Cinchona Alkaloids in Organic Catalysis

Bredig/Fiske (1912):

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\text{PhMe, 25 °C, 24 h}
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Pracejus (1960):

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\text{PhMe, 25 °C, 1–7 h}
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Active sites in cinchona alkaloids and their derivatives:

- \( R^1 \) = i. a., OH or thioureas
  - 1. H-bond donor or acid
  - 2. metal coordination

Nitrogen of quinuclidine
- 1. metal-binding ability
- 2. Brønsted base
- 3. Lewis base catalyst
- 4. N-alkylation: phase-transfer catalysis

Significance: In 1912, Bredig and Fiske published the first example of asymmetric (nonenzymatic) (organo)catalysis. They reported the addition of HCN to benzaldehyde catalyzed by the pseudo-enantiomeric alkaloids quinine and quinidine, with low but reproducible enantioselectivities. About four decades later, Pracejus, for the first time, achieved reasonable enantioselectivities (74% ee) by using \( O \)-acetylquinine as an organocatalyst. This groundwork paved the way to a variety of cinchona-alkaloid-catalyzed asymmetric transformations in industry and academia.

Comment: Cinchona alkaloids are among the most privileged asymmetry inducers in the area of enantioselective catalysis. They possess a chiral skeleton that is easily modifiable. In the last century, methodologies were developed in which they were used as chiral bases, as chiral Lewis base catalysts, in ligand-accelerated catalysis, or as quaternized ammonium salts in phase-transfer catalysis, among others. Current research continues to showcase their importance and utility in asymmetric catalysis, for example by incorporating other privileged organic catalophores such as thioureas.