually no selectivity.



While this report was a huge step in the right direction, there is still much work to be done on the Baylis-Hillman reaction. The ability to synthesize the opposite enantiomers of the products is not noted. Additionally, a kinetic study would shed light on the proposed model for selectivity, which relies on a 13-member ring, to rigidify the transition state (Figure 1). Another plausible mechanism would be second order in catalyst; having additional chiral direction and a hydrogen bond donated by a second molecule of catalyst.

⁵ (a) Pracejus, H.; Mätje, H. *J. Prakt. Chem. 4. Reihe*, **1964**, *24*, 195.

(b) Samtleben, R.; Pracejus, H.; *J. Prakt. Chem.* **1972**, *314*, 157.

⁶ Tennyson, R.; Romo, D. *J. Org. Chem.* **2000**, *65*, 7248-7252.

⁷ Dimerization of methylketene; (a) Calter, M. A.; Guo, X.; Liao, W.; *Org. Lett.* **2001**, *3*, 1499-1501. (b) Calter, M. A.; Guo, X. *J. Org. Chem.* **1998**, *61*, 8006-8007. α -Lactam synthesis; (c) Taggi, A. E.; Hafez, A. M.; Wack, H.; Young, B.; Drury, W. J., III; Lectka, T. *J. Am. Chem. Soc.* **2000**, *122*, 7831-7832. α -Silylthioester synthesis; (d) Blake, A. J.; Friend, C. L.; Outram, R. J.; Simpkins, N. S.; Whitehead, A. J. *Tetrahedron Lett.* **2001**, *42*, 2877-2881.

⁸ Wack, H.; Taggi, A. E.; Hafez, A. M.; Drury, W. J., III; Lectka, T. *J. Am. Chem. Soc.* **2001**, *123*, 1531-1532.

⁹ Muñiz, K. *Angew. Chem. Int. Ed.* **2001**, *40*, 1653-1656. And references therein.

¹⁰ Iwabuchi, Y.; Nakatani, M.; Yokoyama, N.; Hatakeyama, S. *J. Am. Chem. Soc.* **1999**, *121*, 10219-10220.

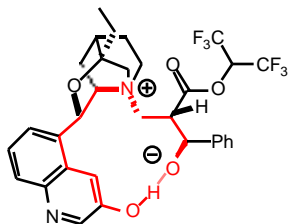
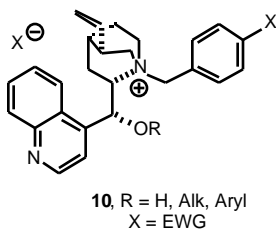
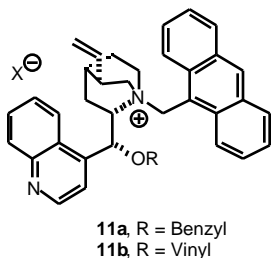


Figure 1. Proposed Baylis-Hillman Intermediate

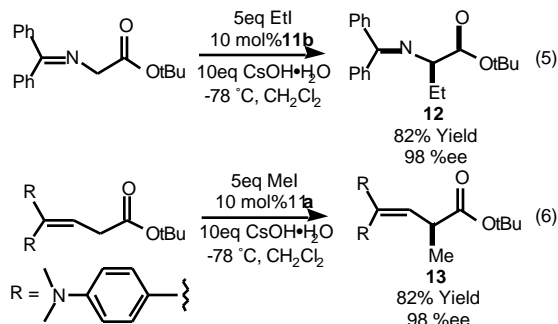
Until now, the focus has been on cinchona derivatives which derive their catalytic activity through a nucleophilic or a Lewis basic interaction with the tertiary amine. The field of Phase Transfer Catalysis (PTC) relies on an ammonium salt of the alkaloid. Previously, the catalyst of choice was the cinchona alkaloid derived salt (**10**). The catalyst was then “tuned” with various electron withdrawing groups to enhance the positive charge and possibly even provide additional steric bulk.¹¹



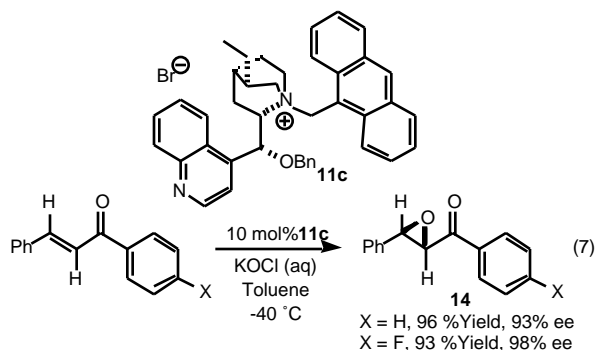
In the last four years, Corey¹² and Lygo¹³ have revolutionized the field of asymmetric PTC by introducing the use of N-(9-anthracenylmethyl)-cinchonidinium salts (**11**) to replace the once prevalent N-benzyl-cinchonidinium salts (**10**). In Corey’s model, the sterically larger anthracenylmethyl moiety joins with the quinuclidine ring and the lower half of the cinchonidine to block three of the four faces of the ammonium salt where the counterion could associate. The fourth face remains sufficiently open enough to allow for a close ion interaction.¹²



Corey was able to effectively apply these catalysts to enolate alkylations^{12,14} by using 10 mol% **11** in the presence of the insoluble base CsOH•H₂O (eqs 5,6). The ammonium salt associates with the hydroxide ion and transports it into the organic phase where it reacts to form the enolate. PTC **11** then associates with the enolate and provides a chiral environment during the acylation step.



Utilizing the same catalyst, Corey has also had success with the epoxidation of conjugated systems, forming products in very high selectivity and yield (eq 7).¹⁵ 10 mol% of **11c** is used in conjunction with potassium hypochlorite to produce the desired epoxide (**14**). The double bond in **11c** was removed to prevent unwanted catalyst modification.



While the cinchona alkaloids have many uses as purely organic catalysts, they also have been used effectively as ligands for metals. Due to the dense functionality of the cinchona alkaloids, it is possible to coordinate a metal in four different positions.¹⁶ Also, additional binding sites could be added to the cinchona core. It was this method that led to one of the most notable uses of a cinchona-metal complex: the dihydroxylation of olefins.

¹¹ Arai, S.; Tsuge, H.; Shiori, T. *Tetrahedron Lett.* **1998**, *39*, 7563-7566.

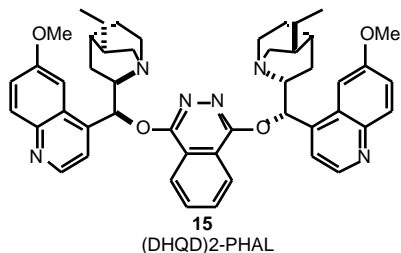
¹² Corey, E. J.; Xu, F.; Noe, M. C. *J. Am. Chem. Soc.* **1997**, *119*, 12414-12415.

¹³ Lygo, B.; Wainright, P. G. *Tetrahedron Lett.* **1997**, *38*, 8595-8598.

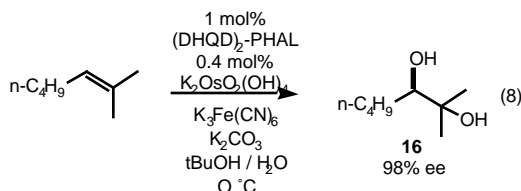
¹⁴ a) Corey, E. J.; Noe, M. C.; Feng, X. *Tetrahedron Lett.* **1998**, *39*, 5347-5350. b) Corey, E. J.; Bo, Y.; Busch-Petersen, J. *J. Am. Chem. Soc.* **1998**, *120*, 13000-13001.

¹⁵ Corey, E. J.; Zhang, F. *Org. Lett.* **1999**, *1*, 1287-1290.

¹⁶ Hubel, R.; Polborn, K.; Beck, W. *Eur. J. Inorg. Chem.* **1999**, 471-482.

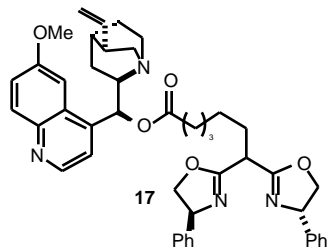


To find a suitable catalyst for the catalytic asymmetric dihydroxylation of olefins, Sharpless examined over 500 possible ligands before discovering the ligand (DHQD)₂-PHAL (**15**).¹⁷ These ligands have proven to be superior to others for the dihydroxylation of olefins with aliphatic substituents. Sharpless proposes that the OsO₄ bound to the ligand acts on the olefin through a [2 + 2] cycloaddition, while Corey postulated a [3 + 2] mechanism.¹⁸ Ongoing discussions on the mechanism notwithstanding, (DHQD)₂-PHAL shows excellent selectivities over a range of aliphatic and aromatic substituted olefins (eq 8). When the catalyst is changed to the quinine derivative (DHQ)₂-PHAL, the opposite selectivity is observed, though with slightly diminished enantioselectivities. This decrease is observed with all DHQ dihydroxylation ligands.

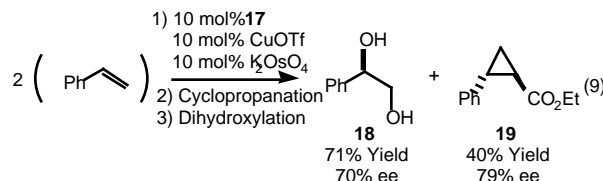


Sharpless has also modified the dihydroxylation to create the first osmium-catalyzed asymmetric aminohydroxylation reaction.¹⁹ -Hydroxyamino groups are biologically important, most notably occurring in the taxol side chain.

Very recently, Benaglia designed a cinchona ligand with a bis(oxazoline) (box) appended to the -alcohol of dihydroquinidine (DHQD).²⁰ This ligand (box-DHQD, **17**) can be used to perform multiple different catalytic asymmetric reactions.



When preloaded with CuOTf bound to the bis(oxazoline) portion and K₂OsO₄ bound to the DHQD, **17** can either perform a cyclopropanation, dihydroxylation or both sequentially in moderate enantioselectivity and yield (eq 9).



Due to the lack of optimal selectivities and yields, **17** may not be ready for synthetic use, nevertheless it provides an insight into a possible future direction of ligands for catalytic asymmetric synthesis. Much like an enzyme, box-DHQD is designed with multiple domains which can perform different catalytic asymmetric reactions in sequence. Future catalysts could be designed to carry out entire syntheses or series of reactions. Instead of adding a new catalyst for each step, the entire asymmetric synthesis could be carried out sequentially in one pot.

Cinchona alkaloid derived catalysts are central to many catalytic asymmetric reactions today. Due to the many functionalities in the cinchona backbone, a wide array of catalysts have been synthesized without need for extensive, time-consuming chiral resolution that often plagues other catalyst syntheses. Catalytic asymmetric synthesis is an extremely important tool and based on their track record, cinchona alkaloids will continue to play a pivotal role.

¹⁷ (a) Jacobsen, E. N.; Marko, I.; Mungall, W.S.; Schröder, G.; Sharpless, K. B.; *J. Am. Chem. Soc.* **1988**, *110*, 1968-1970. (b) Becker, H.; Sharpless, K. B. *Angew. Chem Int. Ed. Engl.* **1996**, *35*, 448-451. (c) Fache, F.; Schultz, E.; Tommasino, M. L.; Lemaire, M. *Chem. Rev.* **2000**, *100*, 2159-2231.

¹⁸ Corey, E. J.; Noe, M. C. *J. Am. Chem. Soc.* **1996**, *118*, 11038-11053.

¹⁹ Li, G.; Chang, H. -T.; Sharpless, K. B. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 451-454.

²⁰ Annunziata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F. *Eur. J. Org. Chem.* **2001**, 1045-1048.

