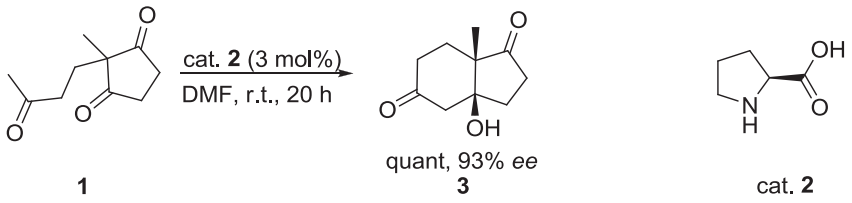
4 Introduction

Foreseeing a whole era of research, *K. B. Sharpless* summarized his findings on the asymmetric epoxidation reaction in 1986 as follows: "Is the asymmetric epoxidation an anomaly? I think not. Investigations by chemists should unearth more highly selective non-enzymatic catalysts in the years ahead. Asymmetric epoxidation is at the tip of a new iceberg that has selective abiological catalysis as its base."[1]

Discovering efficient catalytic processes to obtain enantiomerically pure substances defines the task of a major part of chemical research. The need for pharmaceuticals, agrochemicals and synthetic intermediates is apparent and increasing. Asymmetric organocatalysis has emerged as a new concept between the "extremes of transition metal catalysis and enzymatic transformations."[2]

4.1 Organocatalysis

Even though metal-free catalysis of organic transformations has long been known, the term organocatalysis only emerged relatively recently, defining a fast-growing field of organic chemistry.[3] Dating as far back as 1860, *J. von Liebig*'s formaldehyde-catalyzed oxalamide synthesis merits acknowledgment as the first "man-made" organocatalytic reaction.[4] Furthermore, the more recent (1970s) discovery of the *L*-proline (**2**)-promoted asymmetric Robinson annulations, the so-called *Hajos-Parrish-Eder-Sauer-Wiechert* reaction, represents the most prominent cornerstone of the entire field (Scheme 1).[5]



Scheme 1 *L*-proline-catalyzed Robinson annulations.[5]

This reaction is still among the most powerful organocatalytic reactions, frequently applied in industrial processes. *L*-proline catalysis belongs to the field of covalent catalysis, indicating a covalent ("true") bond between the catalyst and a substrate within the reaction pathway. Conversely, non-covalent organocatalysis has emerged as a second field. Weaker catalyst-substrate interactions such as neutral guest-host complexation or acid/base association plays a

mechanistically essential role herein. As an example of this kind of catalytic method, hydrogen-bond catalysis will be described in this work.

Why has so much interest been drawn to this relatively new field of catalysis? The advantages of asymmetric, organocatalytic approaches compared to their metal-catalyzed equivalents are manifold. Organocatalysts are usually bench-stable and are, in most cases, readily available, rendering them comparatively inexpensive and environmentally friendly. Small organic molecules enabling enantioselective transformations constitute a valuable alternative to metal-catalyzed transformations. Developing asymmetric methodologies to obtain enantiomerically pure compounds is without a doubt one of the major tasks of organic chemistry, being applied in natural product synthesis or, even more importantly, in the large-scale production of pharmaceuticals and agrochemicals. Considering atom-economy, any method of obtaining an enantiomerically enriched compound *via* catalysis, as compared to the resolution of a racemic mixture, is always favored. Ideal catalysts are only required in substoichiometric amounts and can ideally be re-isolated. Various methods for the resolution of racemic mixtures exist, such as the resolution *via* chromatographic or crystallographic separation of the enantiomers, or the separation of diastereomeric adducts, usually obtained through the use of chiral auxiliaries. Regardless, only 50% of the desired enantiomer can be obtained by these means. Obviously this does not take into account the dynamic kinetic resolution method, in which theoretically 100% of one enantiomer can be obtained.[6] The applicability of this method is unfortunately not yet too versatile. Above all, any resolution of enantiomers not only involves additional synthetic steps, which can be avoided through asymmetric synthesis, but also, according to *Knowles*, "every organic chemist is frustrated about having to resolve racemic mixtures."[7] The most apparent method, making use of "chiral pool" synthesis, and thus using enantiomerically pure compounds available from nature, is not always feasible, either because the desired compound cannot be synthesized from any commercially available, chiral starting material, or else, only the undesired enantiomer exists in nature.

Despite its many advantages, organocatalysis does not yet rival metal catalysis. Powerful catalytic processes that have found their way into industrial application, such as the asymmetric *Noyori* hydrogenation,[8] or the *Sharpless*[9] and *Jacobsen-Katsuki*[10] epoxidation, remain unmatched in organocatalysis. Major drawbacks, such as high catalyst loadings or the lack of versatility with respect to varying substrates, continue to compell fundamental research in this field to ultimately overcome these obstacles.

4.1.1 Hydrogen-bond interactions

The hydrogen bond is a tremendously important interaction that plays a vital role in all fields of chemistry, in particular in molecular interaction and recognition in biological systems.[11]

According to *Steiner*, a hydrogen bond is a [X-H · · · A] interaction, if it a) constitutes a local bond, and if b) X-H acts as a proton donor to A. In the hydrogen bond [X-H · · · A], the group X-H is called the hydrogen-bond donor and A is called the hydrogen-bond acceptor.[12] The strength of hydrogen bonds has been classified into three types: strong, moderate and weak (Table 1).[13]

Table 1 Properties of hydrogen bonds.[14]

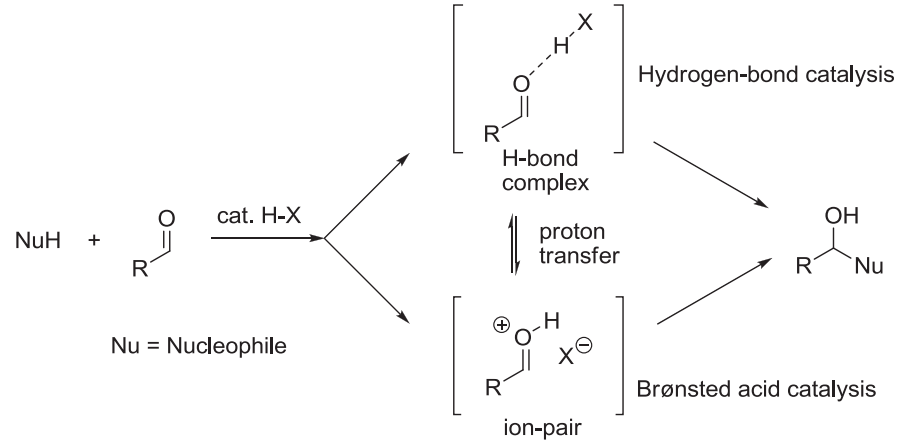
	Strong	Moderate	Weak
Type of bonding	Mostly covalent	Mostly electrostatic	Electrostatic
Length of H-Bond (Å)	1.2-1.5	1.5-2.2	2.2-3.2
Bond angles (°)	175-180	130-180	90-150
Bond energy (kcal/mol)	14-40	4-15	<4

The transition between the three classes of hydrogen bonding is diffuse, and often hard to define. Hydrogen-bond interaction occurring in organocatalytic mechanisms usually belongs to the weaker class of hydrogen bonds. Organocatalytic approaches that are based on hydrogen-bond interactions can be divided into two groups: hydrogen-bond catalysis and Brønsted-acid catalysis. The scope of this introduction does not allow an exhaustive presentation of all existing catalytic systems, though key examples will be mentioned.

4.1.2 Organocatalysis based on hydrogen-bond interactions

The last decade has given rise to the development of various hydrogen bond-based organocatalytic systems.[15] The most prominent systems include Thiourea-[16], TADDOL-[17], and BINOL-[18]derived catalytic systems. Though a classification of these systems is not straightforward, the first two systems are defined hydrogen-bond catalysts, whereas acids such as BINOL-derived phosphoric acids[15i,j,19] are considered Brønsted-acid catalysts. One

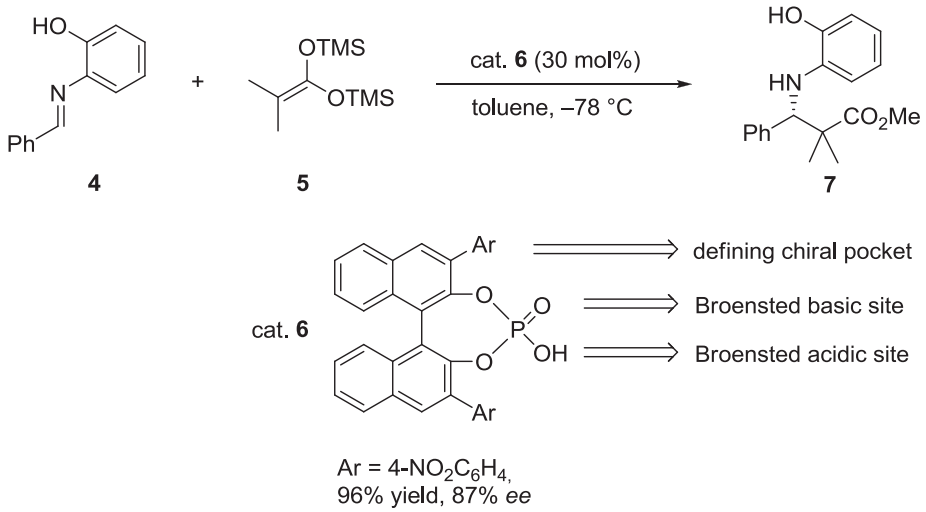
possible definition is illustrated in Scheme 2. If a catalyst H-X activates a carbonyl compound for nucleophilic attack, either a hydrogen-bond complex is formed (hydrogen-bond catalysis), or else an ion-pair is formed (Brønsted-acid catalysis).[14]



Scheme 2 Hydrogen-bond catalysis versus Brønsted-acid catalysis.

4.1.3 Brønsted-acid catalysis

Especially BINOL-derived phosphoric acids (**6**), in particular, proved to be a powerful chiral catalytic system.[15i,20] *Akiyama* developed the first application of this class by catalyzing the addition of silyl ketene acetales to aldimines (Scheme 3).[20]



Scheme 3 BINOL-derived phosphoric-acid (**6**) catalyzed addition of silyl ketene acetales to aldimines.[20]

The binaphthyl skeleton of these compounds bears axial chirality, and, together with bulky substituents in 3,3´ position, a chiral pocket is defined. For Ar = H, enantioselective transformation cannot be observed. Activation of the aldimine substrate occurs through

double activation *via* protonation of the aldimine on one side, and hydrogen-bond formation between the *ortho*-hydroxy group and the Brønsted basic site of the catalyst. This class of catalysts has been applied in various organic transformations, such as hydrophosphonylations,[21] Diels-Alder reactions,[22] Friedel-Crafts-type reactions,[23] (Nazarov)-cyclyzations[24] as well as transferhydrogenations,[25] the latter being described in more detail later in this work. Further advancing the aforementioned concept, *Yamamoto* developed even more acidic *N*-triflyl phosphoramides, synthesized from BINOL-derived phosphoric acids.[26] This modification enabled the activation of less Lewis-basic substrates compared to the imine (**4**). Ethyl vinyl ketone, activated for enantioselective Diels-Alder reactions with siloxy dienes, is just one example of this improvement in activity.

Furthermore, TADDOL-based phosphoric acid diesters (**8**) (Figure 1) have been developed and applied successfully in Mannich-type reactions.[27]

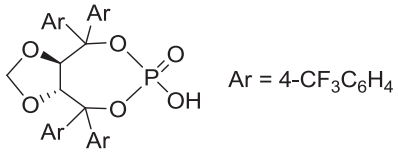


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Figure 1 TADDOL-derived phosphoric acid derivatives.

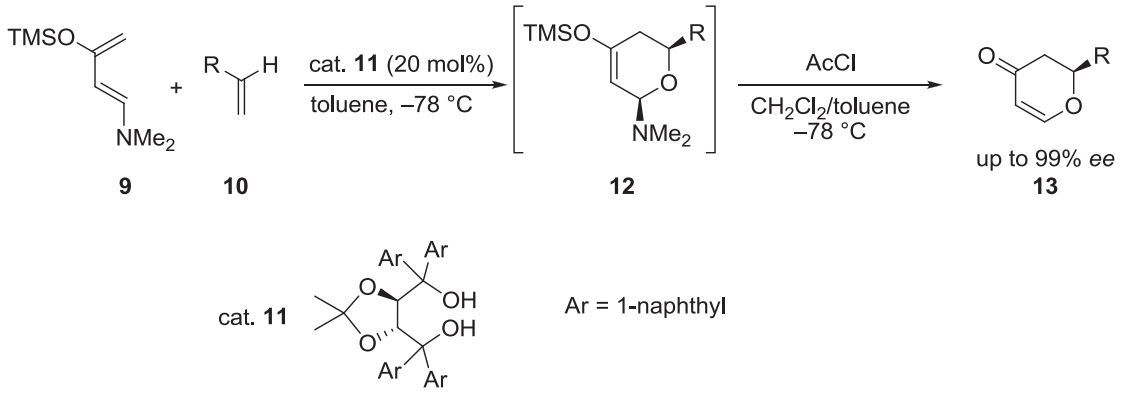
Organocatalysts based on the TADDOL moiety occur in the literature more often in their role as hydrogen-bond catalysts.

The large field of hydrogen-bond catalysis primarily divides into the different approaches to create sterically defined hydrogen-bond donor systems. Two major groups, chiral diols and thiourea systems, will be described below.

4.1.4 Chiral diols

Chiral diols and biphenols turned out to be highly potential hydrogen-bond catalysts. Once again, derivatives of BINOL and TADDOL most significantly represent this class of compounds. The initially assumed mode of action for these catalysts included the activation of substrates through two independent hydrogen bonds. Earlier studies on Diels-Alder reactions catalyzed by achiral biphenylenediols reinforced this assumption.[28] TADDOL derivatives have been widely investigated and applied as chiral auxiliaries by *Seebach* and others.[29] The first application of TADDOL derivatives as chiral hydrogen-bond donors (**11**)

was revealed by *Rawal* in the hetero-Diels-Alder reaction of aminosiloxydiene (*Rawal´*s diene) with benzaldehydes[30] (Scheme 4) and α,β-unsaturated aldehydes.[17]



Scheme 4 TADDOL-catalyzed hetero-Diels Alder reaction.[30]

Yamamoto et al. applied the same catalyst in a regio- and enantioselective nitroso-aldol cyclyzation reaction.[31] Based on the same structural idea, *Yamamoto* and *Rawal* also developed axially chiral 1,1`-biaryl-2,2`-dimethanol (BAMOL) as an effective catalyst in Diels-Alder reactions.[32] X-ray analysis of a BAMOL-benzaldehyde adduct revealed the probable mode of action of this class of catalysts (Figure 2). The diol forms an *intra*molecular hydrogen bond, thereby enhancing the acidity of the second hydroxy functionality. This leads to a highly coordinated and strong intermolecular hydrogen bond with the respective carbonyl substrate.

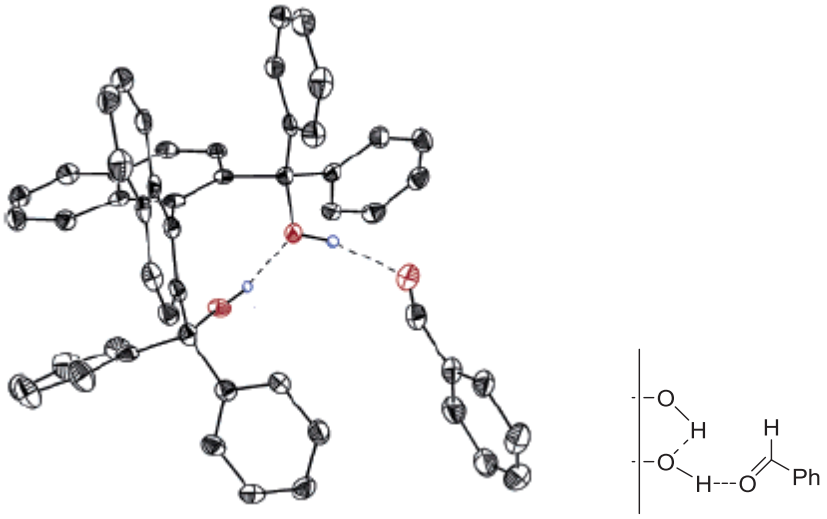
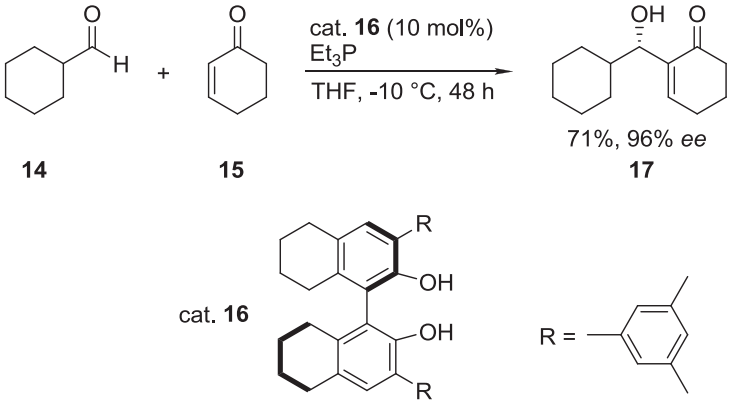


Figure 2 X-ray structure of an HBHB-supported catalyst-substrate complex (BAMOL-benzaldehyde) (left) and the illustrated principle (right).[32]

This principle, which also applies to TADDOL-derived hydrogen-bond catalysts, is often referred to as a hydrogen-bond-promoted hydrogen bond (HBHB) or a Brønsted-Acid-

Assisted Brønsted Acid (BBA).[14] This is yet another example to demonstrate the similarities between Brønsted-acid- and hydrogen-bond catalysis in this case.

Furthermore, BINOL-derivatives themselves were applied as hydrogen-bond donor catalysts. *Schaus et al.* developed the hydrogen-bond-mediated enantioselective Morita-Baylis-Hillman reaction of cyclohexenone (**15**) with different aldehydes (Scheme 5).[18] The diol **16** used stabilizes the phosphonium enolate of cyclohexenone *via* hydrogen bonding, creating a chiral nucleophile.



Scheme 5 Morita-Baylis-Hillman reaction, promoted by saturated BINOL derivatives.[18]

4.1.5 Thiourea catalysis

The field of thiourea catalysis was discovered by *Curran* as early as 1994.[33] However, it is through the work of *Jacobsen et al.* in 1998 that this subject has become as prominent as it is today.[34]

The discovery of (thio)urea derivatives capable of catalyzing organic transformation started with the biphenylenediols **18** and **19** (*Hine et al.*, 1985) (Figure 3).[28] They were found to effectively catalyze the aminolysis of epoxides (Figure 3 a)) and also promote the Diels-Alder reaction between cyclopentadiene and α,β-unsaturated aldehydes and ketones through double hydrogen bond donation to the dienophile (Figure 3 b)).[35]

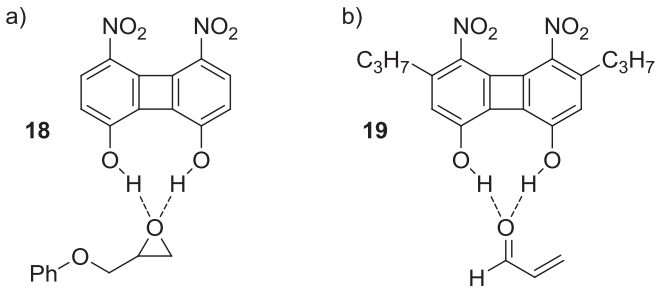


Figure 3 Activation of epoxides (a) and unsaturated ketones (b) through biphenylenediols.[35]

Even though these catalytic systems were not very efficient, they lay the foundation for the principle of catalysis with conformationally restricted double hydrogen bond donors.

The first studies on ureas and their capacity to form restricted hydrogen bonds to substrates with Lewis-basic functionalities derived from the field of supramolecular chemistry. *Etter et al.* proved that rigid urea systems could build co-crystallizable adducts (**20**) with substrates such as electron-deficient ketones, nitroaromatics or sulfoxides through the formation of two defined hydrogen bonds (Figure 4).[36]

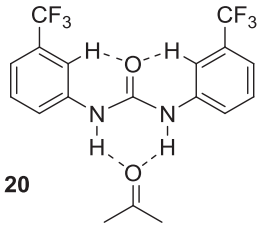
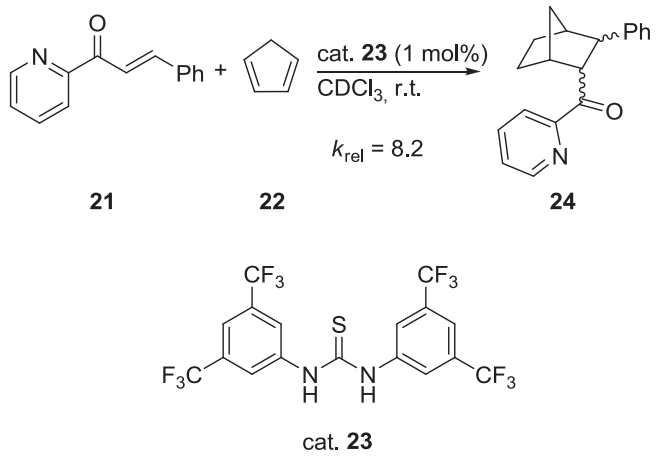


Figure 4 Co-crystallization of electron-deficient ureas with ketones.[36]

Similar urea derivatives were subsequently discovered as catalysts in the allylation of sulfinyl radicals[33] and also Claisen rearrangements by *Curran et al.*[37] A common problem in the application of urea derivatives in organic transformations, namely their poor solubility in common organic solvents, was then solved through the introduction of lipophilic side-chains or through the use of a sulfur analogue, the thiourea. One of the most powerful catalysts to date was developed by *Schreiner et al*. in 2002. Simple *N*,*N*′-diarylthiourea derivatives proved to be efficient catalysts in the Diels-Alder reaction of cyclopentadiene and a range of enones and α,β-unsaturated carbonyl compounds. The tetra(trifluoromethyl)-substituted thiourea **23** turned out to be especially effective, enhancing the reaction rate to k_{rel} = 8.2 (Scheme 6).[38]



Scheme 6 *Schreiner´*s electron-deficient *N*,*N`*-diphenyl thiourea and its application in a Diels-Alder reaction.[38]

This structure bears several advantages compared to the aforementioned catalysts. Using a thiourea instead of urea functionality improves the solubility in organic solvents. Furthermore, as a weaker hydrogen-bond acceptor than its urea analogue, the thiocarbonyl group results in less self-association of the catalyst and therefore a higher concentration of the free catalyst in solution. Additionally, thiourea derivatives are more acidic compared to urea derivatives, proving an essential tool for the formation of stable catalyst-substrate complexes formed through hydrogen bonds.[14] The capability of this system is further reinforced by the rigidifying S-H interaction between the *ortho*-aryl-hydrogen atoms and the Lewis-basic sulfur atom, thus leading to a high rotational barrier of the catalyst and consequently to stable catalyst-substrate complexes. This can be explained through the smaller entropy loss that rigid thiourea systems undergo when binding to a substrate, compared to those with a low rotational barrier. The enthalpic binding energy between carbonyl substrates and thiourea systems is rather low (~7 kcal mol^{-1} at r.t.), which makes the loss of entropy even more important. Due to its versatility, *Schreiner´*s catalyst is often used as a benchmark catalyst for initial studies on new organocatalytically promoted transformations.

The first application of thiourea catalysis in asymmetric transformations was developed by *Jacobsen et al*. Through a combinatorial approach, the so-called "Schiff-base"-derived thiourea **26** was developed, promoting asymmetric Strecker reactions with high yields and high enantioselectivity (Scheme 7).[39]