CHAPTER 1

INTRODUCTION: A HISTORICAL POINT OF VIEW

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Organocatalysis is commonly accepted as the use of small organic molecules to catalyze organic transformations. The term "organocatalysis" was coined by David W. C. MacMillan at the beginning of the twenty-first century and was the starting line for breathtaking progress in this area over the last decade. During recent years, this area has grown into one of the three pillars of asymmetric catalysis, complementing and sometimes improving bio- and metal catalysis. The rapid growth in this area can be easily explained: The field offers several advantages to researchers in academia and industry, such as (a) easy and low-cost reactions and (b) reactions that are insensitive to air or moisture (unlike organometallic chemistry). Furthermore, the small chiral organic molecules used as catalysts can be often be derived from nature; thus, they are accessible and inexpensive to prepare, and often the processes are environmentally friendly. Moreover, the need in industrial large-scale production for removal of impurities related to toxic metal catalysts from the waste stream, which has a huge financial impact, could be avoided with the use of organocatalysts; this has made the field very interesting from the industrial point of view.

The renaissance of organocatalysis was at the beginning of the twenty-first century, but the origins of small organic molecules acting as catalysts can be traced back to the earliest works of Emil Knoevenagel [1]. In these works, Knoevenagel studied the use of primary and secondary amines, as well as their salts as catalysts for the aldol condensation of β-ketoesters or malonates with aldehydes or ketones. Knoevenagel also suggested the same intermediates that Westheimer later proposed in his retro-aldolization studies. Another key development in the history of organocatalysis was the work of Dakin in 1910 regarding the catalytic activity of primary amino acids in the Knoevenagel reaction [2]. Twenty years later, Kuhn and Hoffer found secondary amines that catalyzed not only the Knoevenagel reaction but also the aldol reactions between aldehydes [3].

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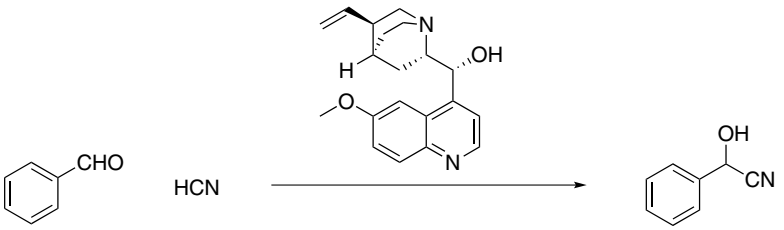


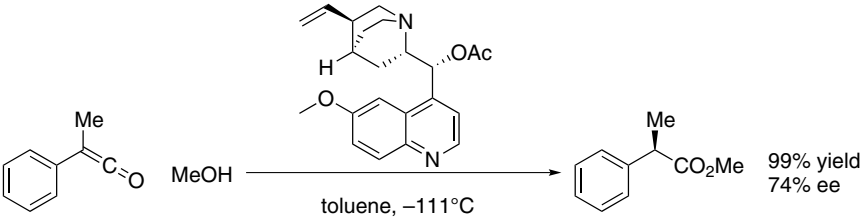
SCHEME 1.1. Hydrocyanation reported by Bredig in 1913.

Another important highlight in organocatalysis was developed by Bredig, who reported the addition of HCN to benzaldehyde in the presence of cinchona alkaloids as catalysts to obtain mandelonitrile with less than 10% ee. However, the importance of this reaction is, from a conceptual point of view, groundbreaking (Scheme 1.1) [4].

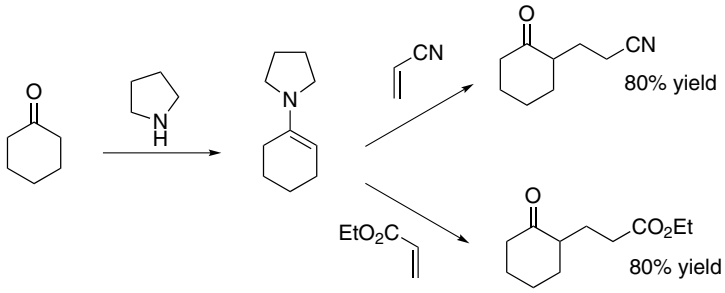
Following the earliest works of Bredig, Pracejus developed the first reactions with good levels of enantioselectivity. Pracejus reported the addition of methanol to methyl phenyl ketene catalyzed by *O*-acetyl quinine (Scheme 1.2) [5].

Later, Fisher and Marshall used primary amino acids to catalyze aldol and condensation reactions of acetaldehyde [6]. Following these inspiring results, in 1936 Kuhn discovered that carboxylic acid salts of amines effectively catalyze the aldol reaction [7]. Piperidinium acetate was used by Langenbeck and Sauerbier in their studies on the catalytic hydration of crotonaldehyde [8]. Interestingly, Langenbeck suggested a Kuhn–Knoevenagel-type covalent catalysis mechanism and introduced secondary amino acids (sarcosine) as catalysts for aldolization. An important contribution to the field of organocatalysis was made by G. Stork with his work on enamine chemistry. Most of the subsequent work in organocatalysis was first conducted by Stork's research group with preformed enamines (Scheme 1.3) [9]. These studies and findings arguably led to one of the most important highlights in organocatalysis: the Hajos–Parrish–Eder–Sauer–Wiechert reaction.

As stated above, the studies of Wieland and Miescher, as well as Woodward, on the intramolecular aldol reaction of diketones and dialdehydes were encouraged by this previous work. Wieland, Miescher, and Woodward studied the application of the intramolecular aldol reaction, catalyzed by secondary amine salts, to the synthesis of steroids and believed that their aldolizations proceed via enamine intermediates [10]. This was corroborated by the mechanistic studies carried out by Spencer in 1965 [11]. Based on these works, Hajos and Parrish (1974) and Eder, Sauer, and Wiechert



SCHEME 1.2. Addition of methanol to ketenes reported by Pracejus.



SCHEME 1.3. Reactions developed by Stork with preformed enamines.

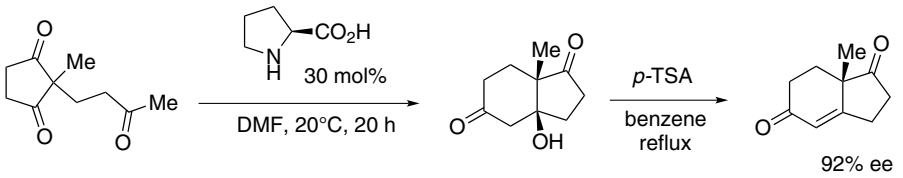
(1971) independently developed the first asymmetric, amine-catalyzed aldolization [12]. They choose proline as a catalyst based on previous work that showed the viability of amino acids as catalysts for aldol reactions (Scheme 1.4). However, neither of these groups proposed the enamine mechanism for the reaction.

Woodward probably conducted the most outstanding work on iminium catalysis before its rebirth in 2000. In this work, Woodward applied proline catalysis in a triple organocascade reaction consisting of a deracemization (via a retro-Michael, Michael addition) and an intramolecular aldol reaction that determine the stereochemical outcome of the reaction (Scheme 1.5), leading to the synthesis of erythromycin [13].

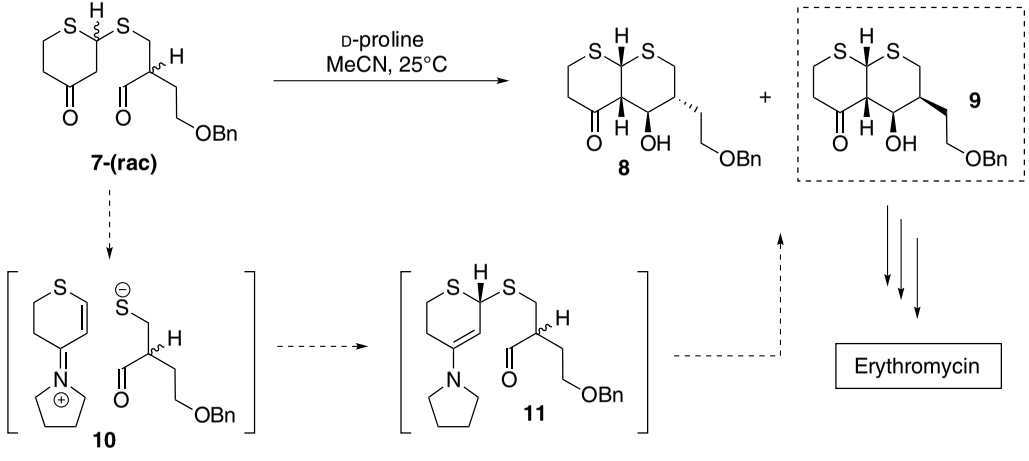
Based on Pracejus's previous work with cinchona alkaloids, Bergson and Langstrom developed the Michael addition of β-ketoesters to acrolein catalyzed by 2-(hydroxymethyl)quinuclidine. Soon after, Wynberg developed several organocatalytic reactions using cinchona alkaloids as chiral Lewis base/nucleophilic catalysts [14].

During the period between the late 1970s and early 1980s, a large number of reactions that proceeded via ionic pairs were developed. Inoue conducted remarkable work on the use of chiral diketopiperazines as chiral Brønsted acids in the hydrocyanation of aldehydes [15]. The mechanism of this reaction, which exhibits high levels of autocatalysis, remains elusive despite the work of Schvo that suggests the presence of two molecules of the catalyst in the transition state [16]. This early work is the first example illustrating that a simple peptide-based catalyst could perform asymmetric transformations and was probably the source of inspiration of the later works of Lipton, Jacobsen, and Miller [17].

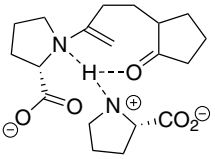
Another important fact was reported in the 1980s; Agami and co-workers studied the application of proline in an enolendo aldolization reaction. Their mechanistic studies showed nonlinear and dilution effects that suggested the involvement of two molecules of proline in the transition state (Scheme 1.6) [18].



SCHEME 1.4. Reaction of Hajos and Parrish in 1974.



SCHEME 1.5. Key step for Woodward's synthesis of erythromycin.



SCHEME 1.6. Mechanism suggested by Agami.

Another important highlight in organocatalysis was also developed in the 1980s. Julia and Colonna reported the epoxidation of enones by H_2O_2 catalyzed by poly-L-leucine. This example is formally the first use of hydrogen-bonding catalysis in asymmetric synthesis (Scheme 1.7) [19].

In middle of the 1980s, efficient asymmetric phase-transfer reactions using catalytic amounts of *N*-benzylcinchoninium chlorides were developed by researchers at Merck. This catalyst was able to alkylate 2-substituted-2-phenyl indanones with high ee (up to 94% ee) [20].

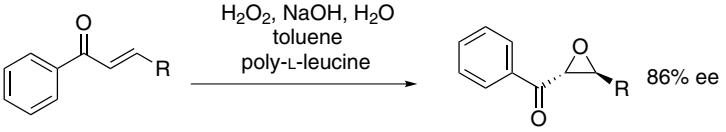
An important addition was the work by Kagan involving chiral amines in cycloaddition reactions. Kagan showed that chiral bases such as quinidine or prolinol catalyze the cycloaddition between anthrones and maleimides with moderate enantioselectivities [21].

In the 1990s, Yamaguchi and Taguchi used proline derivatives (or lithium or rubidium salts of proline) as catalysts for the enantioselective Michael reactions of enals and suggested iminium ion activation as the catalytic principle [22].

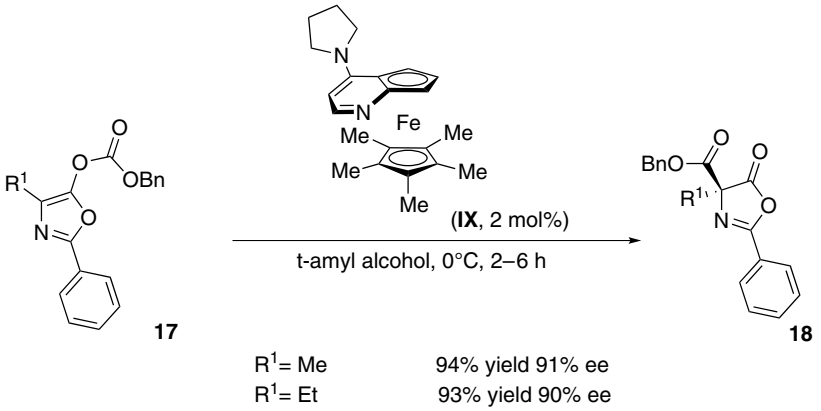
In the late 1990s, several research groups worked on the development of chiral DMAP analogs. The works of Fu [23], Vedejs [24], and Fuji [25] led to the synthesis of powerful catalysts and the development of enantioselective organocatalytic reactions such as Steglich rearrangements, kinetic resolutions of secondary alcohols, kinetic resolution of amines, and so on (Scheme 1.8).

In 1996, Shi made a huge development in this area, reporting the asymmetric epoxidation of alkenes using chiral dioxiranes generated *in situ*. The epoxidation works well for disubstituted *trans*-olefins, and trisubstituted olefins using a fructose-derived ketone as a catalyst and oxone as an oxidant (Scheme 1.9) [26].

However, all of these wonderful contributions had a limited impact in the field of organic chemistry. The "renaissance" of organocatalysis came with the works of List, Barbas, and Lerner [27] in enamine chemistry and the works of D. W. C. MacMillan [28] in iminium chemistry in 2000. Since then, enormous efforts have been made by the chemical community toward the development of new catalysts and methodologies without the use of metals.

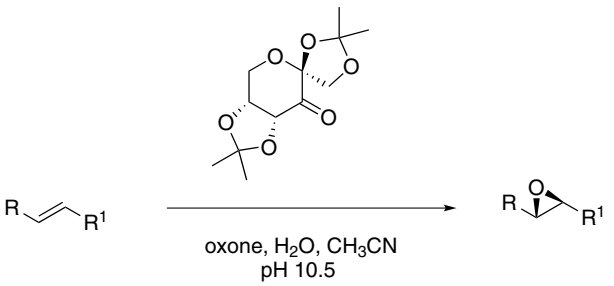


SCHEME 1.7. Julia–Colonna epoxidation.



SCHEME 1.8. Steglich rearrangement developed by Fu.

Owing to the huge number of reactions and methodologies, it would be difficult to highlight the most important developments. However, some of the most significant achievements in the area of organocatalysis in later years are as follows: the Friedel–Crafts reaction developed by MacMillan in 2001 [29], development of bifunctional base–thiourea catalysts by Takemoto in 2003 [30], reduction of enals developed independently by List and MacMillan in 2005 [31], development of new phosphoric acid derivatives as chiral Brønsted acids by Akyama and Terada in 2004 [32], the first organocascade reaction by MacMillan in 2005 [33], enantioselective reductive amination developed almost simultaneously by Rueping, List, and MacMillan in 2005 [34], epoxidation of enals reported by Jorgensen in 2005 [35], the first aldehyde addition of nitroalkenes developed by Hayashi in 2005 [36], the multicomponent organocatalytic cascade developed by Enders in 2006 [37], development of asymmetric counteranion-directed catalysis (ACDC) by List in 2006 [38], the first amine conjugate addition to enals developed by MacMillan in 2006 [39], the first organocatalytic aziridination of enals developed by Cordova in 2007 [40], development of SOMO catalysis by MacMillan in 2007 [41], and development of photoredox catalysis by MacMillan in 2009 (Figure 1.1) [42].



SCHEME 1.9. Shi epoxidation of olefins.

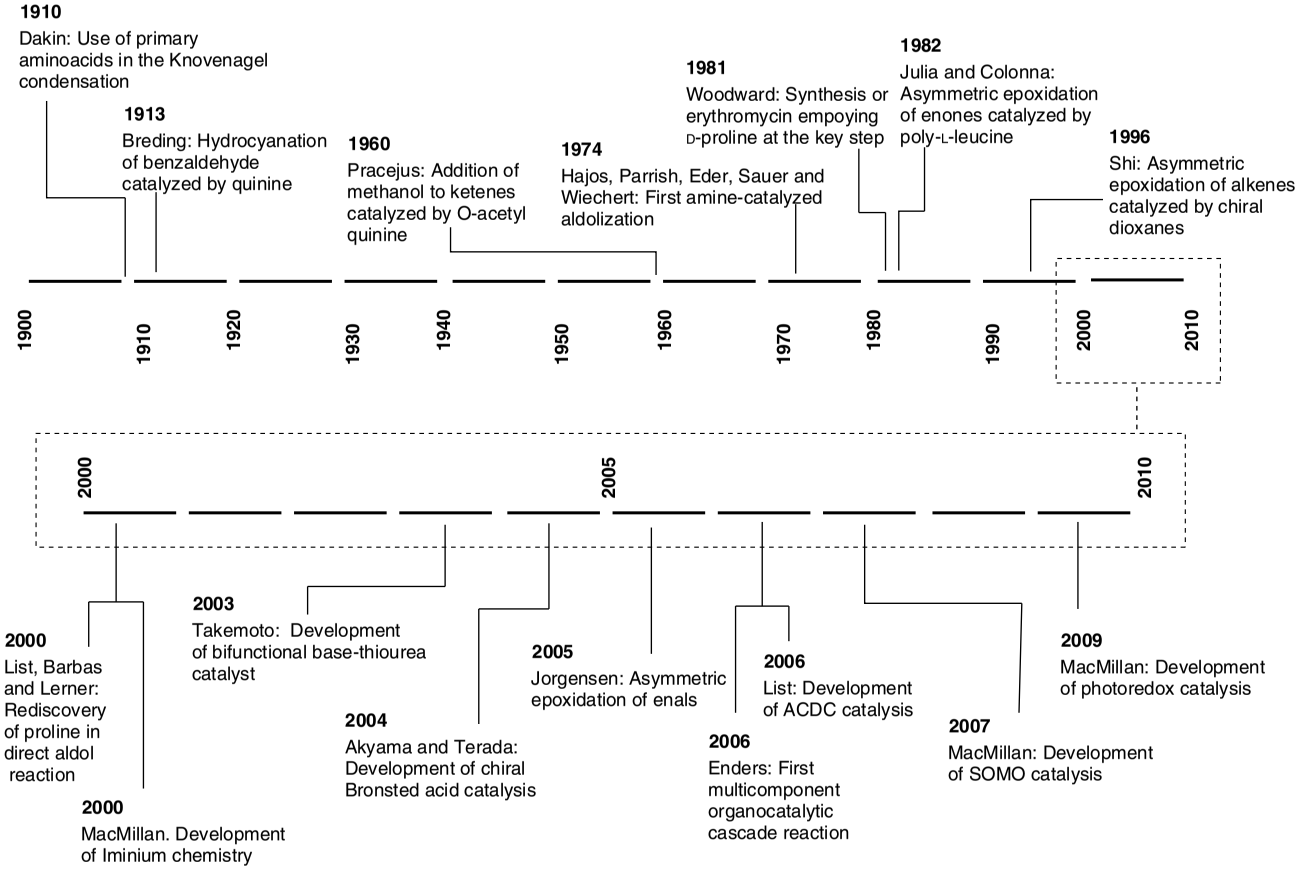


FIGURE 1.1. Organocatalysis timeline.

The importance of organocatalysis is clear, owing to the number of studies reported in the literature. In recent years, new avenues have been explored in organocatalysis, providing new activation modes and new powerful methodologies. Moreover, the possibility of joining an organocatalytic reaction and organometallic reaction together in a one-pot procedure has recently increased the scope of this field. For this reason, I envision a great future for organocatalysis in which reactions of increasing complexity, along with new and more active catalysts, will be developed.

In this book, we try to give an overview of the field of organocatalysis with particular emphasis on later developments in the field. First, we will introduce the different activation modes and catalysts. Next, we show a different approach of organocatalysis not based on the different activation modes, but based on the nature of the bond formed. From C–C bond forming reactions to C-heteroatom bond formation through cascade, multicomponent reactions, we will try to give a clear of the state-of-the-art picture of this field.

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