Cinchona Alkaloids in Organic 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.

**Bredig/Fiske (1912):**

\[
\text{PhMe, 25 °C, 24 h}
\]

**Pracejus (1960):**

\[
\text{PhMe, 25 °C, 1–7 h}
\]

**Active sites in cinchona alkaloids and their derivatives:**

\[R^1 = \text{H, a, OH or thioureas}\]

1. H-bond donor or acid
2. Metal coordination
3. Aminocatalysis
4. H-bond donors (e.g. ureas, squaramides, amides)

**Nitrogen of quinuclidine:**

1. Metal-binding ability
2. Brønsted base
3. Lewis base catalyst
4. N-alkylation: phase-transfer catalysis