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Privileged Catalyst Structures in Organocatalytic Reactions

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1.1 Introduction

Enantioselective organocatalysis employs chiral small organic molecules as catalysts to drive asymmetric reactions [1]. This approach has recently evolved into a versatile platform for the synthesis of a wide array of chiral molecules [2]. To a certain degree, organocatalysis inherits several advantageous features from enzymatic catalysis, notably high stereocontrol and mild reaction conditions [3]. Furthermore, it showcases the benefits of chemical catalysts, such as easy modification, high stability, and low molecular weight. The catalysts are the key to enantioselective organocatalysis, and their structures exhibit a rich diversity. They can range from the simplicity of molecules like proline to the intricate designs of synthetic polypeptides. The elegance of organocatalysts lies in their versatility and adaptability. They can be designed to incorporate multiple functional groups, enabling them to engage in various interactions with substrates. This flexibility allows for the precise adjustment of catalytic processes, facilitating high reactivity and selectivity under mild conditions. While multiple interactions can be introduced, the catalytic process is primarily governed by the structure and reactivity of the core catalytic group within the organocatalyst. Organocatalysis can be categorized into several types based on the interactions between catalysts and substrates (Scheme 1.1) [1]. Enamine catalysis [4], iminium catalysis [5], and singly occupied molecular orbital (SOMO) catalysis [6] are developed for asymmetric transformations of aldehydes, ketones, and their α,β-unsaturated derivatives using chiral amines as the catalysts, relying on imine/iminium intermediates formed between primary/secondary amine catalysts and aldehydes/ketones (Scheme 1.1a) [7]. Carbonyl catalysis, reverse to the process of enamine catalysis, also involves imine intermediates, utilizing chiral aldehydes/ketones as catalysts to promote asymmetric α-C—H transformations of primary amines (Scheme 1.1a) [8]. Brønsted acid–base interactions relate to Brønsted acid

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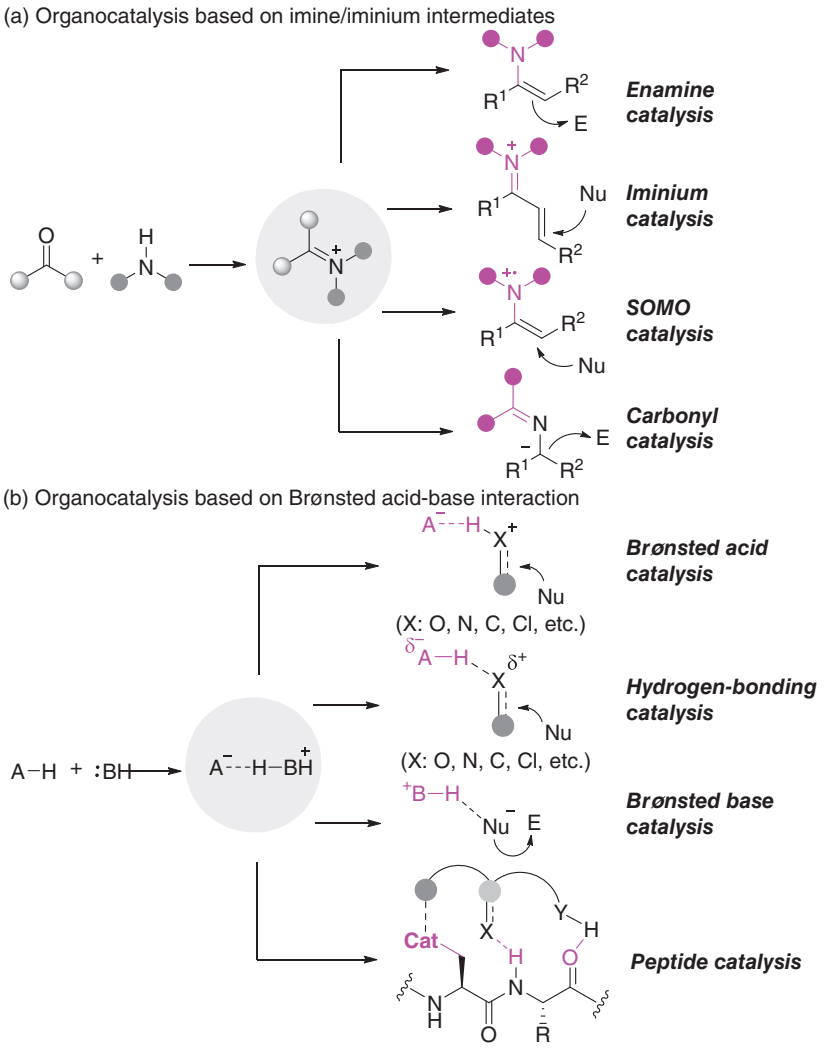
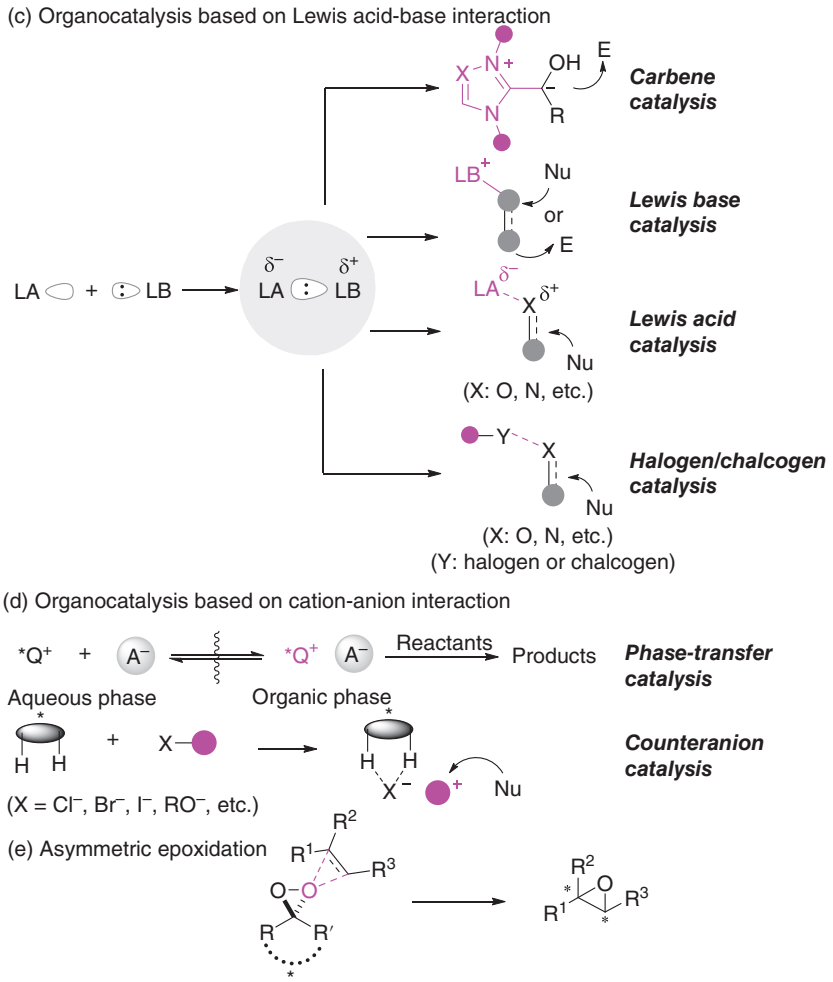


Scheme 1.1 Representative organocatalytic modes.

catalysis [9], hydrogen-bonding catalysis [10], Brønsted base catalysis [11], and peptide catalysis [12], enabling asymmetric reactions of proton-acceptor-containing electrophiles and proton-donor-containing nucleophiles (Scheme 1.1b). Enantioselective organocatalysis involving Lewis acid–base interactions includes carbene catalysis [13], Lewis base catalysis [14], Lewis acid catalysis [15], and halogen/chalcogen catalysis (Scheme 1.1c) [16]. They activate substrates containing blank orbitals or electron pairs through Lewis acid–base interactions, facilitating a wide array of asymmetric transformations. Although carbene catalysis also falls under Lewis base catalysis, it is treated separately due to its unique and versatile catalytic power and the resulting numerous transformations. Chiral cation–anion



Scheme 1.1 (*Continued*)

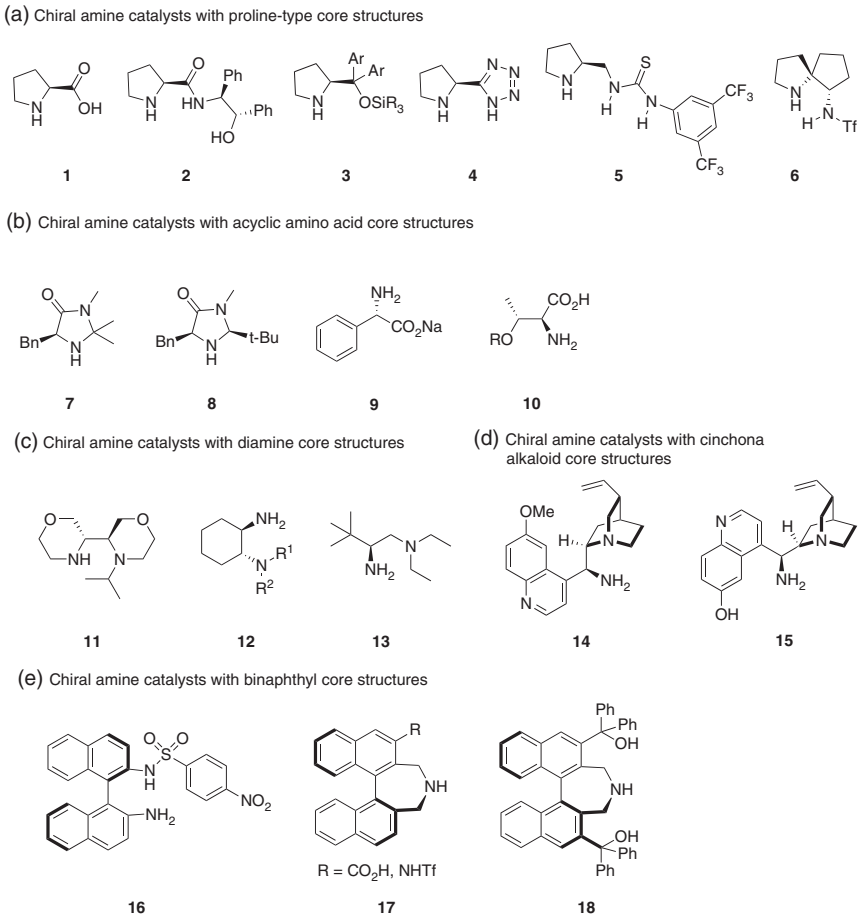
catalysis involves phase-transfer catalysis and counteranion catalysis (Scheme 1.1d). Phase-transfer catalysis provides an efficient strategy to facilitate asymmetric heterogeneous reactions [17]. Chiral counteranion catalysis utilizes chiral anions to create a chiral environment that influences the enantioselectivity [18]. Asymmetric epoxidation employs chiral ketones as catalysts to convert oxidants such as oxone into active dioxirane species, which enantioselectively transfer the electrophilic oxygen onto olefins (Scheme 1.1e) [19].

Along with the development of organocatalysis, a diverse range of chiral organic small molecule catalysts with privileged structural frameworks have emerged, facilitating numerous significant catalytic reactions and demonstrating limitless applications in chiral synthesis. This chapter will briefly discuss these representative organocatalysts, their activation modes, and the reactions they enable.

1.2 Catalysts for Organocatalysis Based on Imine/Iminium Intermediates

1.2.1 Chiral Amine Catalysts

The essence of amine-based asymmetric catalysis draws inspiration from biological enzymes, wherein the amino groups on the amino acid residues of enzymes serve as active sites for numerous biological reactions or as intramolecular bases for cooperative catalysis [3, 20]. Reports of amine catalysis can date back to the 1930s [21], but it was not until the year 2000s [22] that amine catalysis began to flourish [4, 5, 23]. Many privileged chiral amine catalysts have been developed. Proline (**1**) and its derivatives represent one of the most classic amine catalysts (Scheme 1.2a) [4, 22a, 24]. Despite a large number of substituted chiral prolines, the core structures involve prolinamide **2** [25], diarylprolinol/silicon-protected diarylprolinol **3** [26],



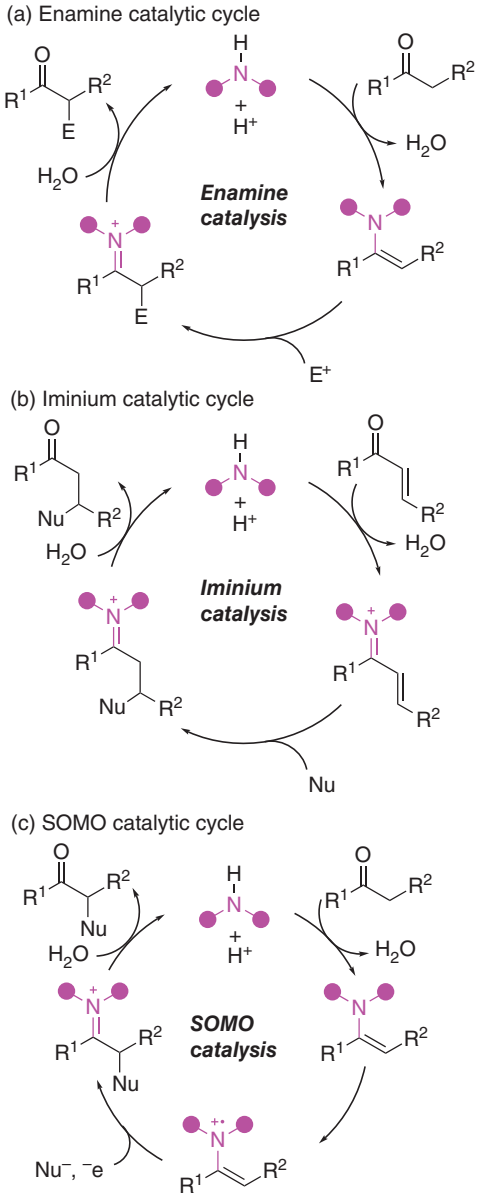
Scheme 1.2 Representative chiral amine catalysts with privileged core structures.

proline tetrazole **4** [27], proline thiourea **5** [28], and spiro-pyrrolidine **6** [29]. The five-membered secondary amines tend to form a relatively stable enamine or a highly activated iminium species with a carbonyl compound, assisted by an intramolecular carboxylic acid group or a hydrogen-bonding donor moiety or by an additional Brønsted acid co-catalyst. Acyclic amino acid-based chiral amine catalysts chiefly involve imidazolidinones and amino acids (salts) (Scheme 1.2b). Chiral imidazolidine-4-ones **7** and **8**, commonly referred to as Macmillan catalysts, can be readily prepared from phenylalanine. These catalysts possess the ability to catalyze the Diels–Alder cycloaddition reaction through an iminium activation mechanism [5, 22b, 30]. Phenyl glycine salt **9** [31] and threonine-derived compound **10** [32] could be used directly as catalysts [33]. Chiral amines with diamine moieties such as morpholine derivative **11** [34], diaminocyclohexanes **12** [35], and aliphatic diamine **13** [3, 23b, 36] have been recognized as valuable amine catalysts for many asymmetric transformations (Scheme 1.2c). Cinchona alkaloid derivatives **14** [37] and **15** [38] are a type of highly effective primary amine catalysts (Scheme 1.2d). The biaryl amines**16** [39], **17** [40, 41], and **18** [41] could demonstrate a distinctive catalytic proficiency due to the strategic placement of functional groups at the 2, 3, or 3,3′ positions on the biaryl framework (Scheme 1.2e).

Despite a wide array of chiral amine catalysts available, their principal activation mechanisms remain enamine and iminium catalysis [4, 5]. The structural diversity of these catalysts enables the creation of tailored chiral environments for specific reactions, which is essential for the production of significant enantioenriched compounds [4, 5, 23]. In the enamine activation mode (Scheme 1.3a), the principal reaction types include aldol reactions, Mannich reactions, Michael addition, and addition to other electrophiles [4, 5, 22a, 23]. On the other hand, in the iminium activation mode (Scheme 1.3b), reactions such as the Diels–Alder reaction, epoxidation, reduction, Friedel–Crafts reactions, conjugate addition, and nucleophilic addition to α,β-unsaturated or simple carbonyl compounds are typically studied [4, 5, 22b, 23]. Cascade, one-pot, and multicomponent reactions that proceed via the enamine or iminium activation mechanisms offer straightforward and efficient routes to synthesize chiral polycyclic and heterocyclic compounds [23c]. The selective one-electron oxidation of the enamine intermediate results in a 3π-electron SOMO-activated intermediates (Scheme 1.3c). This intermediate is capable of facilitating diverse α-functionalization reactions of carbonyl compounds [42].

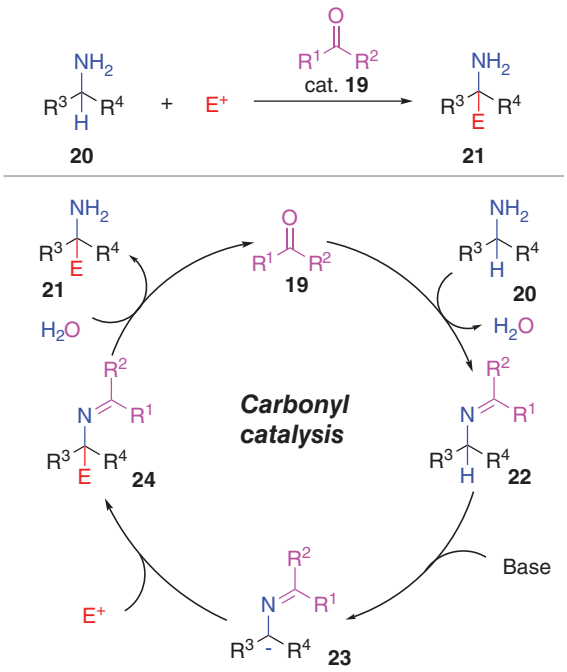
1.2.2 Carbonyl Catalysts

With the continuous development in recent years, carbonyl catalysis [43] has become a powerful strategy to access chiral α-substituted amines via catalytic enantioselective α-functionalization of primary amines. As a reverse strategy of enamine catalysis, carbonyl catalysis employs an appropriate aldehyde or ketone to activate a primary amine for direct α-C—H functionalization without protecting group manipulations toward the NH_2 group, producing diversified α-substituted amines in a one-step and atom-economic way [8, 44]. The catalytic cycle of carbonyl catalysis is illustrated in Scheme 1.4. Condensation of carbonyl catalyst **19** with



Scheme 1.3 The enamine, iminium, and SOMO catalysis cycles.

primary amine **20** forms imine **22**, which undergoes deprotonation of the α-C—H bond to furnish delocalization-stabilized carbanion **23**. The addition of active carbanion **23** to electrophiles (E^+) and subsequent hydrolysis deliver α-substituted amine **21** and regenerate carbonyl catalyst **19**, completing the catalytic cycle of the carbonyl catalysis. Notably, the α-C—H bond acidity of amine **20** is greatly

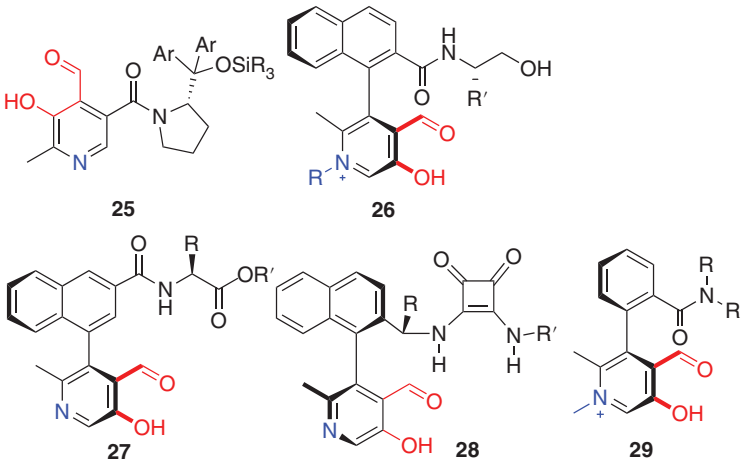


Scheme 1.4 Catalytic cycle of carbonyl catalysis.

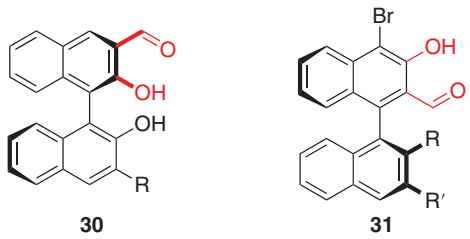
improved through the formation of imine **22** with carbonyl catalyst **19**, facilitating the C—H deprotonation [45].

The proposal of carbonyl catalysis was inspired by the enzymatic aldol reaction of glycine and aldehyde catalyzed by vitamin B_6-dependent L-threonine aldolase [43, 46], which is a classical process of biological carbonyl catalysis. Till now, a series of chiral carbonyl catalysts and novel asymmetric transformations have been reported. The carbonyl catalyst structures discussed in this section include vitamin B_6-derived chiral pyridoxals and 1,1′-Bi-2,2′-Naphthol (BINOL)-derived aldehydes (Scheme 1.5). Zhao group has developed a variety of pyridoxals with axial chirality (**26–29**) [3, 45a, c, 47] for enantioselective α-C—H functionalization of primary amines and pyridoxal with central chirality (**25**) [48] efficient for asymmetric transamination of α-keto acids. Chiral pyridoxals possessing diverse side chains (**26–29**) are highly effective carbonyl catalysts that can even activate highly challenging primary amines, such as propargylamines [45a] and benzylamines [45b] bearing inert α-C—H bonds. These chiral pyridoxals are capable of promoting the α-transformation of α-amino acid esters [3, 43, 47] and inert primary amines [45] without protection of the NH_2 group. The enzyme-like cooperative bifunctional activation accounts for the high activity and excellent stereoselectivity of the pyridoxal catalysts. Meanwhile, Guo group reported BINOL-derived chiral aldehydes **30** and **31** [49], which were utilized as a solo carbonyl catalyst or a co-catalyst combined with transition metals in α-functionalization of activated primary amines such as α-amino acid esters and aza-aryl methylamines. So far,

(a) Vitamin B_6-based chiral pyridoxal catalysts:



(b) BINOL-based chiral aldehyde catalysts:



Scheme 1.5 Representative chiral carbonyl catalysts.

various novel transformations of primary amines, such as aldol reaction [47c], Mannich reaction [43], 1,4-conjugated addition [47d, 49c], 1,6-conjugated addition [49e], α-alkylation [47f, 49b], allylic substitution [49d], and α-propargylation [45a, 49f], have been realized owing to those chiral carbonyl catalysts.

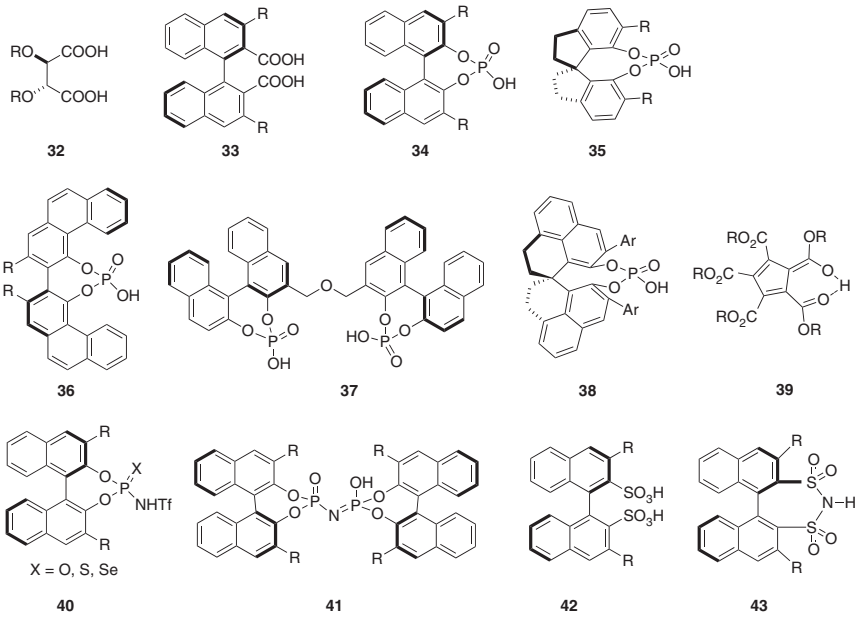
1.3 Catalysts for Organocatalysis Based on Brønsted Acid–Base Interactions

1.3.1 Brønsted Acid Catalysts

Chiral Brønsted acids have emerged as one of the most robust and significant organocatalysts [9, 50], with a booming development process since the first chiral phosphoric acid was invented by Akiyama and Terada in 2004 [51]. Although hydrogen-bonding catalysts, such as alcohols, squaramides, guanidines/guanidiniums, and (thio)ureas, can be classified into the category of weak Brønsted acids, the chiral Brønsted acid catalysts discussed herein mainly refer to protonic acids with relatively low pK_a values, such as carboxylic acids, phosphoric acids, and sulfonic acids. The acidity of these chiral Brønsted acids is

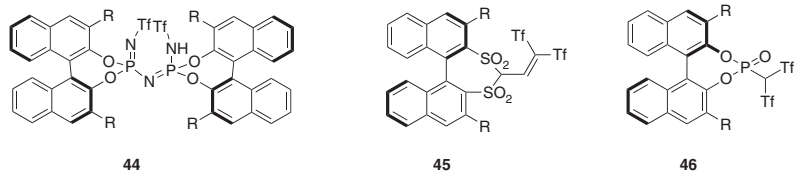
mainly determined by their acidic moieties. For example, α,α,α′,α′-Tetraaryl-1,3-dioxolane-4,5-dimethanol (TADDOL)-carboxylic acid **32** [52] and BINOL-derived carboxylic acid **33** [53] stand for typical weak Brønsted acid catalysts. Compared to chiral strong acids containing frameworks, like BINOL (**34)** [9, 50, 51] 1,1′-Spirobi[indane]-7,7′-diol (SPINOL) (**35)** [54], Vaulted 3,3′-Biphenanthrol (VAPOL) (**36)** [55], bisphosphoric acid unit (**37**) [56], 2,2′,3,3′-tetrahydro-1,1′-spirobi[phenalene]-9,9′-diol (SPHENOL) (**38)** [57], and 2,3,4,5-pentacarboxycyclopentadiene (PCCP) (**39**) [58], stronger acidic *N*-triflylphosphoramides **40** [59], imidodiphosphate **41** [60], sulfonic acid **42** [61], and disulfonimide **43** [62] typically demonstrate a superior ability to activate more challenging substrates. Recently, there has been a significant advancement with the development of axially chiral super Brønsted N–H acids **44** [63] and C–H acids **45** [64] and **46** [65] (Scheme 1.6). These catalysts have displayed unexpected catalytic abilities, opening up new opportunities in the field of asymmetric Brønsted acid catalysis and expanding the scope of the reactions [63c, d, 66].

(a) Weak to strong chiral Brønsted acids



32 33 34 35 36 37 38 39 40 41 42 43

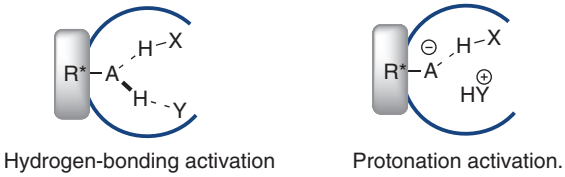
(b) Super strong chiral Brønsted acids



44 45 46

Scheme 1.6 Representative chiral Brønsted acid catalysts.

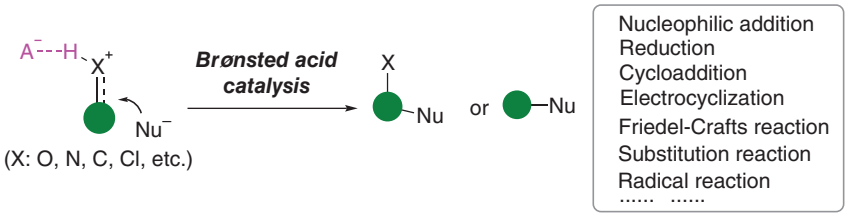
Chiral Brønsted acids are versatile catalysts that can facilitate a wide array of chemical reactions, primarily through hydrogen-bonding or protonation mechanisms (Scheme 1.7) [67]. Within the chiral environment created by the backbone of these Brønsted acids, one substrate is activated by the acidic proton of the catalyst through either hydrogen bonding or protonation. Concurrently, the other reactant also forms an interaction with the chiral Brønsted acid, leading to the formation of enantioenriched products. There is no single, unifying rule that determines which activation mode is followed by chiral Brønsted acids. Even when the same chiral Brønsted acid is employed, different catalytic mechanisms may be observed depending on the substrates used. It is noteworthy that stronger Brønsted acids tend to favor the protonation activation pathway.



Hydrogen-bonding activation Protonation activation.

Scheme 1.7 Activation modes of chiral Brønsted acid catalysis.

Aldehydes, ketones, and imines are among the most commonly used substrates that can be effectively activated by chiral Brønsted acids, enabling their reactions with a wide range of nucleophiles [9, 50] (Scheme 1.8). In addition to various nucleophilic additions, the asymmetric transformations also encompass hydrogen-transfer reduction, Friedel–Crafts reactions, cycloaddition, and electrocyclization [9, 50, 68]. Moreover, chiral Brønsted acids demonstrate their versatility by being able to activate alcohols and cyclic ethers through protonation. This activation leads to enantioselective substitution and rearrangement reactions, further expanding the application scope of chiral Brønsted acid catalysts [9, 50, 68]. Of particular note are the chiral Brønsted superacids, which exhibit exceptionally high catalytic activity and are capable of catalyzing transformations of more challenging substrates, such as asymmetric hydroalkylation [63b], hydroarylation [69], hydrolactonization [70], and cation shift of olefins [63g], demonstrating their remarkable catalytic capabilities [63c, f]. Furthermore, Brønsted superacids can react with Si reagents, generating silylium Lewis acid catalysts in situ, which enables the construction of previously inaccessible C—C bonds, opening new avenues for asymmetric catalysis [65, 71]. More recently, the applications of chiral Brønsted acid catalysis have been extended to radical reactions initiated through

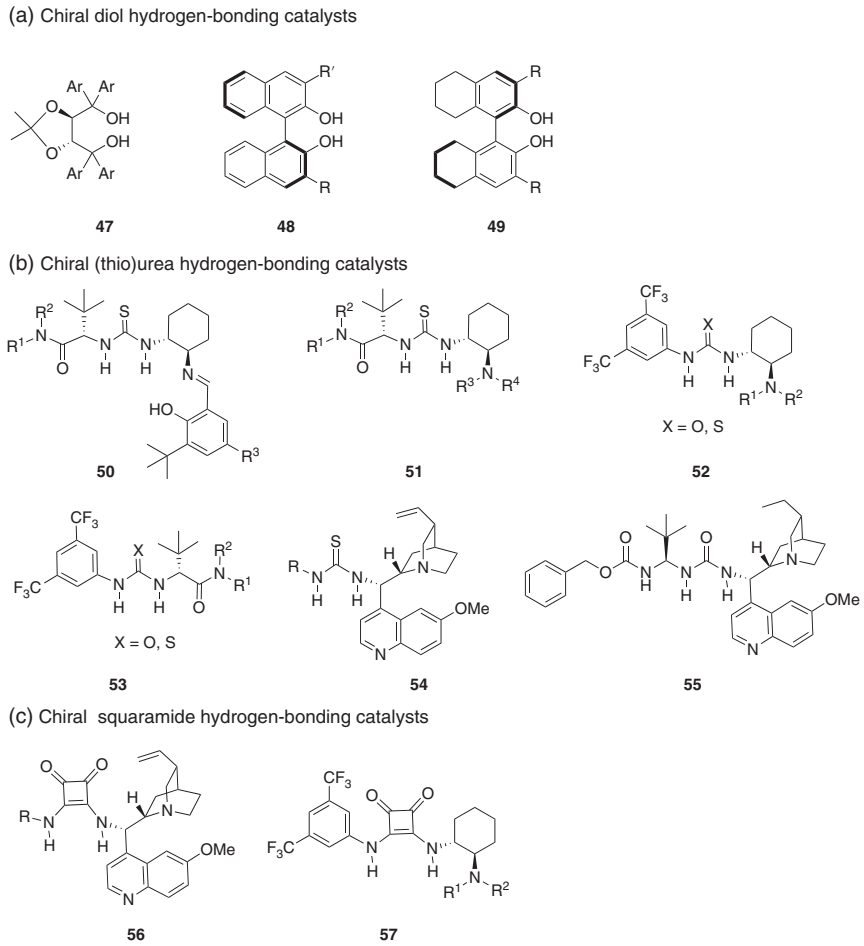


Scheme 1.8 Asymmetric reactions enabled by chiral Brønsted acids.

photoredox or electrolysis mechanisms [72], further broadening the horizons of the chemistry of chiral Brønsted acid catalysis (Scheme 1.8). This expanded scope of applications demonstrates the versatility and potential of chiral Brønsted acid catalysis in chiral synthesis [72].

1.3.2 Hydrogen-bonding Organocatalysts

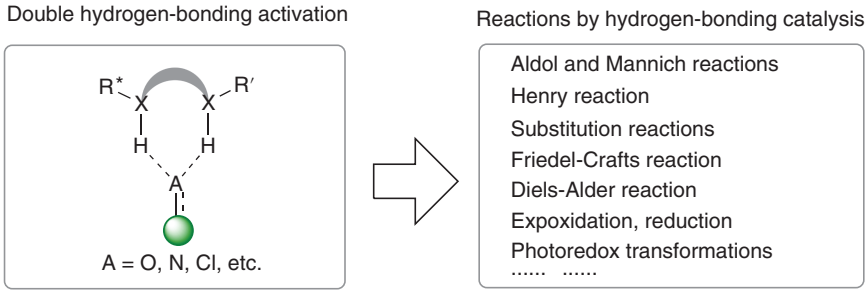
Hydrogen-bonding interactions are ubiquitous in enzymatic catalysis, where substrates can be activated or stabilized in optimal conformations through these interactions, facilitating various biological transformations. Likewise, hydrogen-bonding interactions are widely utilized in asymmetric organocatalysis [10, 73]. The most frequently employed chiral hydrogen-bonding organocatalysts are diols [74], (thio)ureas [75], and squaramides [76] (Scheme 1.9). Among these, chiral diols, such as TADDOLs **47** [77], BINOLs **48** [78], and H_8-BINOLs **49** [79] utilize their unrestricted OH groups to carry out asymmetric hydrogen-bonding



Scheme 1.9 Representative hydrogen-bonding organocatalysts.

catalysis. On the other hand, (thio)urea and squaramide catalysts often incorporate amino acid moieties, like Jacobsen catalysts **50** [80], **51** [81], and **53** [82]; chiral diamines (catalysts **52** and **57)** [83]; or cinchona alkaloids, like catalysts **54** [84] and **56** [85] to establish chiral environments for stereocontrol. Moreover, catalysts that possess multiple hydrogen-bonding sites, resembling the catalytic manner of enzymes, such as cinchona alkaloid derivative **55** [86], have the potential to achieve even higher activity and selectivity in asymmetric transformations [87].

Most of these catalysts are double hydrogen-bond donors, capable of forming double hydrogen bonds with substrates, which leads to stronger activation and better stereocontrol. The ability to interact with a diverse range of substrates endows hydrogen-bonding catalysts with impressive catalytic power [88]. Compounds containing hydrogen-bond acceptors, including alcohols, aldehydes, ketones, imines, diazo compounds, nitroalkenes, and more, can serve as potential substrates for hydrogen-bonding catalysis, enabling a broad spectrum of asymmetric transformations [10, 73]. Also, hydrogen-bonding catalysis enables asymmetric radical reactions, which have recently attracted significant attention [89]. Due to the broad substrate tolerance of hydrogen-bonding activation, the corresponding asymmetric reactions encompass a diverse range, spanning crucial C—C bond-forming reactions, oxidation, reduction, and innovative asymmetric transformations featuring photochemical synergies (Scheme 1.10).

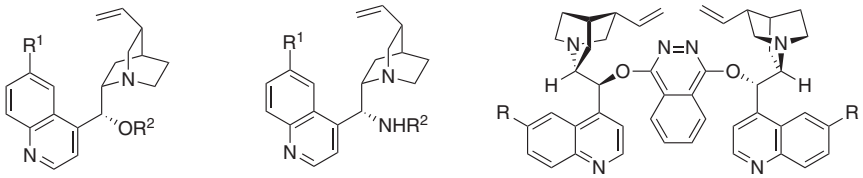


Scheme 1.10 Asymmetric reactions enabled by hydrogen-bonding catalysis.

1.3.3 Brønsted Base Catalysts

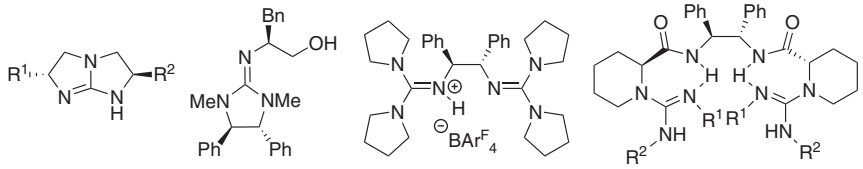
Brønsted organic bases, capable of accepting protons, have proven effective in promoting asymmetric transformations involving the formation of carbon–carbon and carbon–heteroatom bonds [11, 90]. In 1912, Bredig and Fiske initially employed cinchona alkaloid as a chiral organic base to accomplish enantioselective cyanation of aldehydes [91]. Despite many subsequent reports on cinchona alkaloids-catalyzed reactions in the following decades, the momentum for chiral Brønsted base catalysis did not emerge until the 1960s [92]. An early symmetrical study was reported by Wynberg in the 1980s [93]. Since then, natural and modified cinchona alkaloids have gained prominence in the field of asymmetric organocatalysis (Scheme 1.11a) [94]. Meanwhile, chiral guanidines with stronger basicity such as bicyclic **61** [95],

(a) Chiral Brønsted bases with cinchona alkaloid core structures



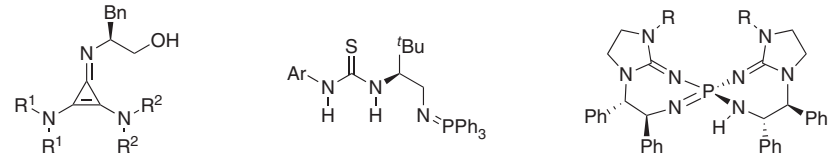
58 59 60

(b) Chiral Brønsted bases with guanidine core structures



61 62 63 64

(c) Chiral cyclopropenimines and chiral iminophosphoranes

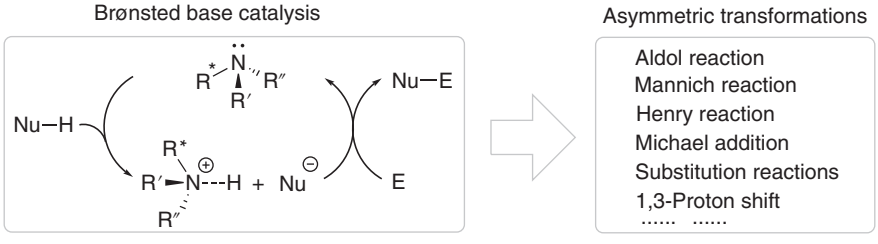


65 66 67

Scheme 1.11 Representative chiral Brønsted base catalysts.

monocyclic **62** [96], and acyclic bisguanidinium **63** [97] and **64** [98] have been developed to unlock more enantioselective transformations (Scheme 1.11b) [99]. More recently, chiral cyclopropenimine **65** [100] and iminophosphorane **66** [101] and **67** [102] have been utilized as organic superbases, aiming to enable asymmetric reactions involving weakly acidic pronucleophiles as substrates (Scheme 1.11c) [103].

During Brønsted base catalysis, pronucleophiles undergo activation through deprotonation by the catalysts [11, 90]. This process generates active anionic nucleophiles that react with various electrophilic compounds (Scheme 1.12). The

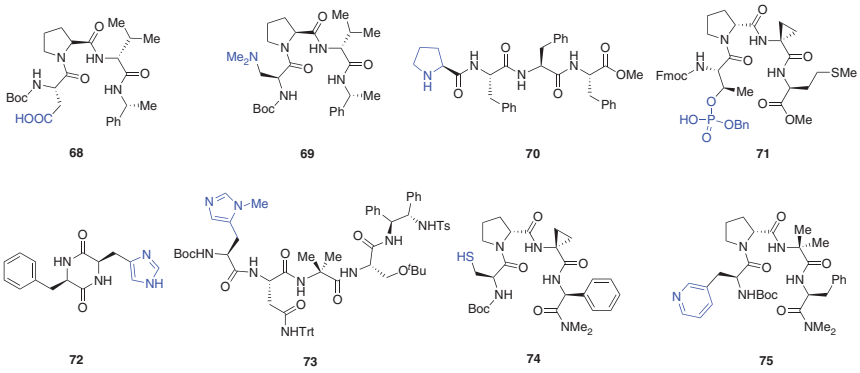


Scheme 1.12 Chiral Brønsted base catalysis for asymmetric transformations.

chiral setting of the Brønsted base catalysts plays a crucial role in stereocontrolling the bond formation between nucleophilic and electrophilic partners. Through Brønsted base catalysis, chemists have achieved numerous asymmetric transformations, including aldol reaction, Mannich reaction, Henry reaction, Michael addition, nucleophilic substitution, 1,3-proton shift of imines, and others, establishing a versatile platform for synthesizing chiral molecules with high enantiopurities [11, 90].

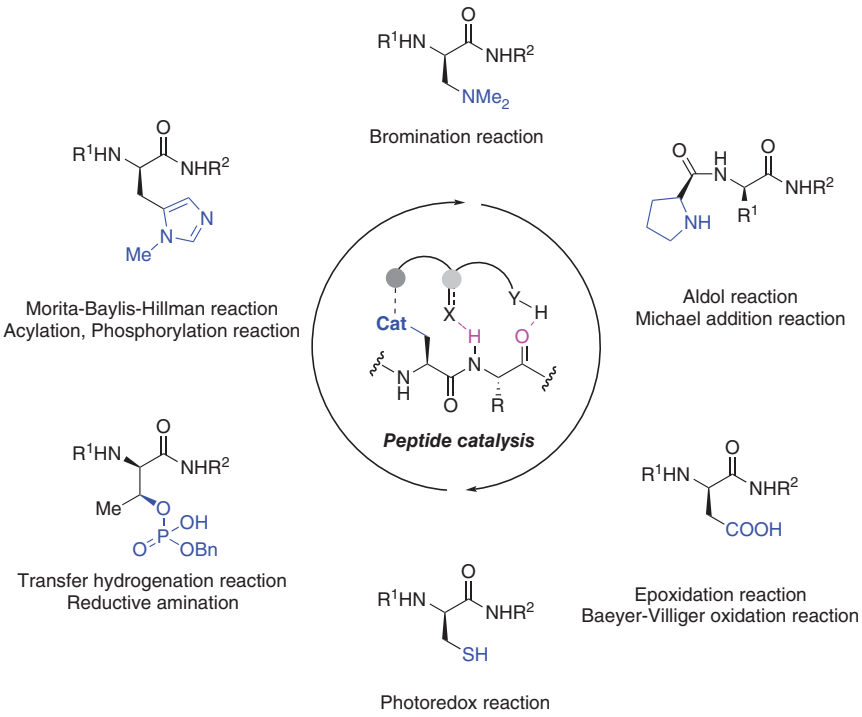
1.3.4 Synthetic Peptide Catalysts

Short-chain synthetic peptides have demonstrated remarkable versatility as catalysts for asymmetric transformations [12, 104]. These peptide catalysts are synthesized by linking amino acid residues with catalytic moieties, offering several appealing advantages [12, 104]. First, polypeptide chains can be constructed using a modular strategy, which simplifies synthesis and facilitates catalyst modification. Second, the potential quantity of synthetic peptide catalysts is vast, establishing a solid foundation for their application across a wide range of reactions. The beauty of these catalysts lies in their adaptability. A diverse array of catalytic groups can be readily integrated into the polypeptide chain, endowing them with the ability to catalyze various reactions [12, 104]. These catalytic groups may include carboxylic acid **68** [105], amines **69**–**70** [106], phosphate **71** [107], imidazoles **72**–**73** [108], thiol **74** [109], pyridine **75** [110], and more. When combined with polypeptide fragments, they give rise to a vast array of chiral peptide catalysts, each with its unique catalytic properties (Scheme 1.13).



Scheme 1.13 Representative short-chain peptide-based catalysts.

Peptide catalysts can carry out substrate recognition, activation, and stereoselective control through intricate networks of hydrogen bonds and other weak interactions [10, 12, 104]. In most cases, the catalysis is mainly driven by the core catalytic group that propels the reaction forward, while the peptide backbone contributes to the synergistic enhancement of catalysis efficiency



Scheme 1.14 Peptide catalysis with different catalytic groups.

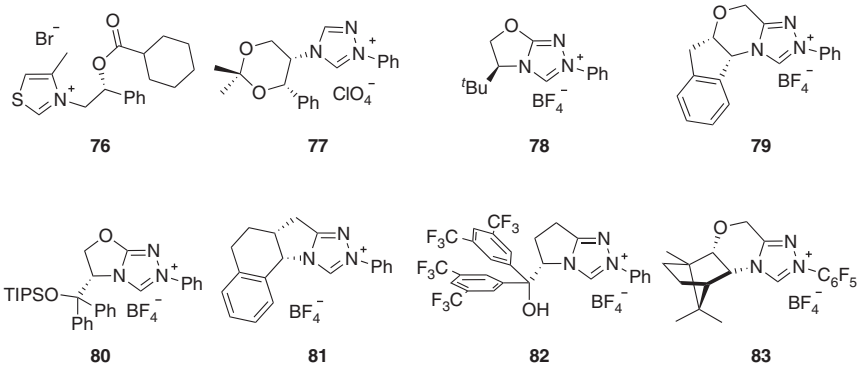
and precise stereocontrol (Scheme 1.14). For instance, peptide catalysts bearing carboxylic acid groups can facilitate asymmetric epoxidation of olefins and Baeyer–Villiger oxidation of ketones [105]. Peptides incorporating N-methyl imidazole are effective nucleophilic catalysts, efficiently promoting asymmetric Morita–Baylis–Hillman reactions, phosphorylation, acylation, and other synthetically valuable processes [108b, 111]. Peptides containing primary and secondary amines are adept at imine catalysis and enamine catalysis, catalyzing a range of asymmetric reactions, including asymmetric aldol and Michael addition reactions [106, 112]. Furthermore, peptides with thiol groups can synergize with photocatalysis, enabling them to promote asymmetric radical transformations with high enantiocontrol [109].

Although synthetic peptides possess immense potential in asymmetric catalysis for numerous chemical transformations, several challenges persist within the area of peptide catalysis [12, 104]. First, the inherent flexibility of peptide structures poses a significant obstacle in the rational design of efficient peptide catalysts for specific reactions. Second, the intricate interactions between peptide catalysts and their substrates, which include hydrogen bonding and other delicate non-covalent forces, are complex and easy to change. This complexity and variability limit the adaptability of a specific peptide catalyst to diverse substrates, limiting their potential applications in asymmetric catalysis.

1.4 Catalysts for Organocatalysis Based on Lewis Acid–Base Interactions

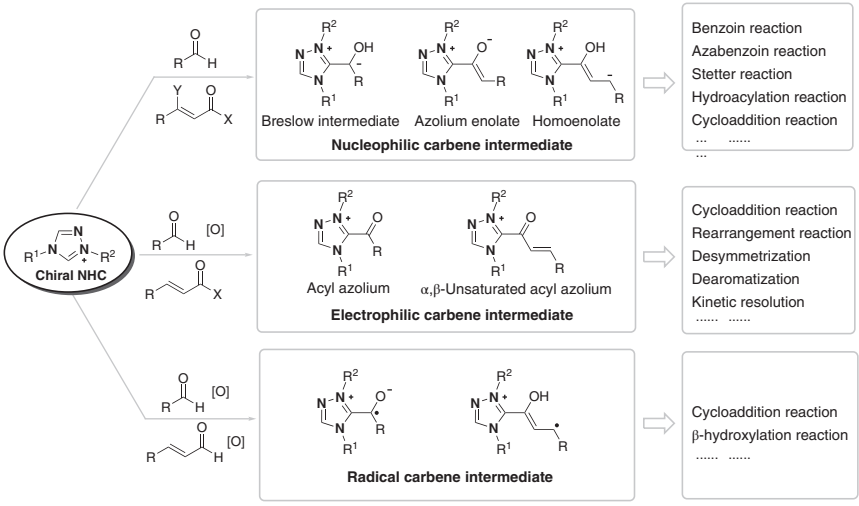
1.4.1 Carbene Catalysts

N-Heterocyclic carbenes (NHCs) are heterocyclic compounds characterized by a divalent carbon atom and at least one nitrogen atom within the ring structure. Like thiamine (vitamin B_1), which serves as a vital class of coenzymes facilitating numerous biological transformations [113], biomimetic chiral NHC catalysts exhibit remarkable power in promoting a broad range of asymmetric reactions [13, 114]. Although the first report of chiral NHC catalysts dates back to 1966 with Sheehan's pioneering work [115], the significant development of carbene catalysis surged predominantly from the late 1990s onward [13, 114]. Notably, compared to classic NHC catalysts **76** [115] and **77** [116], chiral bicyclic NHCs such as compounds **78**–**83** have displayed particularly outstanding performance in stereocontrol (Scheme 1.15) [117]. The inherent rigidity of their chiral framework contributes significantly to their exceptional enantioselectivity.



Scheme 1.15 Representative chiral *N*-heterocyclic carbene (NHC) precursors.

Chiral NHCs exhibit a tendency to react with electrophiles spanning from aldehydes and ketones to imines, ketenes, esters, acyl halides, etc. [13, 114]. This results in the generation of nucleophilic species through the umpolung of electrophiles, including Breslow intermediates [118], azolium enolates [119, 120], and homoenolate intermediates [121], as well as electrophilic acyl azoliums [122] and α,β-unsaturated acyl azoliums [123]. These intermediates demonstrate reactivity toward a diverse array of reaction partners, facilitating a wide spectrum of asymmetric transformations such as benzoin and azabenzoin reactions, Stetter reaction, olefin hydroacylation, and cycloaddition (Scheme 1.16) [13, 114, 118–123]. Recent advancements have unveiled the capability of NHCs to catalyze single-electron transfer reactions through a radical mechanistic pathway, thereby further broadening the scope of NHC catalysis [124].

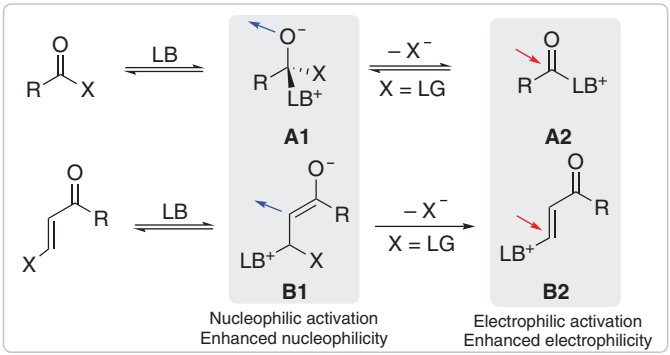


Scheme 1.16 Key intermediates and typical reactions for enantioselective NHC catalysis.

1.4.2 Lewis Base Catalysts

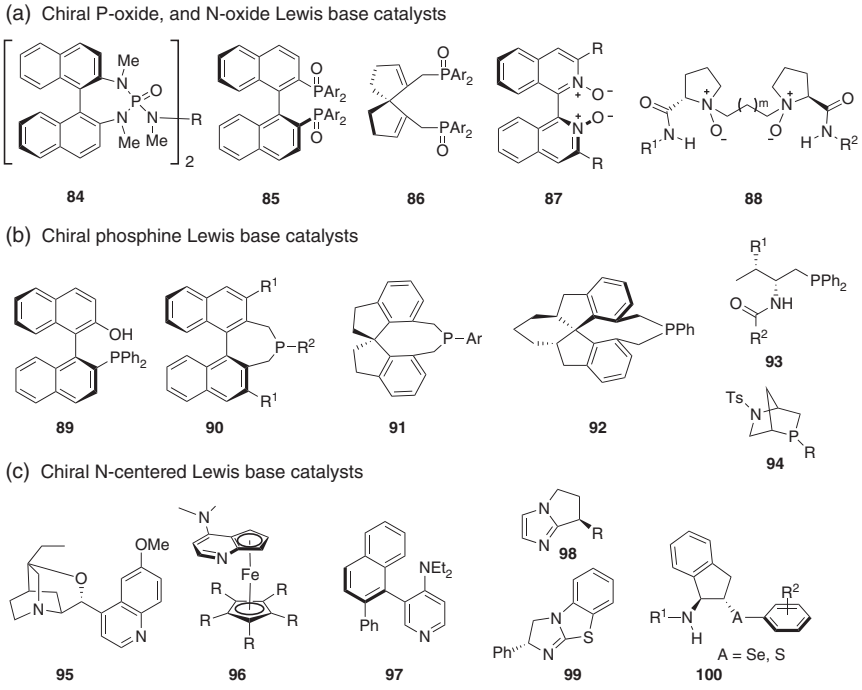
Lewis bases are compounds capable of binding electron-pair acceptors by donating electron pairs [125]. This interaction gives rise to Lewis base catalysis, which has become a versatile tool for a wide range of asymmetric transformations [14, 126]. The acceptors' vacant orbitals can be antibonding orbitals with π^* or σ^* characters or nonbonding orbitals [14]. The most common form of Lewis base catalysis involves n–π^* interactions between Lewis base catalysts and electron-pair acceptors. The donor–acceptor interaction transfers electron density from the Lewis bases to the electron-pair acceptors, typically enhancing the nucleophilicity of the acceptors. In cases where the donor–acceptor adducts are aminium, pyridinium, or phosphonium salts, Lewis base catalysis can also enhance the electrophilic character of the acceptors due to the strong electron-withdrawing nature of these N- and P-centered cations [14, 126]. For example, when a Lewis base adds to a carbonyl group, it forms the zwitterionic, tetrahedral intermediate **A1**, which exhibits improved nucleophilic properties at the oxygen atom (Scheme 1.17). Conversely, the resulting ionic species **A2**, formed by elimination if X is a good leaving group, displays enhanced electrophilic reactivity at the carboxylic carbon. Similarly, in the case of α,β-unsaturated carbonyl compounds, the zwitterionic enolate **B1** formed by conjugate addition possesses enhanced nucleophilic character at the α carbon, while the cationic, electron-deficient olefin **B2** exhibits increased electrophilic reactivity at the β carbon. By employing these distinct activation modes, Lewis bases can facilitate both nucleophilic and electrophilic reactions at different positions of electron-pair accepting substrates, and even reverse the reactivity, enabling a variety of asymmetric transformations with diverse reaction partners [14, 126].

The most widely used Lewis base catalysts include chiral phosphoramide **84** [127], P-oxides **85** [128] and **86** [128c, d, 129], N-oxides **87** [130] and **88** [130b, c, 131],



Scheme 1.17 Nucleophilic and electrophilic activations by Lewis base catalysis.

and chiral phosphines **89**–**94** [132] as well as cinchona alkaloid **95** [133], chiral pyridines **96** [134] and **97** [135], amidines **98** [136] and **99** [137], and chalcogenide catalyst **100** [138] (Scheme 1.18). O-based Lewis base catalysts such as compounds **84**–**88** are primarily employed to activate silicon reagents, leading to the formation of hypervalent silicon species. These species are effective in initiating asymmetric transformations, such as allylation of aldehydes and imines, aldol and Mannich reactions, and ring-opening of epoxides [139]. In contrast to O-based catalysts, chiral P- and N-centered Lewis bases, such as **89**–**94** and **95**–**99**, demonstrate



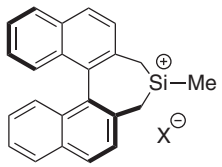
Scheme 1.18 Representative chiral Lewis base catalysts.

enhanced nucleophilicity, allowing them to interact with compounds containing comparatively weaker electrophilic sites, such as electron-deficient alkenes and alkynes, carbonyls, ketenes, and azomethines [134b, c, 135b, c, 136b, 140]. These interactions facilitate enantioselective transformations, including Michael addition, acylation (desymmetrization and kinetic resolution), Morita–Baylis–Hillman reactions, cycloadditions, and various others, yielding a diverse array of important chiral molecules for organic synthesis.

1.4.3 Lewis Acid Catalysts

Lewis acids are compounds capable of accepting a pair of electrons from another molecule, known as a Lewis base [141]. They encompass both metals and nonmetals with vacant orbitals. In comparison, while metallic Lewis acid catalysts have been extensively studied, the investigation of enantioselective Lewis acid organocatalysis has received less attention (Scheme 1.19) [142]. Although chiral boron compounds

(a) Chiral silicon Lewis acid catalysts



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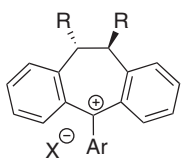
(b) Chiral carbon cation Lewis acid catalysts



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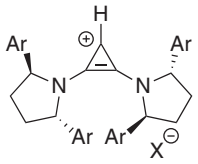

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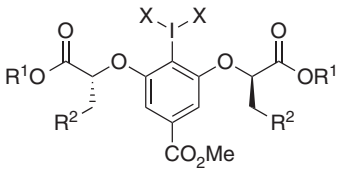
(c) Chiral iodine (III) Lewis acid catalysts



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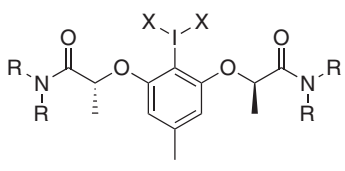

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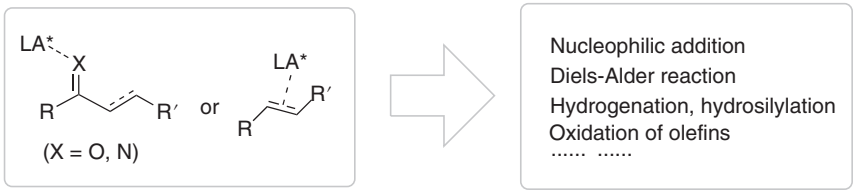
Scheme 1.19 Representative chiral Lewis acid organocatalysts.

represent a significant class of nonmetal catalysts serving as Lewis acids, they have been extensively discussed in numerous reviews outside the context of organocatalysis [143] and, therefore, will not be included in this section. Selected representative chiral Lewis acid organocatalysts are listed in Scheme 1.19. Chiral BINOL-based silicon **101** [144] can serve as an effective Lewis acid catalyst for enantioselective Diels–Alder reactions [145]. Carbon cations, known for their high reactivity, also can act as robust Lewis acids. Several chiral carbon cation catalysts, such as **102** [146] and **103** [147], have been developed, exhibiting decent chiral induction abilities. Furthermore, chiral iodine (III) **104** [148] and **105** [149] generated in situ by chiral aryl iodine and *m*CPBA act as Lewis acids to activate olefins, delivering corresponding products of olefin oxidation [150].

Due to the electron-withdrawing nature inherent in Lewis acids, substrates like carbonyl, imine, or alkene compounds are typically activated by Lewis acid organocatalysts, leading to enhanced electrophilicity. This activation paves the way for asymmetric nucleophilic addition, cycloadditions and reduction (Scheme 1.20) [142, 145]. In the case of chiral iodine catalysts, activated C=C double bond is more receptive to nucleophilic reagents (Scheme 1.20) [150]. On the other hand, chiral Lewis acids can also stabilize the configuration that controls the spatial arrangement of incoming nucleophiles, influencing the stereoselectivity of the reaction.



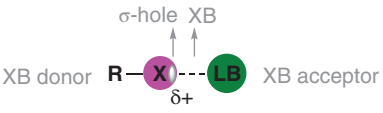
Scheme 1.20 Chiral Lewis acids for asymmetric organocatalysis.

1.4.4 Halogen- and Chalcogen-Bonding Catalysts

Halogen-/chalcogen-bonding catalysis is emerging fields within organocatalysis [16, 151]. Halogen bonds (XBs) or chalcogen bonds (ChBs) involve, respectively, non-covalent interactions between a halogen atom (like iodine, bromine, and chlorine) and a Lewis base, or a chalcogen atom (including sulfur, selenium, and tellurium) and two Lewis bases [16, 151]. In the XB and ChB catalysis, a σ-hole that is a positive electrostatic potential region in a X or Ch atom, has been found crucial for the non-covalent bond interactions (Scheme 1.21) [152]. The unique properties of halogen/chalcogen bonds, such as their directionality and tunable strength, make them suitable for catalytic applications in organic reactions.

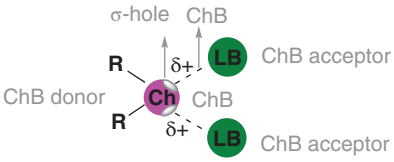
The concept of utilizing halogen bonds in catalysis was first proposed by Bolm and coworkers [153]. The field has since rapidly developed with numerous examples demonstrating the efficacy of XB donors in various catalytic transformations [16b, 151]. However, only a few successful chiral catalysts involving enantioselective halogen bond catalysis have been reported, such as chiral pentanidium **106** for alkylation of sulfenate anions [154], quinidine derivative **107** for Mannich-type reaction [155], bis(imidazolium)-based **108** for Mukaiyama aldol reaction [156], and triazole halogen bond donor **109** for Reissert-type reaction [157] (Scheme 1.22a).

(a) Halogen-bonding catalysis



X = Cl, Br, I
R = electron withdrawing group

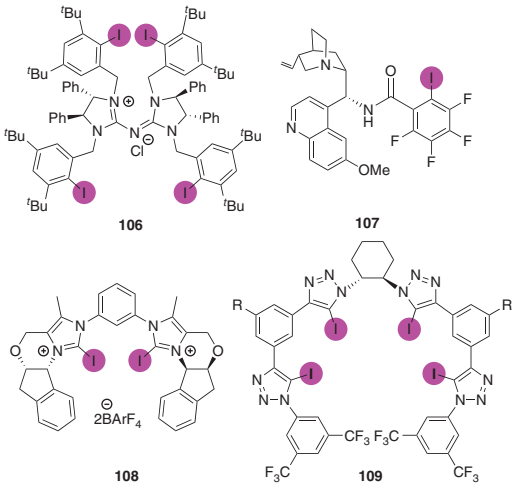
(b) Chalcogen-bonding catalysis

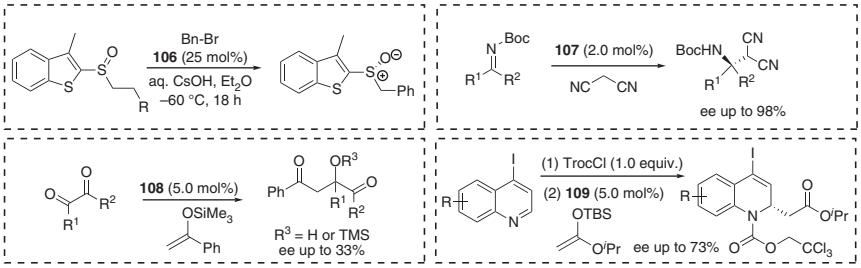


Ch = S, Se, Te
R = electron withdrawing group

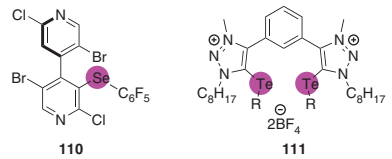
Scheme 1.21 Halogen- and chalcogen-bonding catalysis.

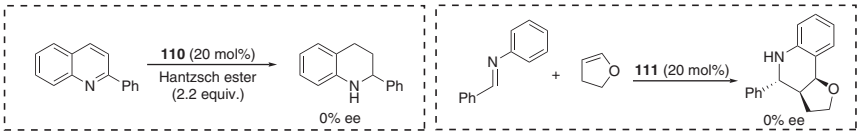
(a) Chiral halogen catalysts and related enantioselective transformations





(b) Chiral chalcogen catalysts and related enantioselective transformations





Scheme 1.22 Chiral halogen/chalcogen catalysts and the related asymmetric reactions.

The first chalcogen-bonding catalyst was reported by Matile et al. [158], and further advancements involve more transformations like transfer hydrogenation, carbon–chlorine bond activation, and Michael additions [16]. Despite the progress, asymmetric chalcogen bond catalysis so far remains challenging. Several chiral chalcogen catalysts have been designed and applied in the asymmetric reactions, but there was not any chiral induction observed in these systems (Scheme 1.22b) [159]. Current research aims at understanding the fundamental interactions and developing enantioselective halogen-/chalcogen-bond catalysis. The potential for the application halogen/chalcogen bonds in asymmetric catalysis continues to grow, promising new methodologies and applications in enantioselective organic synthesis.

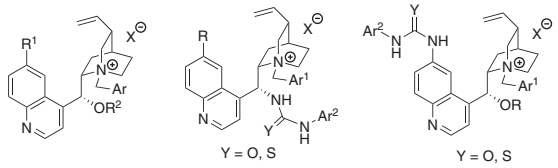
1.5 Catalysts for Organocatalysis Based on Cation–Anion Interactions

1.5.1 Phase-Transfer Catalysts

Chiral phase-transfer catalysts (CPTCs) represent a pivotal class of tool-like compounds in asymmetric synthesis [12, 17, 160]. These catalysts facilitate chemical reactions occurring between substrates situated in immiscible phases, creating a bridge for otherwise hindered interactions. The utilization of CPTCs has significantly expanded the scope of asymmetric catalysis, particularly in producing chiral molecules with high enantiopurity. Initially conceptualized in 1971 by Starks [160a], in most cases, phase-transfer catalysis takes advantage of onium salts to enable organic transformations. Despite various types of CPTCs, the major structures of CPTCs are generally derived from cinchona alkaloids, binaphthyls, chiral diamines, and α-amino acids (Scheme 1.23). Cinchona alkaloid-based quaternary ammonium salts such as compounds **112**–**114** represent one type of the most classic CPTCs (Scheme 1.23a) [160d–f]. Chiral binaphthyl quaternary ammonium salt catalysts **115** and **116** [161] and phosphonium salts **117** [162], developed by Maruoka, stand for another type of important CPTCs. Chiral crown ethers with binaphthyl skeleton (**118**) as a class of neutral binding PTCs that possess the ability to complex with metal cations catalyze some specific asymmetric reactions with excellent performances (Scheme 1.23b) [163]. Varied CPTCs containing chiral diamine backbones such as **119** [164], **120** [165], **121** [165c, 166], **122** [167], and **123** [168] have emerged as influential contributors to this field (Scheme 1.23c). Chiral α-amino acid-derived phosphonium salts, driven by the efforts of Zhao (**124**) [169] and Wang (**125**) [170] et al., have evolved into a new type of effective phase-transfer catalysts (Scheme 1.23d) [171].

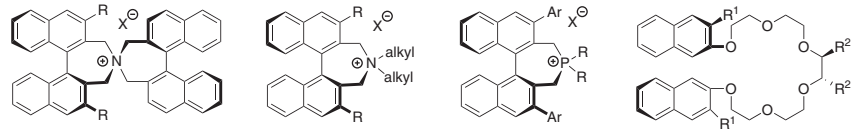
Chiral phase-transfer catalysis involves the process in which onium cations transport anions from the aqueous phase into the organic phase, accelerating the reactions occurring in the organic phase (Scheme 1.24) [12, 17, 160]. The onium anions may serve as bases, nucleophiles, and even electrophiles (e.g. OCl^-). Since the cation phase-transfer catalysis still dominates the area of phase-transfer catalysis, nucleophilic substitution and addition thus are the main two types of

(a) Chiral phase-transfer catalysts with cinchona alkaloid core structures



112 113 114

(b) Chiral phase-transfer catalysts with binaphthyl core structures



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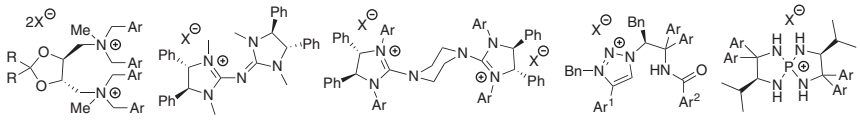
(c) Chiral phase-transfer catalysts diaminel core structures



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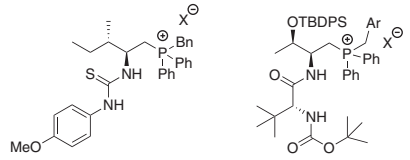
(d) Chiral phosphonium salts derived from α-amino acids



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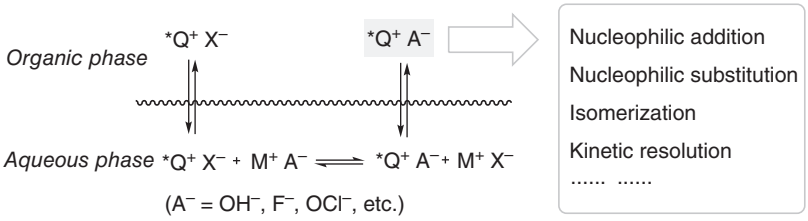
Scheme 1.23 Representative chiral phase-transfer catalysts.



Scheme 1.24 Phase-transfer catalysts for asymmetric transformations.

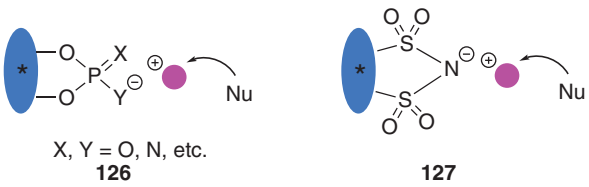
reactions enabled by CPTCs. Alkyl halides, aldehydes, ketones, imines, and Michael acceptors are the commonly utilized electrophiles. These substrates along with versatile nucleophiles go through various asymmetric transformations, like aldol, Mannich, Strecker, conjugate addition, epoxidation, reduction, cycloaddition, α-heterofunctionalizations, and so on [12, 17, 160b–g]. Additionally, isomerization

such as 1,3-proton shift of Schiff bases [172], kinetic resolution [173], and other reactions that typically are promoted by bases can be enabled by these powerful CPTCs [12, 17, 160b–g]. Understanding the stereocontrol mechanisms underlying CPTCs remains an ongoing challenge. There is an increasing emphasis on the role of various interactions, such as hydrogen bonding and cation–anion attraction, between the catalysts and substrates [169b, 174]. These interactions collectively collaborate to induce chirality in enantioselective phase-transfer catalysis.

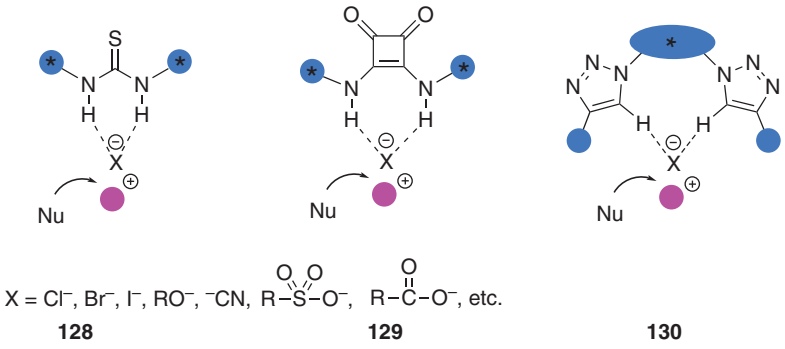
1.5.2 Asymmetric Counteranion Catalysis

Asymmetric counteranion catalysis usually refers to asymmetric reactions where a chiral ion pairing creates an environment for chiral induction [1c, 18, 175]. The interaction between the chiral counteranion and the cationic moiety is strong enough to effectively influence the stereoselectivity of the reaction [176]. Chiral Brønsted acid catalysts such as chiral phosphoric acids **126** [59b, 177] and sulfonimides **127** [62a] (Scheme 1.25a) can leverage the interaction between chiral acid anionic species and cationic intermediates to induce stereocontrol. They thus have been recognized as a class of important asymmetric counteranion catalysts, which have been discussed in chiral Brønsted acid section (Scheme 1.6) [9, 50]. On the other hand, H-bonding catalysts like chiral thioureas **128** [178], squaramides **129** [179], and triazoles **130** [180] have played an exceptionally important role in the

(a) Chiral phosphoric acid and sulfonimide-based counteranion catalysts



(b) Chiral thiourea-, squaramide-, and triazole-based counteranion catalysts

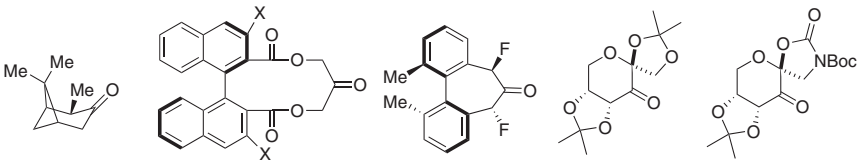


Scheme 1.25 Typical structural skeletons for chiral counteranion catalysts.

area of asymmetric counteranion catalysis, where the catalysts bind the anionic moiety through hydrogen bonding, forming a chiral ion pair that determines the stereoselectivity (Scheme 1.25b) [181, 182]. The first example of H-bonding donor-based counteranion catalysis was reported by Jacobsen in 2004 [178a], and the chiral thiourea-chloride counteranion mode was proposed in 2007 [178b]. The bound anions can also serve as active nucleophiles, allowing a large range of H-bonding donors to be effective substrates for asymmetric counteranion catalysis [18, 175b, c, 181]. After two decades of development, chiral counteranion catalysts have been widely applied in both intramolecular and intermolecular reactions [1c, 18, 175, 176]. These catalysts have facilitated the asymmetric transformations of a diverse range of substrates, establishing themselves as a class of highly efficient organocatalysts with unique catalytic pathways [1c, 18, 175, 176, 181, 182].

1.6 Chiral Ketone Catalysts for Olefin Epoxidation

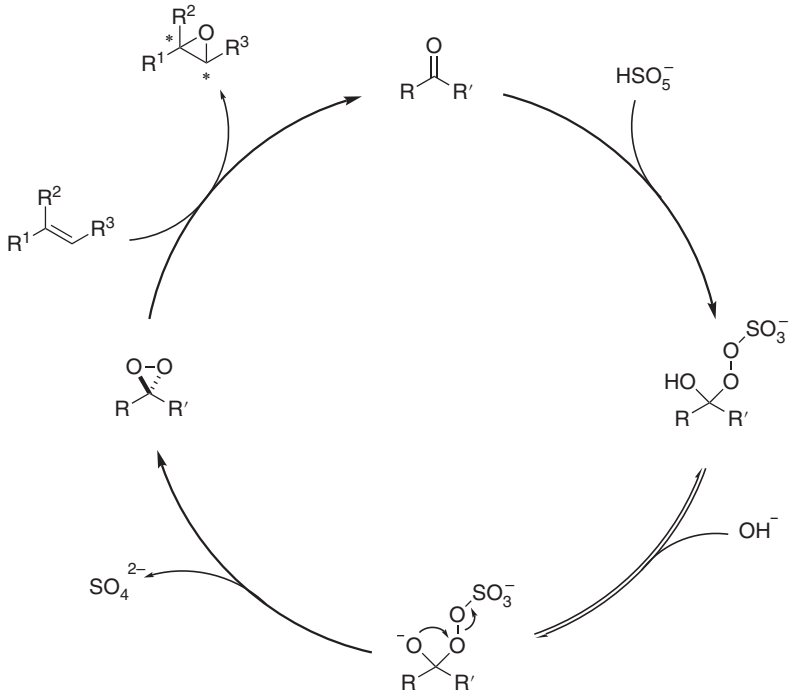
Chiral ketone catalyzed enantioselective epoxidation of olefins is an important reaction by organocatalysis, which has been proven to be one of the most straightforward and efficient methods for accessing optically active epoxides [19, 183]. A variety of structurally diverse chiral ketone catalysts have been invented for asymmetric epoxidation of olefins, including 3-pinanone **131** utilized by Curci [184], binaphthyl-based ketones **132** invented by Yang [185], biphenyl-based ketones **133** reported by Denmark [186], and fructose-derived ketones **134**–**135** developed by Shi (Scheme 1.26) [187]. Among them, fructose-derived ketones are most effective for asymmetric olefin epoxidation in terms of chemo-, diastereo-, and enantioselective control. Substrates including terminal olefins, *trans*- and *cis*-olefins, and trisubstituted and tetrasubstitued olefins can be effectively epoxidized, forming various chiral epoxides with high enantiopurities [19, 183, 188]. This reaction has been widely used in total synthesis of natural products and is known as Shi epoxidation.



131 132 133 134 135

Scheme 1.26 Representative chiral ketone epoxidation catalysts.

Oxone ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$) is the commonly used oxidant for ketone catalyzed asymmetric epoxidation of olefins, which is capable of in situ oxidizing the chiral ketone catalyst into a highly reactive dioxirane intermediate. The chiral dioxirane species transfers the electrophilic oxygen to the olefin in an enantioselective way, delivering the corresponding optically active epoxides (Scheme 1.27) [188].

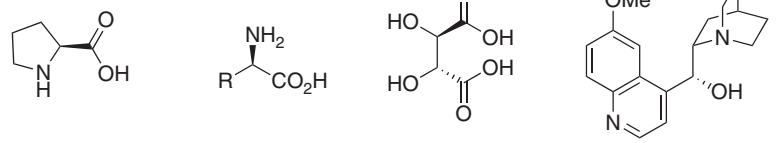


Scheme 1.27 Mechanism for ketone-catalyzed epoxidation of olefins.

1.7 Privileged Structures of Organocatalysts

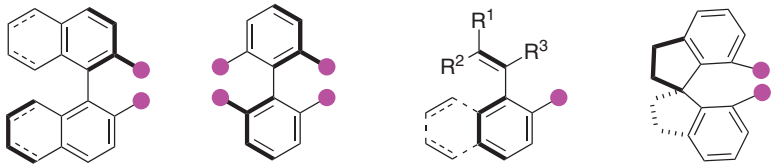
Chiral structural scaffold impacts the performance of organocatalysts in terms of stereocontrol and activity. Many organocatalysts, possessing a centrally chiral backbone, are derived from naturally occurring chiral sources, such as α-amino acids [4, 5, 20b], tartaric acid [52, 77, 164], cinchona alkaloids [94a, 160b–f], and others (Scheme 1.28a). Besides centrally chiral scaffolds, axial chirality, planar chirality, and helical chirality are also frequently introduced as important design elements [189–192]. The resulting organocatalysts display a unique three-dimensional arrangement. This may provide opportunities to integrate appropriate functional components for bifunctional activation and cooperative catalysis, leading to exceptional stereoselectivity and dramatically enhanced activity. For axially chiral organocatalysts, the backbones share restricted rotation around an axis [190]. Typical structural skeletons for axially chiral organocatalysts involve binaphthyl (**136**), biphenyl (**137**), styrene-based compounds (**138**), and spirobiindane **139** (Scheme 1.28b). Installing catalysis moieties onto the backbones creates various axially chiral organocatalysts, such as amine catalysts **16**–**18** (Scheme 1.2) [39–41], carbonyl catalysts **26**–**31** (Scheme 1.5) [43, 45, 47, 49], hydrogen-bonding catalysts **48**–**49** [78, 79, 193], Brønsted acid catalysts **33**–**46** (Scheme 1.6) [53–65, 194], Lewis base catalysts **84**–**87** [127–130] and **89**–**92** [132a–e] (Scheme 1.18), Lewis acid catalysts **101** [144] (Scheme 1.19), phase-transfer catalysts **115**–**118** [161–163]

(a) Naturally occurring chiral sources for centrally chiral catalyst structures



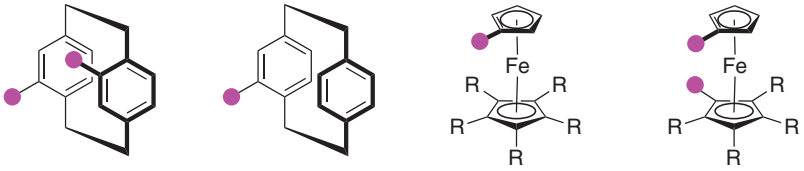
Proline Acyclic a-amino acids Tartaric acid Cinchona alkaloid

(b) Axially chiral catalyst structures



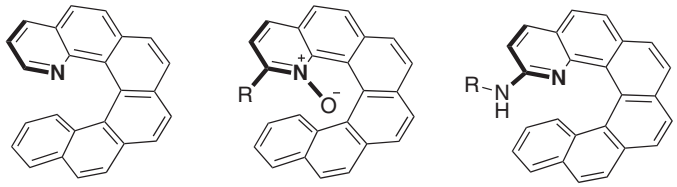
136 **137** **138** **139**

(c) Planar chiral catalyst structures



140 **141** **142** **143**

(d) Helically chiral catalyst structures



144 **145** **146**

Scheme 1.28 Representative privileged structures of organocatalysts.

(Scheme 1.23), and ketone catalysts **132** [185] and **133** [186] (Scheme 1.26). This type of organocatalysts has achieved great success in asymmetric catalysis.

Planar chiral molecular scaffolds [191], typically including paracyclophanes [195] (**140** and **141**) and ferrocene derivatives (**142** and **143**) [134], are also frequently applied to the design of organocatalysts (Scheme 1.28c). For example, *para* cyclophane-based chiral phosphine [196], nicotinamide adenine dinucleotide phosphate (NAD(P)) model [197], and ferrocene-based Lewis base catalysts **96**

[134b, c] are all famous organocatalysts. They have been successfully employed in a wide range of asymmetric reactions.

Helically chiral catalysts, a class of *ortho*-fused polyaromatic compounds, are distinguished by their nonplanar, helical structures [192]. Introducing functional groups at a specific position on the helicene structures produces various effective catalysts [198]. Among the various types of helicenes, azahelicenes, which contain nitrogen atoms within their helical framework, have shown promising applications as chiral organocatalysts [192d, 199], such as azahelicene **144** [200], helicene-*N*-oxides **145** [201], bifunctional helicene **146** [202], and others (Scheme 1.28d) [192d, 199].

Usually, the catalytic centers of organocatalysts are relatively stable organic groups. By combining these catalytic moieties with the diverse chiral scaffolds, it is possible to produce numerous organocatalysts. Furthermore, different chiral components can be freely integrated into a single organocatalyst, like catalysts **26–28** (Scheme 1.5) [43, 45b, 47c, e], offering greater opportunities for rational catalyst design. This is also beneficial for enhancing catalytic activity and improving stereoselective control.

1.8 Conclusion

In summary, after the rapid development, enantioselective organocatalysis has evolved into an important platform for chiral synthesis [1a–d, 2, 203]. This evolution has witnessed the emergence of numerous new reactions and a wide array of structurally novel organic small molecule catalysts. The catalysts are the key to the development of organocatalysis. The catalytic center of organocatalysts can be various organic functional groups, such as amines, aldehydes, ketones, carbenes, Brønsted acids, Brønsted bases, and nonmetal Lewis acids. These diverse groups lead to different activation mechanisms, leading to a multitude of asymmetric transformations. The commonly utilized chiral sources, such as chiral amino acids, vicinal diamines, 1,2-amino alcohols, cinchona alkaloids, axially chiral biaryls, planar chiral molecules, and helically chiral compounds, are frequently utilized in the development of organocatalysts. The catalyst's framework controls stereoselectivity and can also regulate catalytic activity.

While enantioselective organocatalysis showcases notable advantages such as outstanding stereocontrol and environmentally friendly reaction conditions, this field also faces a significant challenge, that is, relatively low catalytic efficiency [1]. In most instances of enantioselective organocatalysis, a catalyst loading of 5–20 mol% is typically required to achieve satisfactory reaction rates [43, 47c, 71a, 172, 203], limiting broader applications of organocatalysis in chiral synthesis [1]. Many organocatalysts draw inspiration from natural enzymes [3]. Although their fundamental mechanisms share similarities, enzymatic catalysis involves a significantly more intricate catalytic pathway compared to organocatalysis. Enzymatic catalysis incorporates a range of interactions such as bifunctional catalysis, cooperative activation, substrate recognition, and more, contributing to the notably

higher catalytic activity than organocatalysis. By closely mimicking enzyme systems and integrating multiple interactions, it will provide an opportunity to enhance the performance of organocatalysis in terms of both activity and enantiocontrol. This can make organocatalysis more efficient and practical for chiral synthesis, expanding its potential impact and applications in organic synthesis.

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