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ACTIVATION OF COVALENT BONDS THROUGH NON-COVALENT INTERACTIONS

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1.1 INTRODUCTION

A large number of fundamental chemical processes involve cleavage and/or transformation of strong covalent bonds, which can require a high energy consumption to fulfill the thermodynamic and kinetic profile of the reaction. The finding of pathways where intermediates with a lower energy consumption are formed is a common tool to facilitate a reaction, and non-covalent interactions can play an important role in the formation and stabilization of intermediates. Usually the energy of non-covalent interactions (hydrogen and halogen bonding, van der Waals forces, π-effects, etc.) is much lower than that of typical covalent bonds [1–6], but, on account of their multiplicity and facile transformation, their overall influence on the course of a reaction can be decisive. Thus, the "soft force" of multiple low-energy and low-level interactions can play a significant role in the activation of covalent bonds, directing the "brute action" of pronounced powers such as heat, current, light, etc. As a result, the cooperation of these "strong" external forces and "weak" non-covalent interactions can be relevant for an effective activation of covalent bonds.

For instance, if hydrogen bonds are under consideration, one can surmise that they influence the reactivity of substrates in several ways (Scheme 1.1). When the oxygen atom of a carbonyl group or the sulfur atom of a thioketone is involved in a strong bifurcated hydrogen bonding, the electrophilic character of the corresponding carbon atom increases toward nucleophilic attack when compared with a simple H-bonding (compare **II** with **I** and **IV** with **III**). In addition, a nucleophilic attack to the carbon atom in a carbonyl is usually more favorable than in a thioketone (compare **I** with **III** and **II** with **IV**). Hence, one can use these considerations to perform a regiospecific activation of a particular moiety.

Similar approaches can be used for the activation of a carbon atom in imines (**V** and **VI**), alkenes (**VII** and **VIII**), and alkynes (**IX** and **X**). Another approach can involve the creation of flexible or cyclic hydrogen bonding systems in a near proximity to the target covalent bond to promote the desired nucleophilic attack (**XI–XVI**). This allows to perform a proper orientation in space of the electron-poor carbon atoms; and an easy attack by an electron-rich nucleophilic group occurs smoothly. In many cases the creation of such supporting non-covalent bondings can be rationalized, but often it is not straightforward to predict the activation effect. Hence, more efforts should be devoted to the study and systematization of this field.

Therefore, the use of non-covalent interactions in synthesis is becoming an active area of research with potential applications in separation processes, medicine, catalysis, and biomolecular systems. Most of the known applications in synthesis are related to the highly widespread hydrogen bonds [1, 5, 6]. However, other types of interactions, such as O···B, O···Si, O···S, N···B, N···N, N···P, N···S, or halogen

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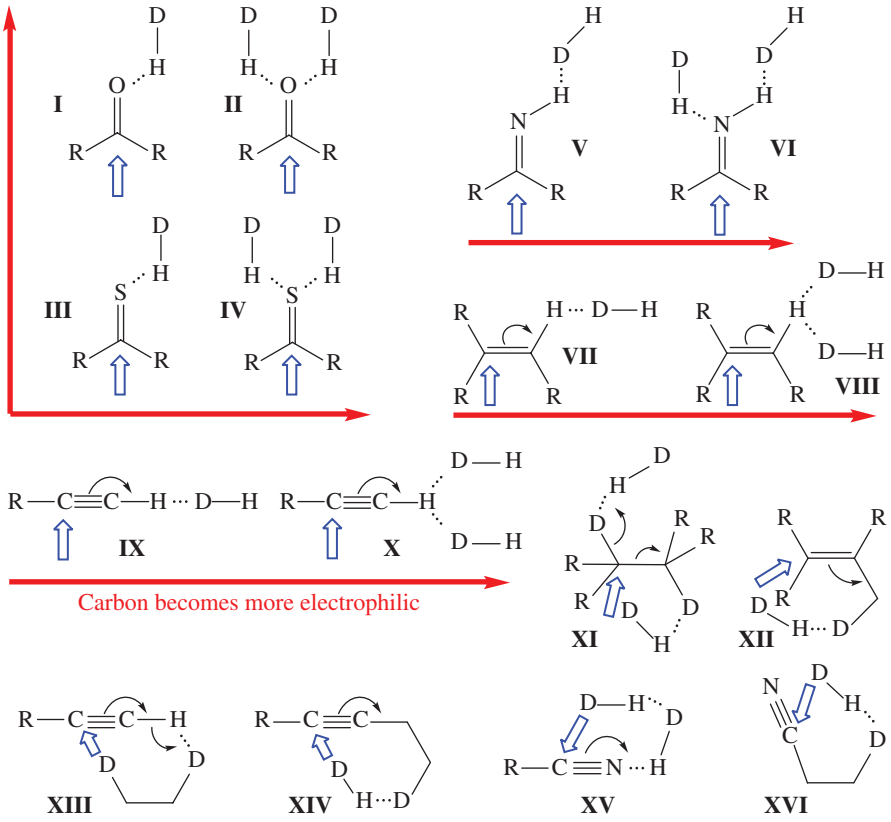


SCHEME 1.1 Some modes of covalent bond activation by hydrogen bonds.

bonding, have also grown from a scientific curiosity to a real tool to promote a number of organic and inorganic transformations and to construct supramolecular assemblies [7, 8]. This chapter provides some examples of activation of different types of covalent bonds (C—C, C=C, C≡C, C—N, C=N, C≡N, C—O, C=O, C—S, and C=S) assisted by non-covalent interactions. We hope it will help the reader to understand some key principles, which can be used for elaboration of new synthetic pathways to target compounds.

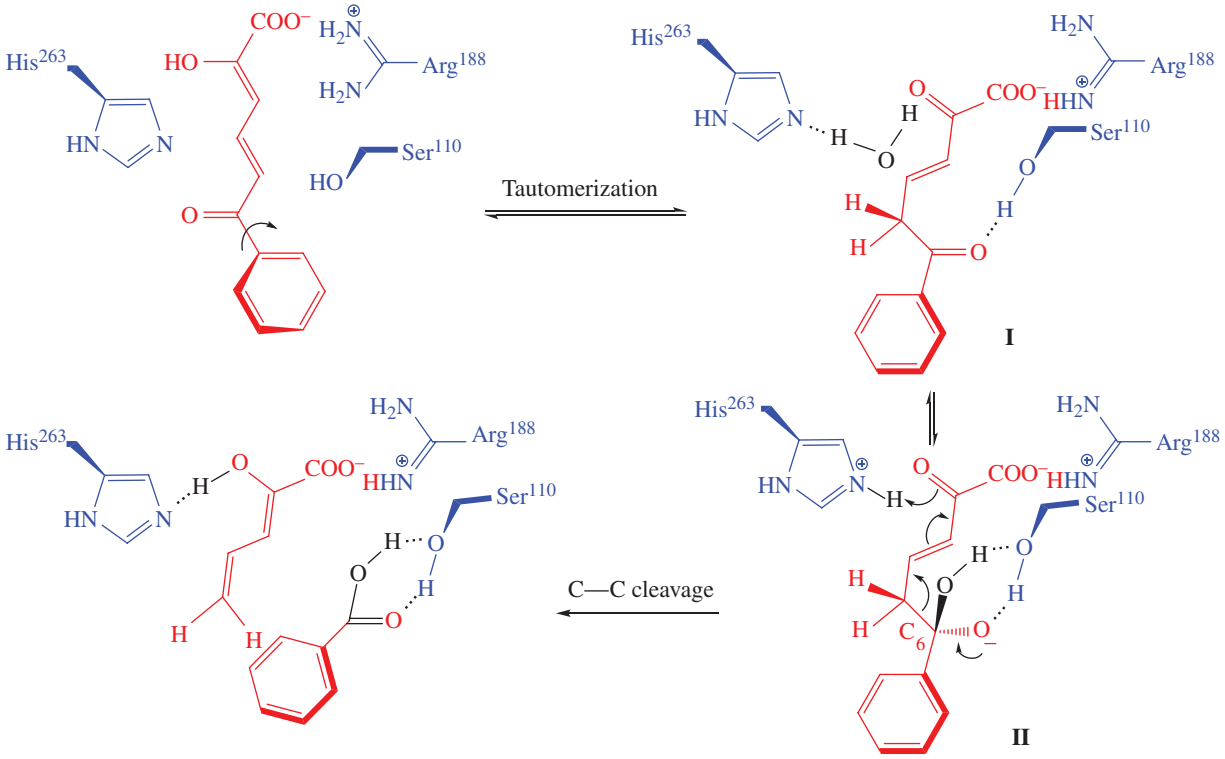
1.2 EXAMPLES OF HYDROGEN BOND-ASSISTED ACTIVATIONS

1.2.1 Activation of C—C Bond

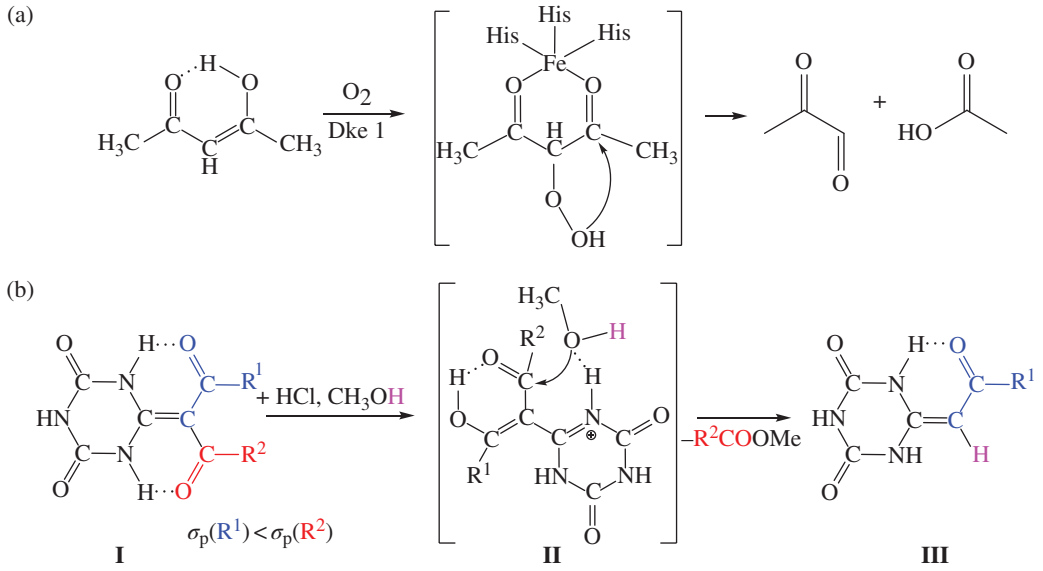
The fission of C—C bonds by incorporation of oxygen (oxidative cleavage) or water (hydrolytic cleavage) is a crucial step in many biochemical pathways through which microorganisms assimilate xenobiotics and environmentally toxic compounds [9]. These reactions are of considerable interest due to their broad array of applications, including fuel production from biomass, removal of organic contaminants, or treatment of diseases. In many cases, the activation of a C—C bond adjacent to a carbonyl moiety is an essential step to reach the goal. For instance, hydrolytic cleavage of C—C bonds catalyzed by hydrolase enzymes is important for the bacterial degradation of aromatic compounds. The proposed mechanism for C—C cleavage in 2-hydroxy-6-keto-6-phenyl-hexa-2,4-dienoic acid, catalyzed by a Ser–His–Arg system (Scheme 1.2), commences by the keto–enol tautomerization of the substrate to give a keto intermediate (**I**), proved by stopped flow kinetic analysis and deuterium isotope exchange studies [10, 11]. Hydrogen bond-assisted nucleophilic attack of H_2O on the C6 carbonyl is then followed by a stereospecific C—C fragmentation (intermediate **II**) to give (*E*/*Z*)-2-hydroxypenta-2, 4-dienoic and benzoic acids [10, 11].

Artificial systems for hydrogen bond-assisted C—C bond activation were elaborated for β-diketones, important precursors for several widely spread heterocyclic compounds (pyrazoles, triazoles, etc.). The cleavage of C—C bonds in β-diketones, also known as retro-Claisen reaction, is of interest due to its relevance to metabolism of aromatics and terpenes, bioremediation, and preparative biocatalysis. Acetylacetone dioxygenase (Dke1) performs oxidative fission of the C—C bond by consecutive coordination of β-diketone to an iron(II) center, dioxygen incorporation with C—O bond formation, and nucleophilic attack of the peroxidate moiety on a carbonyl group (Scheme 1.3a) [9]. A number of retro-Claisen catalytic transformations are known, involving, as catalysts, indium, iron, palladium, copper salts, and complexes [9]. However, a new metal-free C—C cleavage in β-diketones with assistance of, for example, hydrogen bonding can significantly improve the ecological potential of the reaction.

To create an intramolecular hydrogen bond system, which can assist specific nucleophilic attacks to the carbonyl moieties, a triazine moiety was introduced into β-diketones (Scheme 1.3b) [12]. Protonation of the triazine derivatives of



SCHEME 1.2 C─C cleavage in 2-hydroxy-6-keto-6-phenyl-hexa-2,4-dienoic acid [10, 11].



SCHEME 1.3 Acetylacetone dioxygenase (Dke1)-catalyzed oxidative C─C cleavage in acetylacetone (*retro*-Claisen reaction) (a) [9]; regioselective H-bond-assisted C─C cleavage in β-diketones (b) [12].

β-diketone (**I**) leads to the enolic form (**II**). Hydrogen bond-assisted nucleophilic attack of MeOH on this enolic form with liberation of the R^2COOMe ester leads to the formation of the unsymmetrical ketone product **III**. Although the electron donor/acceptor character of substituents within the β-diketone moiety can be rather close [the values of Hammett's σ_p constant are –0.13 for C_3H_7, –0.17 for CH_3, –0.24 for OC_2H_5, –0.27 for OCH_3, and –0.83 for $N(CH_3)_2$], in all the studied cases, the C─C bond breaks selectively at the side of the weaker electron-releasing substituent; the regioselectivity is possibly amplified by the formation of a hydrogen bonding system.

A similar approach was used for the regioselective activation of C─C bond in 4,4,4-trifluoro-1-(thiophen-2-yl)butane-1,3-dione, where an arylhydrazone moiety was introduced to create an intramolecular hydrogen

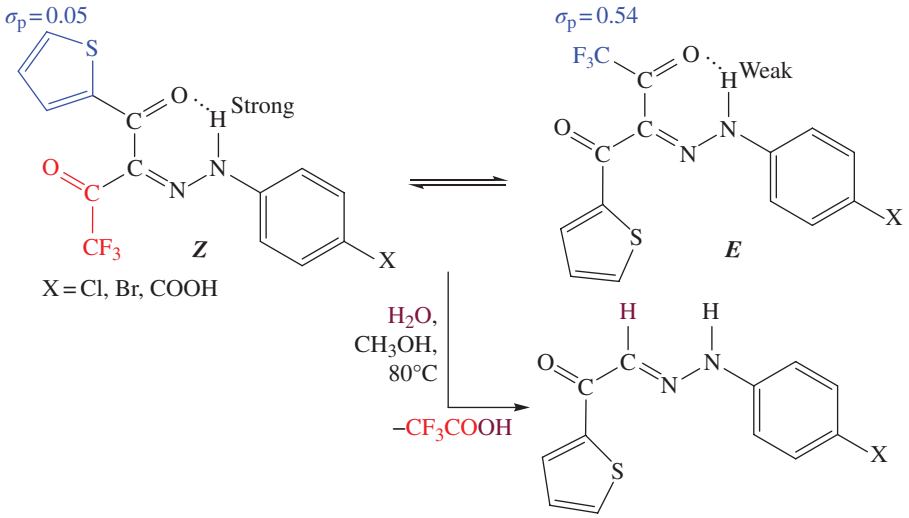
bond at a desired position [13]. In this case, due to the stability of intramolecular hydrogen bonding, the C—C cleavage occurs at the more electron-accepting part of the substituted 1,3-dione (Scheme 1.4). Such hydrogen bond-assisted C—C bond cleavages with elimination of an acetyl group do not require any catalyst and proceed smoothly under ambient conditions, which contrasts to other known reactions of this type.

1.2.2 Activation of C=C Bond

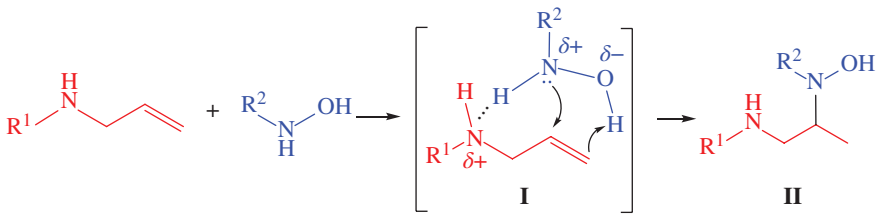
Alkenes are known substrates for many reactions, and economic ways for activation of the C=C double bond, in particular with assistance of the "cost-of-nothing" hydrogen bonding, is becoming a matter of increasing attention. For instance, the hydrogen bonding-directed intermolecular Cope-type hydroamination of alkenes (Scheme 1.5) allows an atom-economical access to various highly functionalized vicinal diamines [14, 15]. In this case, the formed intermolecular hydrogen bonding provides the buildup of positive charges at both N atoms of intermediate **I**. The observed exclusive formation of vicinal diamines **II** most likely originates from the synergy between the H-bonding effect and the propensity of Cope-type hydroaminations to favor Markovnikov addition products.

Michael addition of a nucleophile to electron-deficient olefins is a classical way to construct C—C or C—heteroatom bonds in organic synthesis. A highly enantioselective Michael addition of diethyl malonate with chalcones is catalyzed by cinchona-originated bifunctional tertiary amine–thioureas [16]. The functionalization of the catalyst with hydroxyl group gives rise to multiple hydrogen bonds and thereby significantly enhances the catalytic activity and rigidity of the envisaged transition state, leading to high enantioselectivity and activity (Scheme 1.6). Thus, the carbonyl group in intermediate **I** is activated by the hydrogen bonding interactions between the oxygen atom of the carbonyl with the thiourea moiety and the extra hydroxyl group of **A**. At the same time, diethyl malonate is deprotonated by the basic nitrogen atom of the cinchona moiety. The chiral environment of the alkaloid backbone and the matched amino alcohol moiety enable diethyl malonate to attack the activated chalcone from the *Si*-face (intermediate **I**), giving the *R*-product. If the interaction of chalcone and diethyl malonate is catalyzed by **B**, intermediate **II** is formed and a *Re*-face attack is favored, leading to the *S*-configured product (Scheme 1.6).

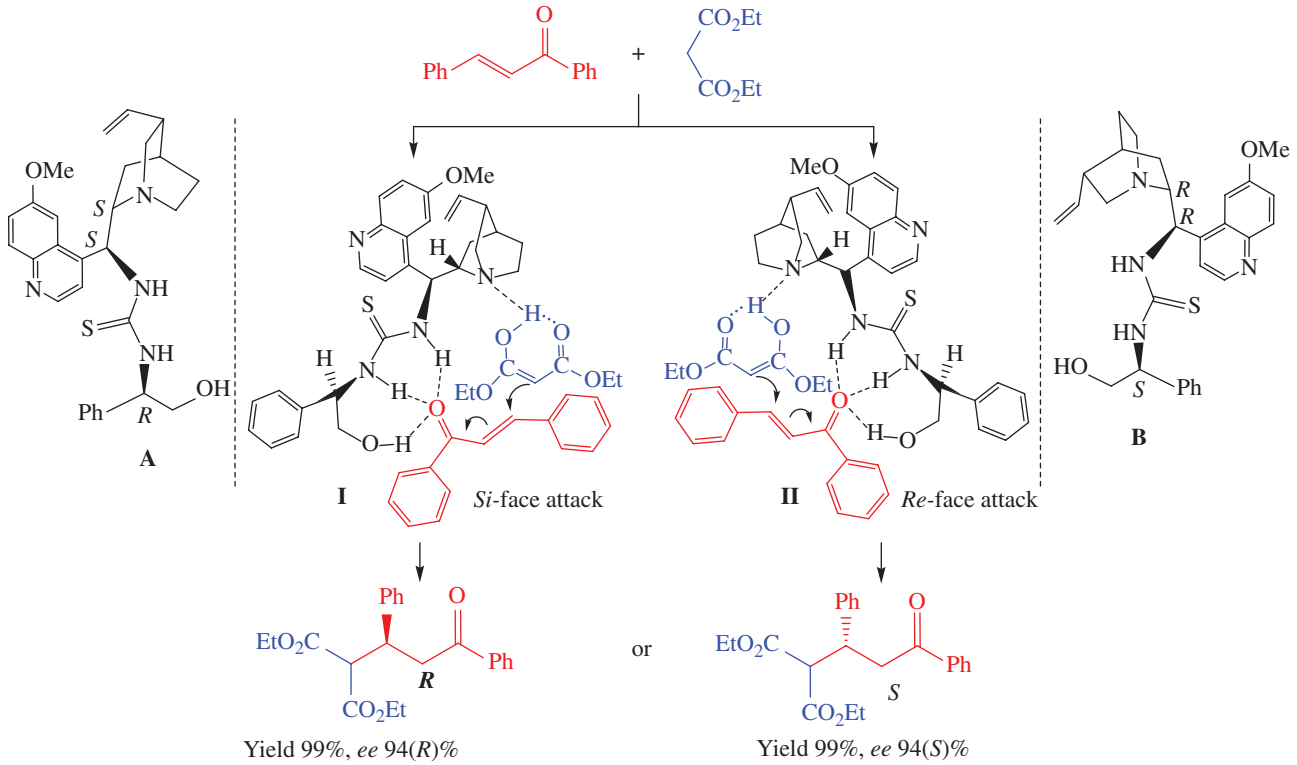
Cyclopropanes are particularly suitable substrates for synthetic applications, and electronic effects of substituents support their specific activation and allow to prepare a high versatility of products with multiple stereocenters [17, 18].



SCHEME 1.4 Regioselective C—C cleavage in (*E*,*Z*)-2-(2-(4-substitutedphenyl) hydrazono)-4,4,4-trifluoro-1-(thiophen-2-yl) butane-1,3-dione [13].



SCHEME 1.5 Cope-type hydroamination of alkenes [14, 15].



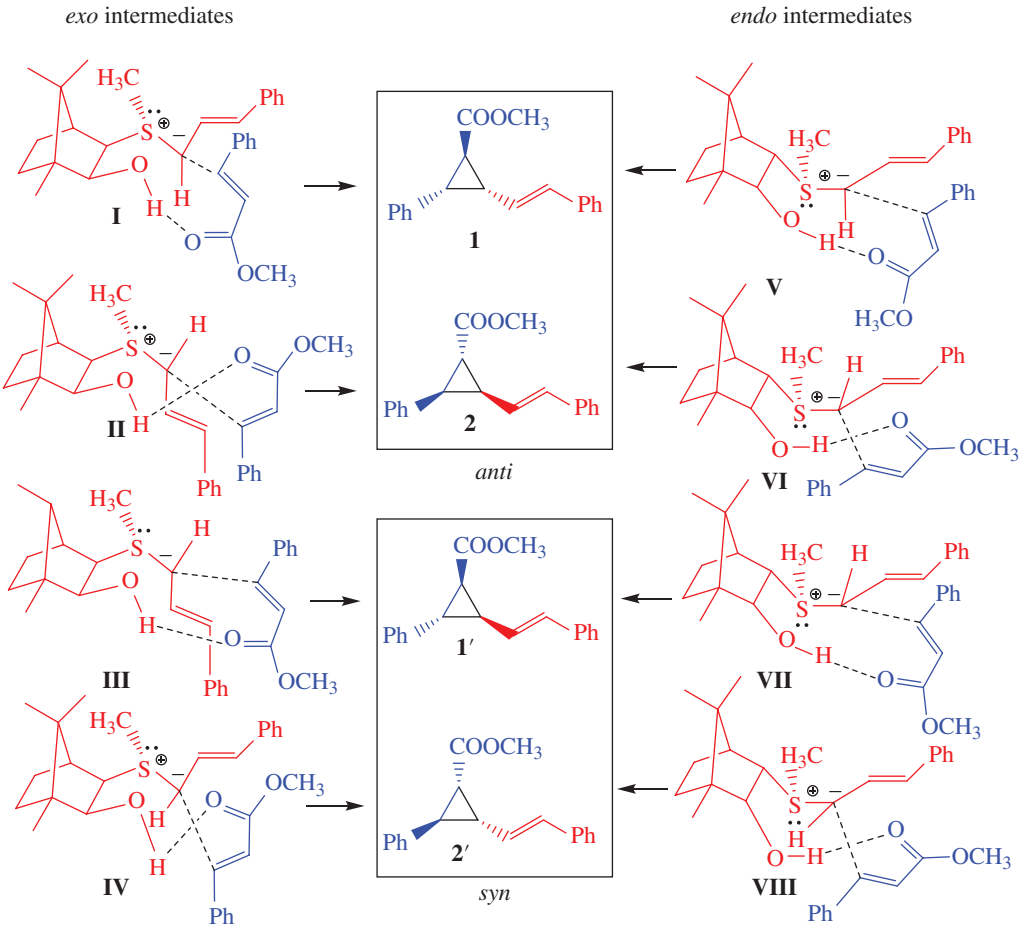
SCHEME 1.6 Asymmetric Michael reaction between chalcone and diethyl malonate [16].

Manifold synthetic methods have been developed for the synthesis of asymmetric vinylcyclopropanes [17], including a hydrogen bond-assisted activation of C=C in methyl cinnamate (Scheme 1.7) [18]. The starting ylide has two conformations, with the vinyl group either *syn* (e.g., in **I** and **IV**; in **V** and **VIII**) or *anti* (e.g., in **II** and **III**; in **VI** and **VII**) to the sulfur lone pair. Hence, theoretically eight hydrogen bond-assisted intermediates can be formed for each ylide (Scheme 1.7). The proposed model with the formation of 10-membered hydrogen bonding ring provides an explanation for the opposite enantioselectivities of *exo* and *endo* sulfur ylide cyclopropanation reactions. Thus, due to the ring constraint and steric CH–O and CH–S hindrances with the norbornyl group, the intermediates **II**, **IV**, **V**, and **VII** are forced to distort. Due to the directionality of hydrogen bonding, the hydroxyl group plays a critical role in the control of enantioselectivity (98 or 99%) and diastereoselectivity (99/1). The solvent also plays an important role in enhancing both diastereo- and enantioselectivity, possibly due of its participation in non-covalent interactions with intermediates [18].

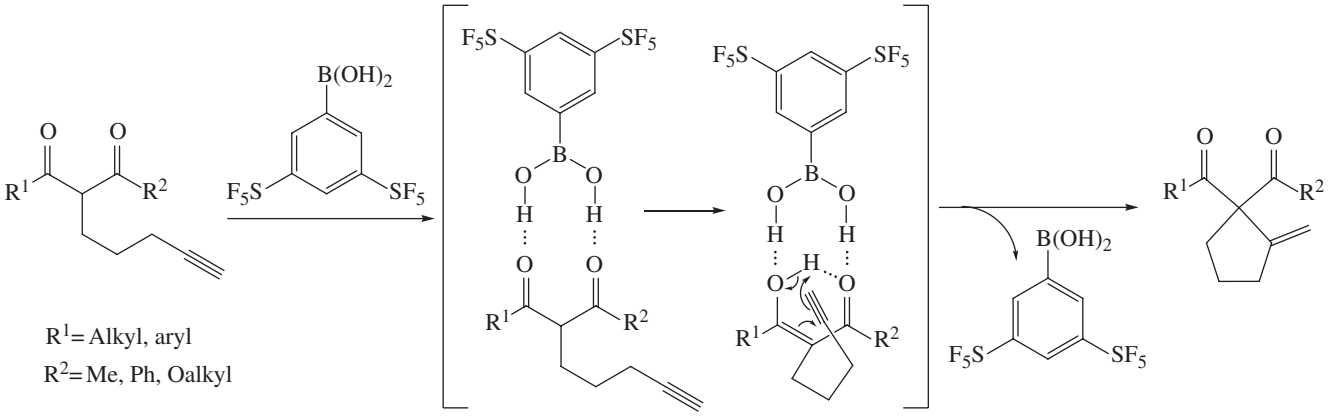
1.2.3 Activation of C≡C Bond

Alkynes can be used as nucleophiles or electrophiles, which provide a wide diversity of reactions in which they can be involved. For instance, intermolecular cycloadditions to alkynes can lead directly to a variety of carbocyclic compounds, but metal-containing catalysts are usually necessary [19]. On the other hand, many substrates in reactions with alkynes can be activated by amines or ammonium salts in combination with inorganic bases; the non-covalent interactions can play an important role in those cases [20]. Thus, hydrogen bond-assisted activation of the C≡C triple bond in acetylenic β-diketones can lead to enantioselective carbocyclization (Conia-ene reaction; Scheme 1.8) [21]. This reaction represents one of the most direct ways to carbocycles and is particularly attractive for the preparation of cyclopentane derivatives. The H-bond acceptor catalyst 3,5-bis(pentafluorosulfanyl)phenylboronic acid is more active in a nonpolar solvent such as toluene and 1,1,1,3,3-pentafluorobutane in comparison to 3-nitro phenylboronic acid, which indicates that the SF_5 function can be a lipophilic and sterically demanding alternative to the NO_2 group in catalyst design. The possible mechanism of this reaction involves H-bond-assisted enolization of starting 2-alkynic β-diketones; a subsequent concerted ene reaction of the enol form affords the product (Scheme 1.8).

H-bond-assisted enantioselective isomerization of 3-alkynoates to chiral allenoates (Scheme 1.9) [22, 23] with benzothiadiazine-1,1-dioxide-type catalysts is of particular importance for the synthesis of many biologically active compounds. The Brønsted base-catalyzed 1,3-proton shift allows to promote the isomerization of alkynoates to allenoates with a high enantioselectivity [22]. The enantioselectivity of the reaction can be explained by the H-bond-assisted deprotonation of both alkynoate enantiomers in intermediates **A** and **B**; this enables their interconversion.



SCHEME 1.7 Hydrogen bond-assisted enantio- and diastereoselective synthesis of vinylcyclopropanes [18].

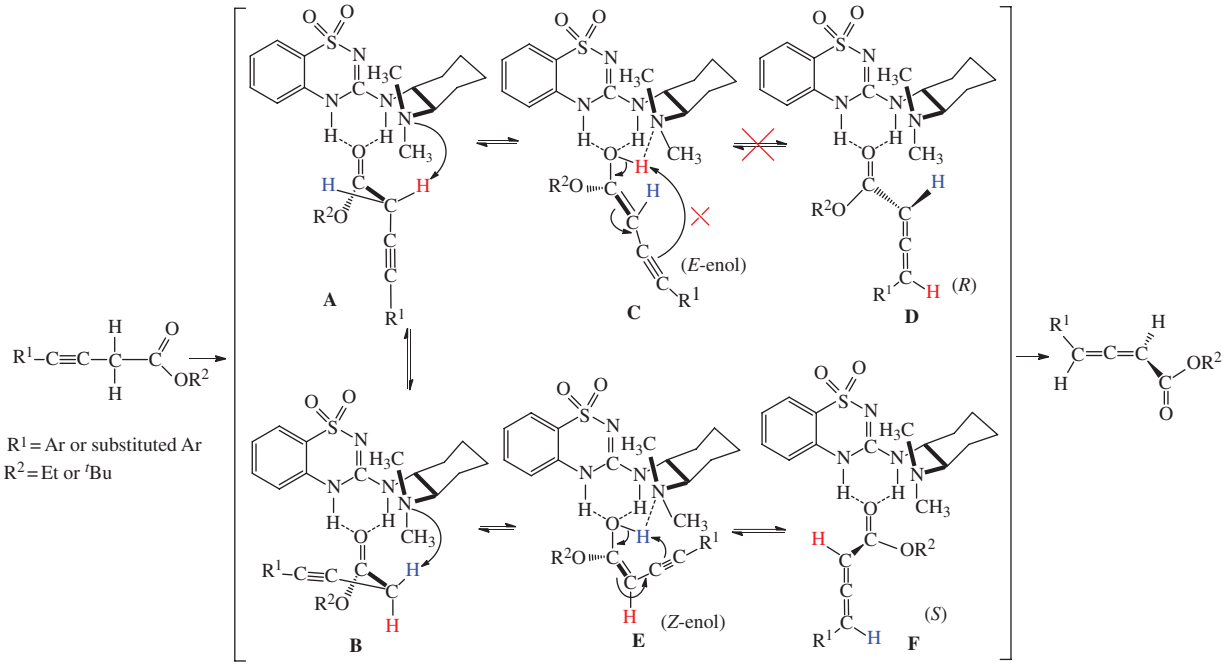


SCHEME 1.8 Enantioselective cyclization of acetylenic β-dicarbonyl compounds [21].

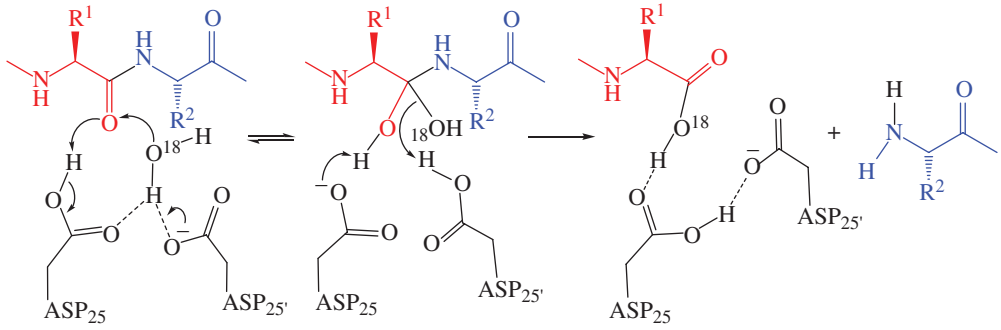
However, the intermediate **C** (*E*-enol), derived from **A**, does not isomerize into (*R*)-allenoate **D**, because the ammonium proton cannot reach the γ-sp-carbon of the alkynoate, while the isomerization of **B** into (*S*)-allenoate **F** occurs smoothly via the H-bond-assisted intermediate *Z*-enol **E** to give the intermediate **F** and finally the targeted allene (Scheme 1.9).

1.2.4 Activation of C—N Bond

To activate the C—N bond in amines and related compounds, different types of catalysts have been used, and in many cases the activation processes occur via an intermediate with hydrogen bonding. For instance, a H-bond-assisted mechanism is



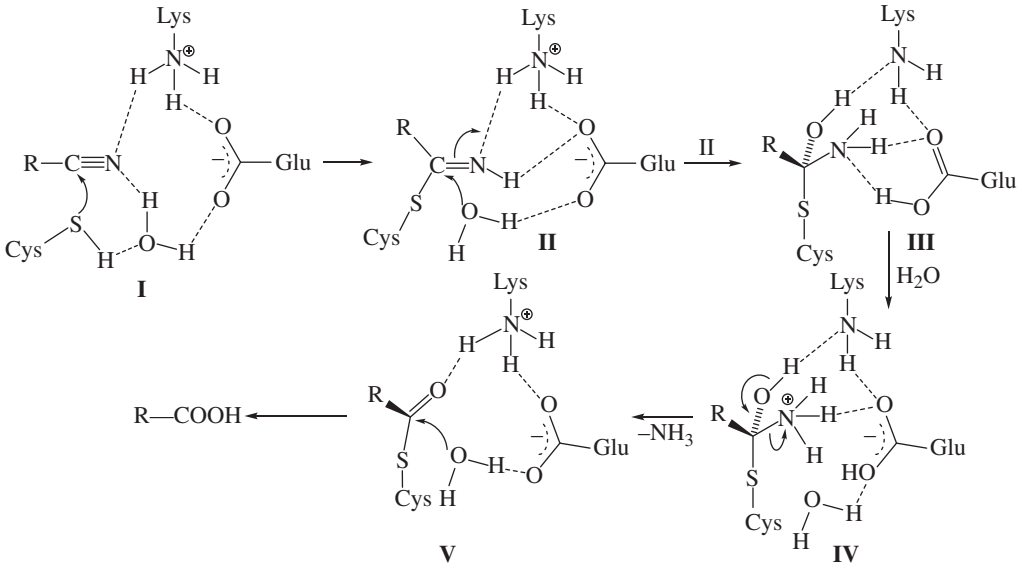
SCHEME 1.9 Activation/isomerization of alkynoates [22].



SCHEME 1.10 Polypeptide hydrolysis within aspartic proteases [24].

considered most likely for polypeptide hydrolysis catalyzed by aspartic proteases (Scheme 1.10). According to a proposed mechanism [24], one aspartate residue of the enzyme undergoes protonation, while the second one is ionized. Indeed, there is experimental evidence that the two aspartates share one proton at a physiological pH [24]. Thus, one aspartate activates a water molecule by abstracting a proton; this enables water to attack the carbonyl carbon of the substrate scissile bond, generating a tetrahedral zwitterionic intermediate; its reorganization leads to protonation of the scissile amide. An additional water molecule interconnects the substrate and the main chain amide groups of the enzyme via H-bond and is thought to twist the scissile peptide bond out of planarity, thereby facilitating its cleavage.

Another example of hydrogen bond-assisted activation of a C—N bond is provided by the hydrolysis of carboxyamides to carboxylic acids. Usually, one-step hydrolysis of a nitrile to a carboxylic acid occurs through the formation of an amide as an intermediate and requires harsh acidic or basic reaction conditions; however, a Glu–Lys–Cys catalytic triad can be used as an organocatalyst for the C≡N bond hydrolysis and for the subsequent C—N bond cleavage in nitriles (Scheme 1.11) [25]. The proposed mechanism suggests a nucleophilic attack on the nitrile carbon atom by a conserved cysteine residue of the catalyst; the formed thioimidate affords subsequently a tetrahedral intermediate with the H-bond-assisted addition of water (intermediates **I**→**II**→**III**). In **III**, glutamate acts as a base, while the lysine residue is involved in stabilization of a tetrahedral transition state. Addition of the water molecule leads to the H-bonding intermediate **IV**. Elimination of NH_3 from this intermediate gives a thioester **V**, which reacts with a second water molecule to afford carboxylic acid.



SCHEME 1.11 Hydrolysis of nitriles with the Glu–Lys–Cys catalytic triad [25].

1.2.5 Activation of C═N Bond

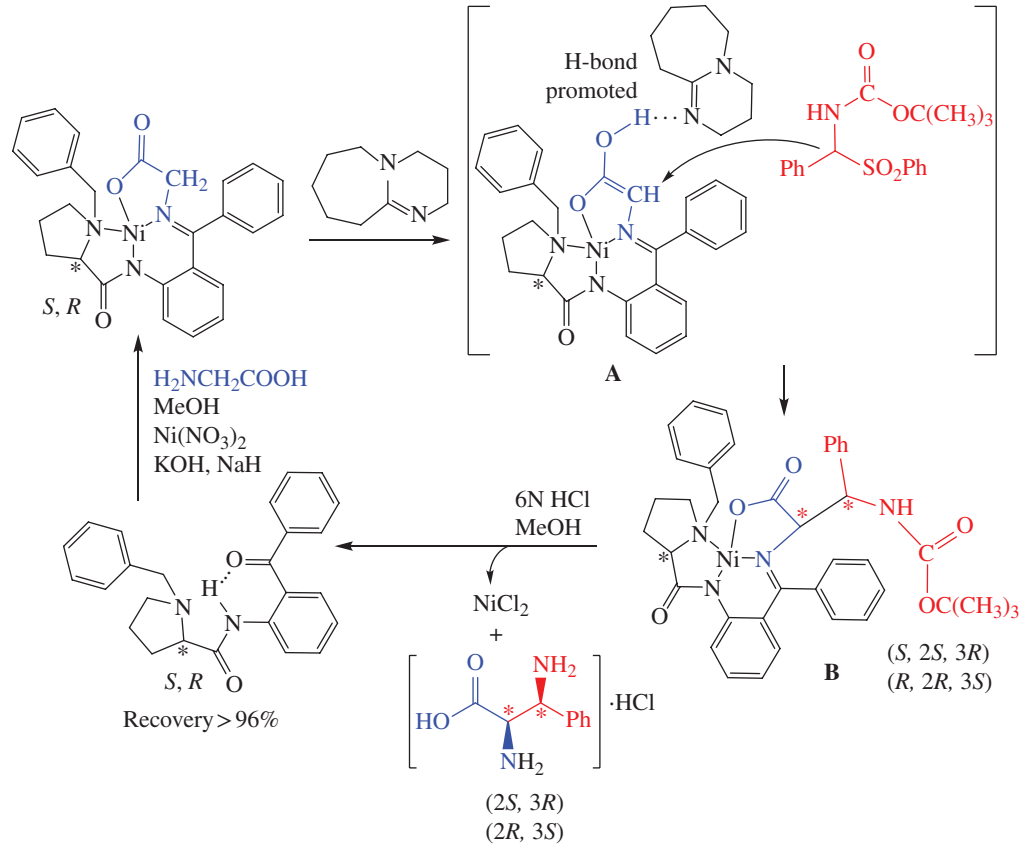
The activation of C═N double bonds of imines provides convenient and versatile routes to many organic compounds such as cucurbituril, oxaziridines, optically active amines bearing a stereogenic center, etc. [26]. Recently much attention has been devoted to the development of new methods for stereoselective generation of nitrogen-bonded chiral centers, among the most thoroughly investigated being addition reactions to C═N functionalities [27]. For instance, enantio- and diastereoselective Mannich reactions between a chiral Ni(II) complex of glycine and α-amino sulfones such as *tert*-butyl(phenyl(phenylsulfonyl)methyl)carbamate involve the H-bond promoted creation of a carbon–carbon bond and two stereogenic centers in a single run (Scheme 1.12) [28]. This method represents an attractive route to the synthesis α,β-diamino acids, versatile chiral auxiliaries and ligands for asymmetric synthesis, and medicinal and peptide/peptidomimetic chemistry [28, 29]. The proposed mechanism (Scheme 1.12) involves three steps: (i) enolization of a (*S*)-Ni(II) complex, promoted by 1,8-diazabicyclo[5.4.0]-undec-7-ene, which creates a hydrogen bond with substrate to form the intermediate **A** (benefiting 9.46 kcal/mol); (ii) reaction of Ni(II)-enolate with *tert*-butyl(phenyl(phenylsulfonyl) methyl)carbamate to give *syn* and *anti* diastereoisomers of compound **B**; and (iii) release of an α,β-diamino acid as a HCl adduct and $NiCl_2$ with the intramolecular hydrogen bond-assisted recovery of the ligand precursor.

The enantioselective hydrogenation of imines is used as one of the most efficient and convenient methods for the preparation of chiral amines and their derivatives. Thus, asymmetric synthesis of nonracemic 1,3-diamines by hydrogen bond-directed diastereoselective reduction of enantiopure *N*-*tert*-butanesulfinylketimines (Scheme 1.13) involves *E*/*Z* isomerization of *N*-*tert*-butanesulfinylketimines, which was found to depend on the solvent [30]. The correlation between facial selectivity of the reduction and *E* or *Z* geometry of the starting ketimines suggests the involvement of a cyclic transition state stabilized with hydrogen bond. The *ortho*-substituent participates in hydrogen bonding thus controlling the geometry of *N*-*tert*-butanesulfinylketimines: *E*-imines are reduced to give *R* configuration at the newly created chiral center, while the *Z*-isomer affords the *S* configuration.

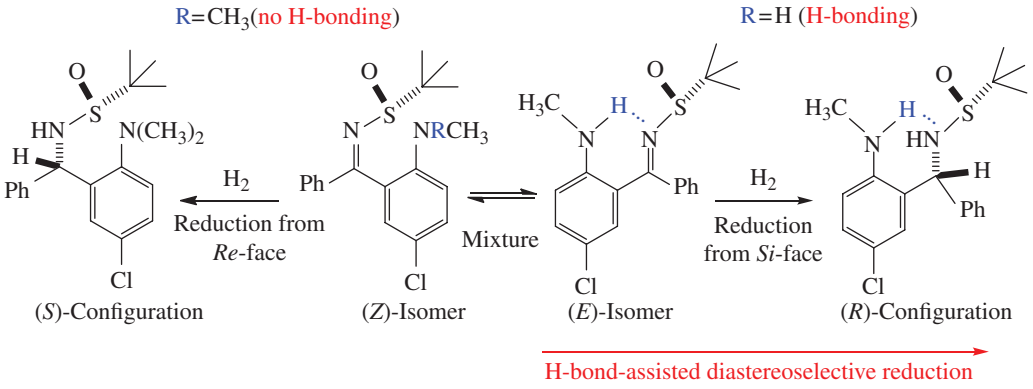
Nucleophilic addition of nitroalkanes to imines to give β-nitroamine derivatives, known as aza-Henry reaction, is another useful C═N bond activation process [31]. Many organocatalysts are applied to reach higher diastereo- and enantioselectivities, which, in many cases, are essentially directed by H-bonding [32]. Thus, upon the asymmetric aza-Henry reaction of ketimines derived from isatins with nitroalkanes using cinchona alkaloids as organocatalysts (Scheme 1.14), the tertiary amine group of the catalyst deprotonates the α-proton of nitroethane, activating it for nucleophilic attack on the *Re*-face of ketimines, which, in their turn, are activated through hydrogen bonding with the ─OH group of the catalyst, providing the (*R*)-enantiomer of the product [33]. Hence, high diastereo- and enantioselectivities were obtained in this reaction through the synergistic activation of ketimines and nitroalkanes by a bifunctional alkaloid organocatalyst.

1.2.6 Activation of C≡N Bond

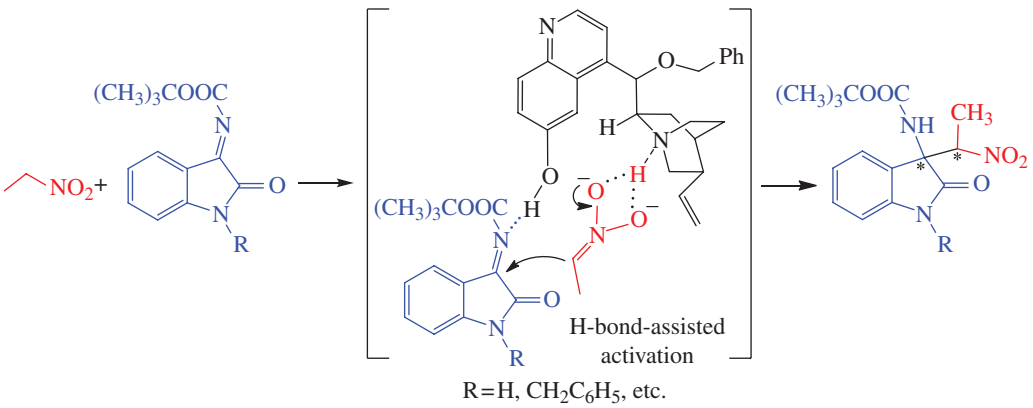
Reactions of electrophiles or nucleophiles with organonitriles are among the most significant ones in organic synthesis [34, 35]. Many methods have been developed to activate the C≡N bond, namely, involving the use of an electron-withdrawing R group in the R─C≡N nitrile molecule, protonation or alkylation of the nitrile N atom, or coordination to a metal center [34]. These methods suffer from various drawbacks,



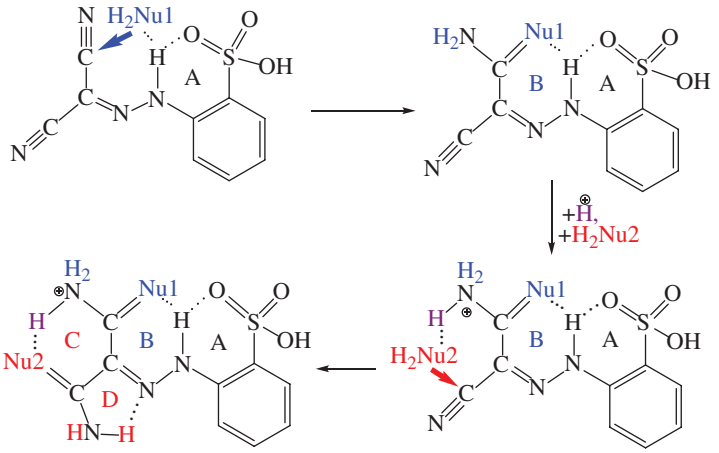
SCHEME 1.12 Stereoselective synthesis of enantioenriched α,β-diamino acids via a chiral imine complex of Ni(II) with sulfones [28].



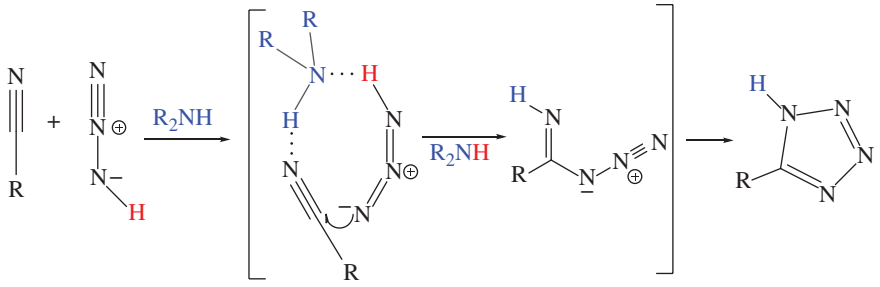
SCHEME 1.13 Diastereoselective reduction of diaryl *N-tert*-butanesulfinylketimines to nonracemic 1,3-diamines [30].



SCHEME 1.14 Proposed dual H-bond-assisted activation for the asymmetric aza-Henry reaction of nitroethane with ketimines [33].



SCHEME 1.15 Regioselective activation of C≡N bonds in an arylhydrazone of malononitrile [36].



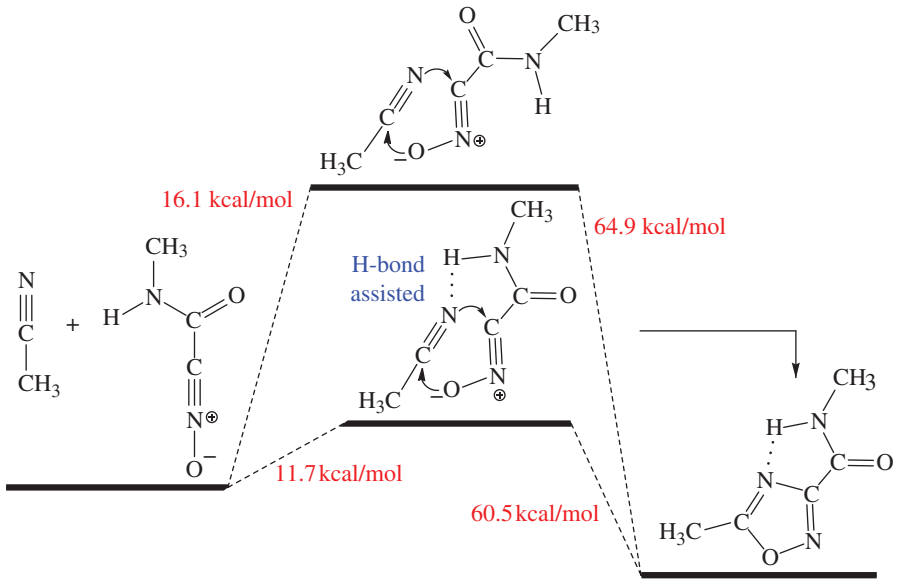
SCHEME 1.16 Proposed [37] mechanism for the direct synthesis of tetrazoles.

for example, high cost of the catalysts, difficulties in the separation of the product and catalyst, the use of an inert atmosphere for handling air-sensitive metal catalysts, etc. As a result, the activation of the C≡N bonds assisted by non-covalent interactions is of a growing interest.

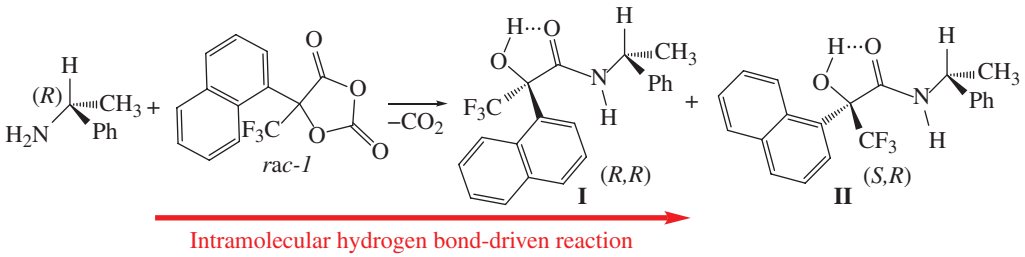
To create a supporting hydrogen bond system for the regioselective activation of C≡N bonds, an arylhydrazone unit was introduced to malononitrile (Scheme 1.15) [36]. The thus obtained compound has a six-membered cycle with hydrogen bonding (A); the product of addition of a nucleophile (Nu1) is further stabilized by another hydrogen bonding system (B), thus "freezing" the product of only one attack. The nucleophilic attack on a second C≡N group is only possible after acidification of this product: addition of an acid leads to protonation of the nitrogen atom of the amino group, promoting the formation of another hydrogen bond, which assists nucleophilic attack by the second nucleophile (Nu2). Stabilization of this product is supported by the formation of two more six- and five-membered H-bond cycles (C and D). Hence, a convenient regioselective metal-free syntheses of a variety of products can be performed.

Another example of hydrogen bond-assisted activation of C≡N bonds is in field of the synthesis of tetrazoles, popular compounds as catalysts, propellants, explosives, ligands in coordination chemistry, and nonclassical isosteres of carboxylic acids in medicinal chemistry [37–39]. This broad utility has prompted significant efforts toward tetrazole synthesis; the most direct method is via the formal cycloaddition of azides and nitriles. Thus, interaction of azide salts with a nitrile under certain conditions produces the corresponding tetrazoles in high yields (Scheme 1.16) [38]. Mechanistic studies support the formation of a quite stable H-bond-assisted intermediate [37]. Its stability increases with the electron-withdrawing potential of the substituent on the nitrile: for R = Me the intermediate is 3.3 kcal/mol less stable than the free reactants, HN_3 and MeCN, while it shows 11.4 kcal/mol lower energy than the free reactants, when $R = CH_3S(=O)_2-$. The transition state involves activation of nitrile by a proton, which facilitates the attack of azide on the carbon of nitrile, and then a 1,5-cyclization occurs to give the tetrazole [37].

Hydrogen bond-assisted interaction of nitrile oxide with aliphatic or electron-rich aromatic nitriles leads to 3-functionalized 1,2,4-oxadiazoles (Scheme 1.17); the reaction proceeds under mild conditions even in the absence of a Lewis acid [40]. Among functionalized 1,2,4-oxadiazoles, carbamoyl-substituted ones have attracted much attention because of their biological activity and utility for diabetes treatment [40]. Furthermore, the carbamoyl group can be used as a precursor to introduce other functional groups. Mechanistic studies support the inverse electron-demanding 1,3-dipolar cycloaddition and suggest that the carbamoyl group of nitrile oxide activates the dipolarophilic nitrile by hydrogen bonding (Scheme 1.17). Thus, the carbamoyl group of nitrile oxide plays an important role not only as an electron-withdrawing group but also as a H-donor to form a



SCHEME 1.17 Possible ways for the 1,3-dipolar cycloaddition of nitrile oxides to acetonitrile [40].



SCHEME 1.18 Reaction of *rac*-(1-naphthyl)(trifluoromethyl) *O*-carboxy-anhydride with (*R*)-α-methylbenzylamine [41].

hydrogen bond with a dipolarophilic nitrile. In order to probe the effect of the hydrogen bond, both intermediates, in which only the orientation of the carbamoyl group is different, were considered (Scheme 1.17). The H-bond-assisted intermediate was found to be more stable than non-H-bonded one in 4.4 kcal/mol; hence, the formation of a hydrogen bond with the carbamoyl group of nitrile oxide facilitates the inverse electron-demanding cycloaddition.

1.2.7 Activation of C—O Bond

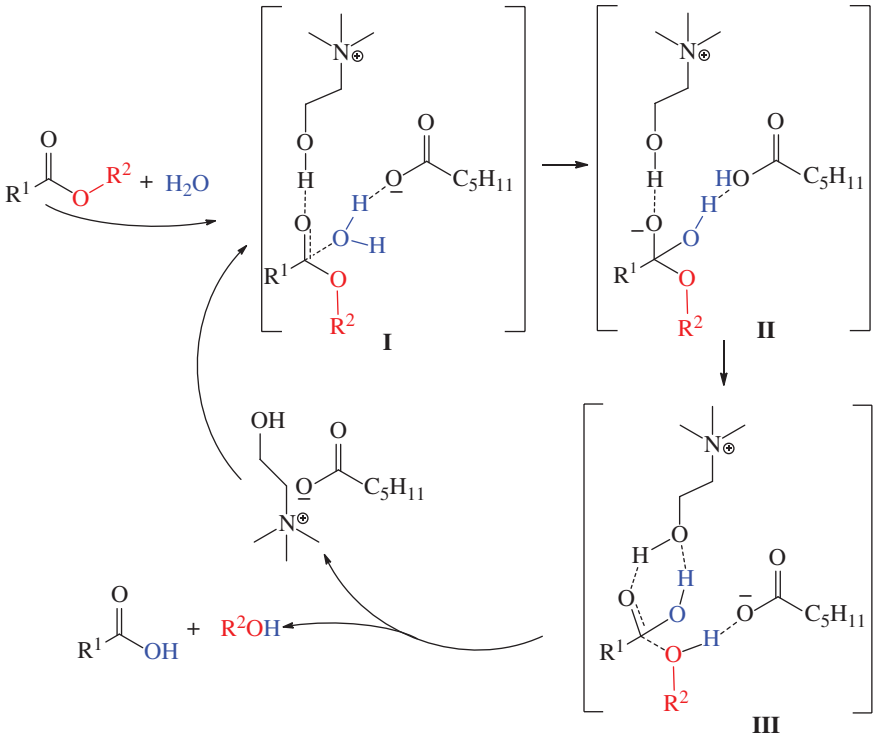
The hydrogen bond-driven reaction between *rac*-(1-naphthyl) (trifluoromethyl) *O*-carboxy-anhydride and (*R*)-α-methylbenzylamine afforded an equimolar mixture of α-hydroxyamides **I** and **II** (Scheme 1.18) [41]. Due to strong intramolecular hydrogen bonding, high $\Delta\delta^{RS}$ values were observed in the ^{1}H NMR spectra of the obtained compounds and have been correlated with a marked preference of the corresponding α-hydroxyamides for the *eclipsed conformation*. This fact can be explained by maximization of the anisotropic effect of the naphthyl group. For comparison, the related O-methylated amides are shown to adopt staggered conformations, which substantiate the critical role of intramolecular hydrogen bonding in maximizing the anisotropic effect. Accordingly, this *O*-carboxy-anhydride can be considered a promising chiral derivatizing agent; hence, further improvements can be expected in both reactivity and resolution efficiency by varying the substitution pattern.

Another example of the hydrogen bond-assisted C—O bond activation is the hydrolysis of esters to acids and alcohols, catalyzed by the ionic liquid cholinium hexanoate, $[(CH_3)_3NCH_2CH_2OH]^+[C_5H_{11}COO]^-$ (Scheme 1.19) [42].

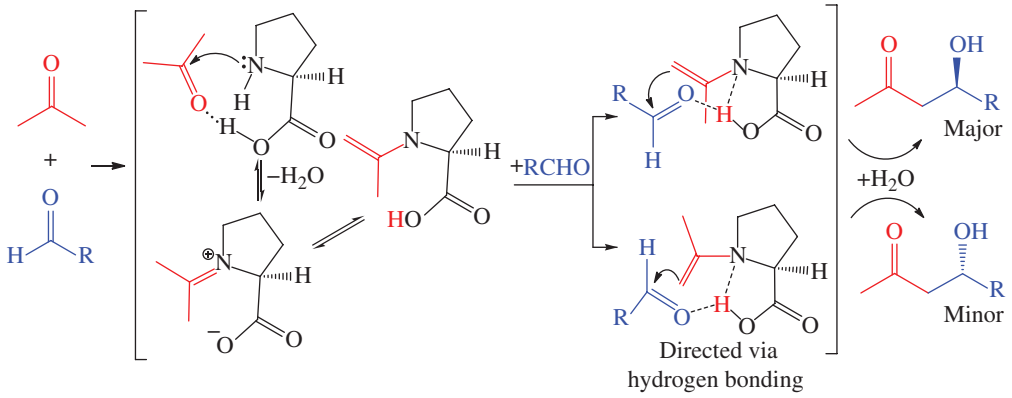
A mechanism of the reaction involves two steps. (i) The hydroxyl group of the cholinium cation establishes a hydrogen bond with the oxygen atom of the carbonyl group of the ester, favoring the nucleophilic attack of water at the carbon (intermediate **I**). As a result, a proton of water molecule shifts to the $C_5H_{11}COO^-$ anion (intermediate **II**). (ii) Intramolecular proton transfer leads to six-membered H-bond system, weakening the C—O bond in intermediate **III**. Finally, the products, the acid and the alcohol, are formed, and the ionic liquid is regenerated, closing the H-bond-assisted catalytic cycle.

1.2.8 Activation of C═O Bond

Activation of the C═O double bond in carbonyl compounds is a strategically important method for the synthesis of a large number of building blocks, such as β-hydroxy carbonyl



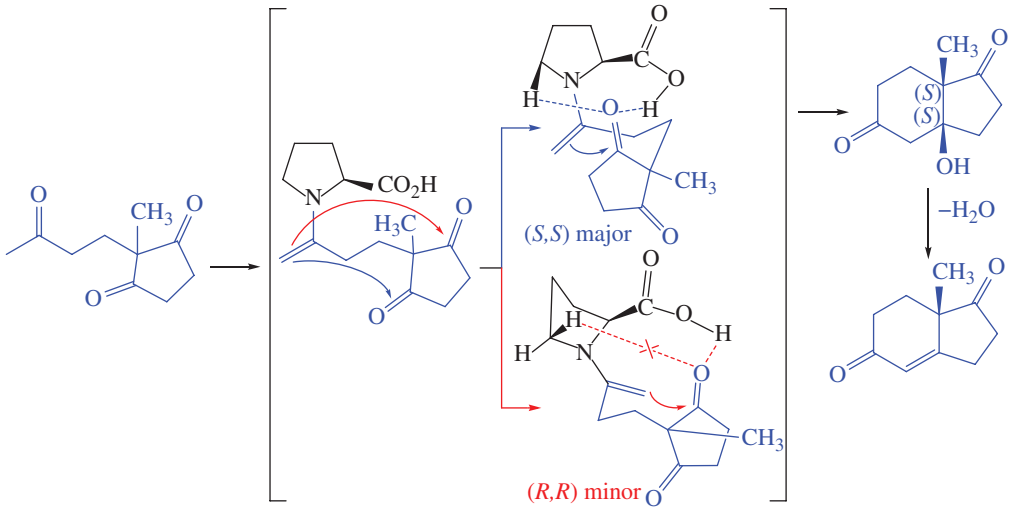
SCHEME 1.19 Hydrogen bonding in the hydrolysis of ethers [42].



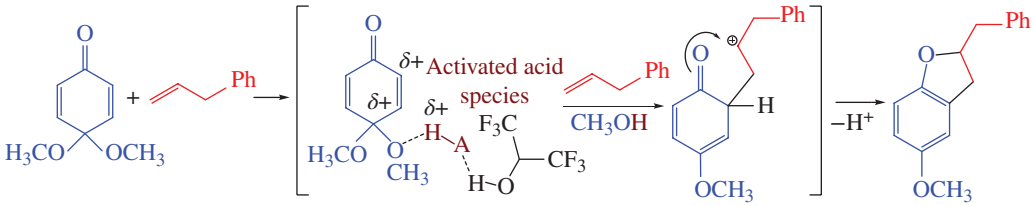
SCHEME 1.20 Proline-catalyzed asymmetric aldol reaction [45].

compounds (Aldol reaction), β-nitro alcohols (Henry or nitro-aldol reaction), thioacetals, hemiacetals, hemiketals, cyanohydrins, etc. [43]. Numerous methodologies, including metal-mediated approaches, for the C═O bond activation have been developed [43, 44]; the viability of non-covalent interactions in the aldol and related reactions has also been proved [45–48]. In those cases, non-covalent interactions weaken the C═O bond of carbonyl compound via hydrogen bonding with the lone pair of the oxygen atom and make it more susceptible for nucleophilic attack. It is not surprising that a plethora of carbonyl chemistry can be performed simply by adding a catalytic quantity of a strong protic acid (proton donor) to a mixture of carbonyl compound and a nucleophile. The formation of β-nitro alcohols from carbonyl compounds and nitroalkanes serves as an example.

Asymmetric aldol reaction involves the C═O bond activation and allows to build a variety of pharmaceutically relevant substances, in particular those with polyoxygenated subunits. Thus, the proline-catalyzed asymmetric aldol reaction is supposed to occur via an enamine intermediate (Scheme 1.20) [45]. In this case, the intermolecular hydrogen bond assists the nucleophilic attack of the amino group of pyroline to the C═O carbon resulting in the pyrrolidinum carboxylate formation and elimination of a water molecule. Hence, proline plays a dual role, forming, as secondary amine, a key nucleophilic enamine intermediate (activation of acetone), while the carboxylic acid group activates the aldehyde toward nucleophilic attack of the enamine. The enantioselectivity of the reaction can be related to the stability of the H-bond-assisted intermediates, which lead to the major product [45].



SCHEME 1.21 C—H···O interaction-directed asymmetric Hajos–Parrish reaction [47].



H-bond donor

SCHEME 1.22 Synthesis of benzofurans based on non-covalent interactions of Brønsted acids with hexafluoroisopropanol [49].

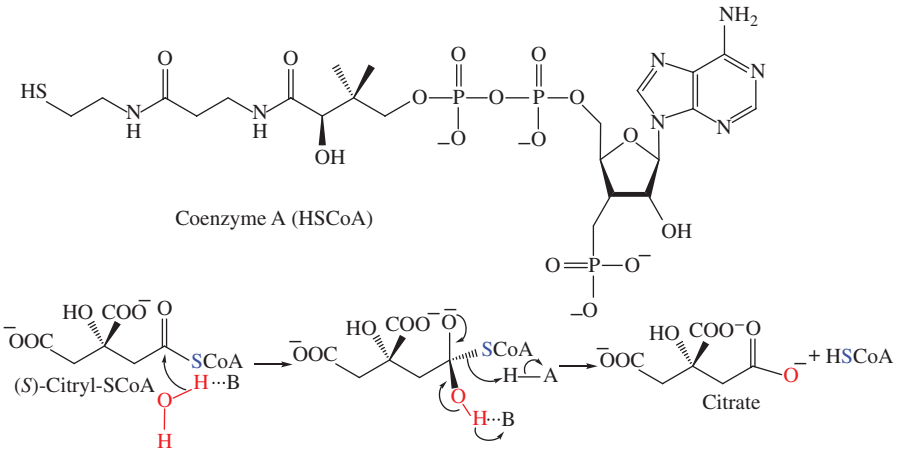
Although the C—H···O/N contacts are weaker than typical hydrogen bonds, they still provide enough stabilization to render control of selectivity [46]. The C—H···O interactions were also found to be important in controlling the stereoselectivity in the Hajos–Parrish-type aldol and Mannich reactions. Thus, proline-catalyzed intramolecular Hajos–Parrish transformation of 2-methyl-2-(3-oxobutyl) cyclopentane-1,3-dione (Scheme 1.21) was shown to be directed by C—H···O interactions [47].

The obtained high stereoselectivity is explained by the following facts: (i) the greater iminium planarity distortion in one H-bonded (*R*,*R*) *syn*-enamine compared to two H-bonded *anti* (*S*,*S*) ones and (ii) the ability of a prolinyl C(sp^3)—H to stabilize the developing negative charge on the carbonyl oxygen, the major (*S*,*S*) product exhibiting a shorter C—H···O interaction and a lower energy (by 3.4 kcal/mol) than the minor (*R*,*R*) product where this interaction is more distant and presumably weaker.

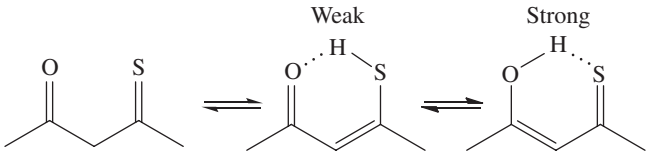
Quinone monoacetals possess both α,β-unsaturated carbonyl and allyl acetal functionalities in one skeleton and are interesting due to their broad utilities in organic transformations, as intermediates and important building blocks for the synthesis of natural products [48]. The reactions of nucleophilic attack on quinone monoacetal carbons include, for instance, addition to the carbonyl carbon (i.e., 1,2-additions), conjugated addition to the enone moiety (e.g., 1,4-additions), and cyclizations involving those processes. Regarding the chemo- and regioselective reactions, many applied organic and inorganic catalysts relay on cooperative action of non-covalent interactions, coordination, etc. [48]. The strategy for the [3+2] coupling of quinone acetal with a series of alkene nucleophiles (Scheme 1.22) utilizes a Brønsted acid activated upon hydrogen bond with the donor solvent, hexafluoroisopropanol [49]. This polar solvent has a high hydrogen bond donor ability and does not behave as a hydrogen bond acceptor. The H-bonded intermediate allows cyclization of the carbonyl moiety in the keto-type tautomer, which is accompanied by aromatization as an additional driving force to afford the formal [3+2] coupling product.

1.2.9 Activation of C—S Bond

The transformations of the thiol (R—SH) or thioether (R—S—R′) groups and their derivatives are key steps of many enzymatic reactions and metabolic processes. For instance, coenzyme A (HSCoA) is a cocatalyst for activations of a number of substrates in organisms; as an example, the conversion of (*S*)-citryl-SCoA to citrate in the Krebs cycle (Scheme 1.23) can be mentioned. The reaction occurs by H-bond-assisted nucleophilic attack of enolate or thioester on the α-carbon of citrylate [50]. The hydrolysis



SCHEME 1.23 Hydrolysis of thioether to citrate in the Krebs cycle.



SCHEME 1.24 Keto–enol tautomerism in 4-thioxopentan-2-one.

of the thioester (citryl-SCoA) formed upon aldol condensation provides a significant free energy reduction ($\Delta G^{\circ\prime} = -31.5$ kJ/mol or -7.5 kcal/mol), which drives forward the net reaction.

1.2.10 Activation of C═S Bond

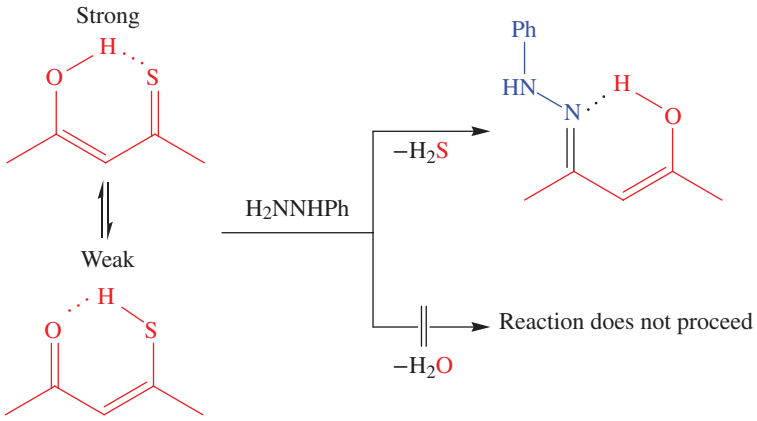
Stereospecific nucleophilic attack on the carbon atom of C═S is a simple and versatile way to construct stereocenters next to heteroatoms with an overall inversion of stereochemistry [51]. In many cases, intermolecular and intramolecular hydrogen bonds not only control the stereochemistry but also influence the reactivity and other properties of thioketones or thioaldehydes. The C═S bond in thioketones is longer than the corresponding C═O bond in ketones, and its length also depends on the substituents. The sulfur atom is a weaker hydrogen bond acceptor to oxygen, and accordingly, the intramolecular O─H···S hydrogen bonding is preferable to the S─H···O one (Scheme 1.24) [52]. This effect is manifested in the reactivity of 4-thioxopentan-2-one: only the regioselective thioketo transformation is found in its condensation with phenylhydrazine (Scheme 1.25) [53].

1.3 HALOGEN BOND-ASSISTED ACTIVATIONS

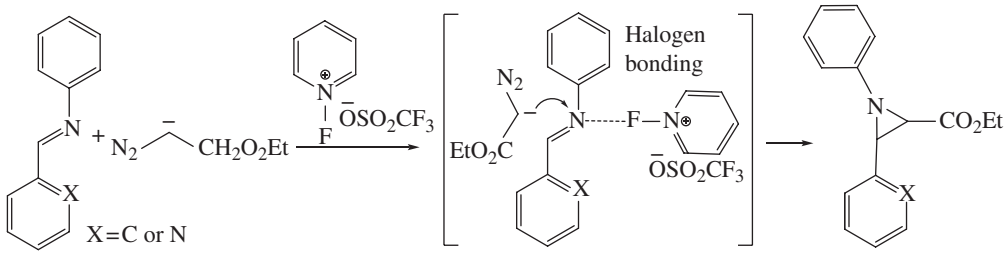
Halogen bonding concerns non-covalent interactions between terminal halogen atoms in compounds of the type R─X (X = Cl, Br, I) and Lewis bases [7, 54]. Stronger halogen bonds are formed when R is highly electronegative, for example, in the case of polyfluorinated alkyl or phenyl substituents. Several primary differences between halogen and hydrogen bondings can be mentioned [54]: (i) halogen bonds tend to be more directional than (single) hydrogen bonds; (ii) the strength of a halogen bonding can be easily tuned, while in the case of a hydrogen bond, considerable changes are required into the residue the donor site is bound to; (iii) halogen bonds are hydrophobic, whereas hydrogen bonds are hydrophilic; (iv) the size of the bond donor (halogen) atom is significantly larger than hydrogen. The halogen bonding has found some useful applications in crystal design and engineering, molecular recognition, synthesis, catalysis, molecular conductors, liquid crystals, and bioorganic chemistry [7, 54]. The role of halogen bonding in organic synthesis is also becoming more prominent.

Thus, the fluoronium cation F^+ derived from an *N*-fluoroheterocyclic salt plays the role of a convenient and effective catalyst to mediate the interaction of *N*-substituted imines and ethyl diazoacetate affording *N*-substituted aziridines (Scheme 1.26) [55]. The highly electrophilic nature of F^+ allows easy imine activation and subsequent nucleophilic attack by ethyl diazoacetate.

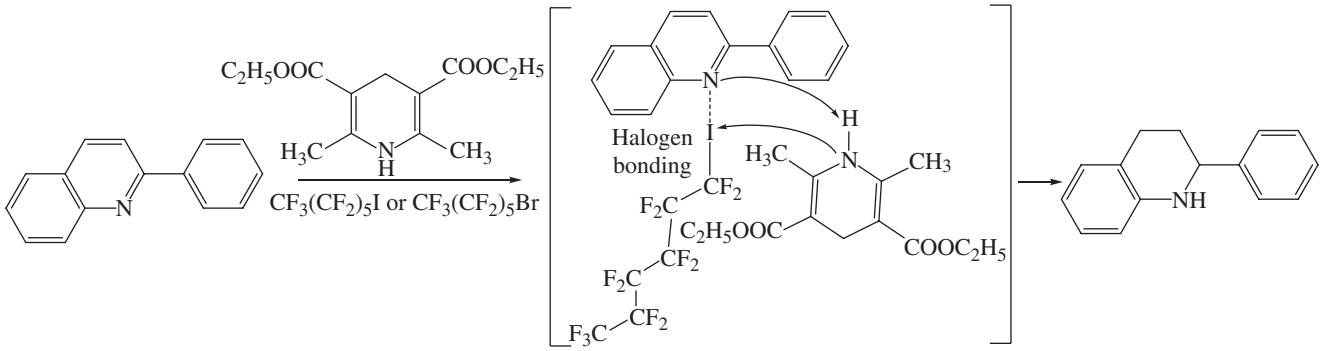
The N···X halogen bonding (X = Br, I) can be also applied for the activation of C═N bonds by haloalkanes toward electrophilic hydride additions. In particular, 2-phenylquinoline was reduced by using a Hantzsch ester (diethyl 2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate) as a reductant (Scheme 1.27) [56]. While there was no reaction in the absence of a haloalkane, yields up to 98% were achieved in the presence of 10 mol% perfluoroiodooctane, $CF_3(CF_2)_7I$. No signal shifts were found in the ^{1}H NMR spectra; this contrasted to the ^{13}C NMR behavior, where the quinoline signals were slightly shifted to lower field (by 0.01–0.06 ppm). This is indicative of a weak interaction between the quinoline nitrogen and iodide of the perfluoro compound, which is supported by the ^{19}F NMR spectra, in which the signal for the CF_2I group resonated at a lower magnetic field ($\Delta\delta = 0.1$ ppm), and all



SCHEME 1.25 Regioselective synthesis of (2*Z*,4*E*)-4-(2-phenylhydrazono)pent-2-en-2-ol [53].



SCHEME 1.26 Synthesis of *N*-arylaziridine [55].

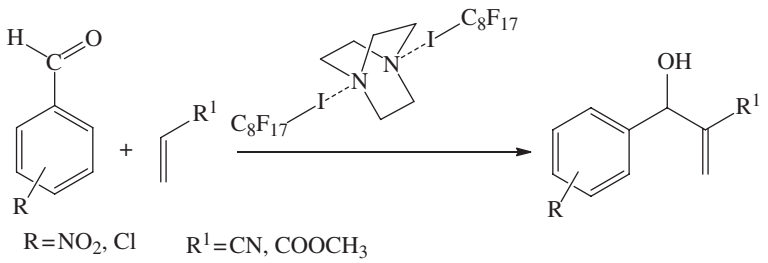


SCHEME 1.27 Reduction of 2-phenylquinoline [56].

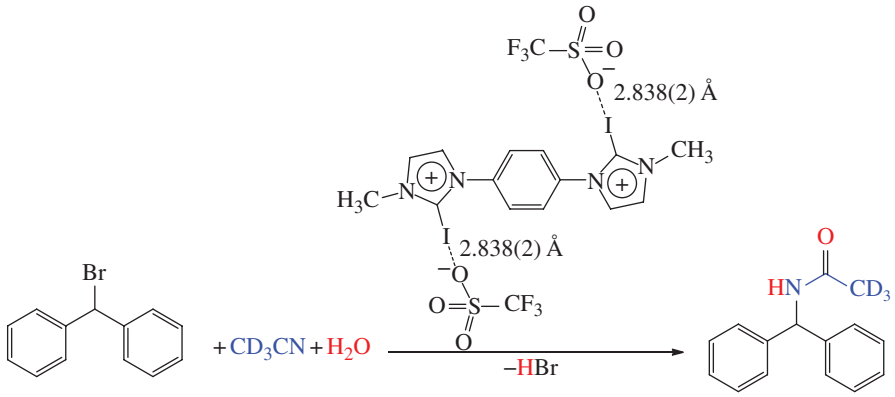
chemical shifts are strongly dependant on concentration. The obtained results can be related to the fact that the fluorinated iodoalkanes, such as $CF_3(CF_2)_7I$ or $CF_3(CF_2)_7Br$, form strong halogen bonds with the sp^2-type nitrogen atoms [56].

Generally, the electrophilic character of halogen atoms in halogen bonding is significant when they are bonded to a strong electron-withdrawing group, such as a fluorocarbon chain, as in $CF_3(CF_2)_7I$. This high halogen-bonding ability of perfluoroalkyl halides can be used as an alternative to covalent perfluorinated ponytails to drag hydrocarbon reactants from an organic phase [57]. Thus, the halogen-bonded adduct between 1,4-diazabicyclo[2.2.2]octane (DABCO) and two molecules of perfluorooctyl iodide (DABCO·$(C_8F_{17}I)_2$) was applied as a recyclable supramolecular fluorous organocatalyst for the addition of aromatic aldehydes to methyl acrylate (Morita–Baylis–Hillman reaction; Scheme 1.28) [58]. The adduct DABCO·$(C_8F_{17}I)_2$ was formed through halogen bonding; after the catalytic reaction, DABCO·$(C_8F_{17}I)_2$ is easily recoverable by filtration.

A halogen-containing catalyst also activates the C—Br bond of benzhydryl bromide in its reaction with deuterated acetonitrile (Scheme 1.29) [59]. Hydrolysis of the resulting nitrilium intermediate by traces of water yielded *N*-benzhydryl acetamide in good yield. Without the catalyst or in the presence of its H-analogue, the yield of the reaction drops to less than 5%. Hence, the halogen-bonding promoter does successfully accelerate this reaction, the best activation being observed in the presence of the BF_4^- anion (yield 97%), while the reaction with CF_3SO_3H afforded 25% yield of the product.



SCHEME 1.28 Baylis–Hillman reaction [58].



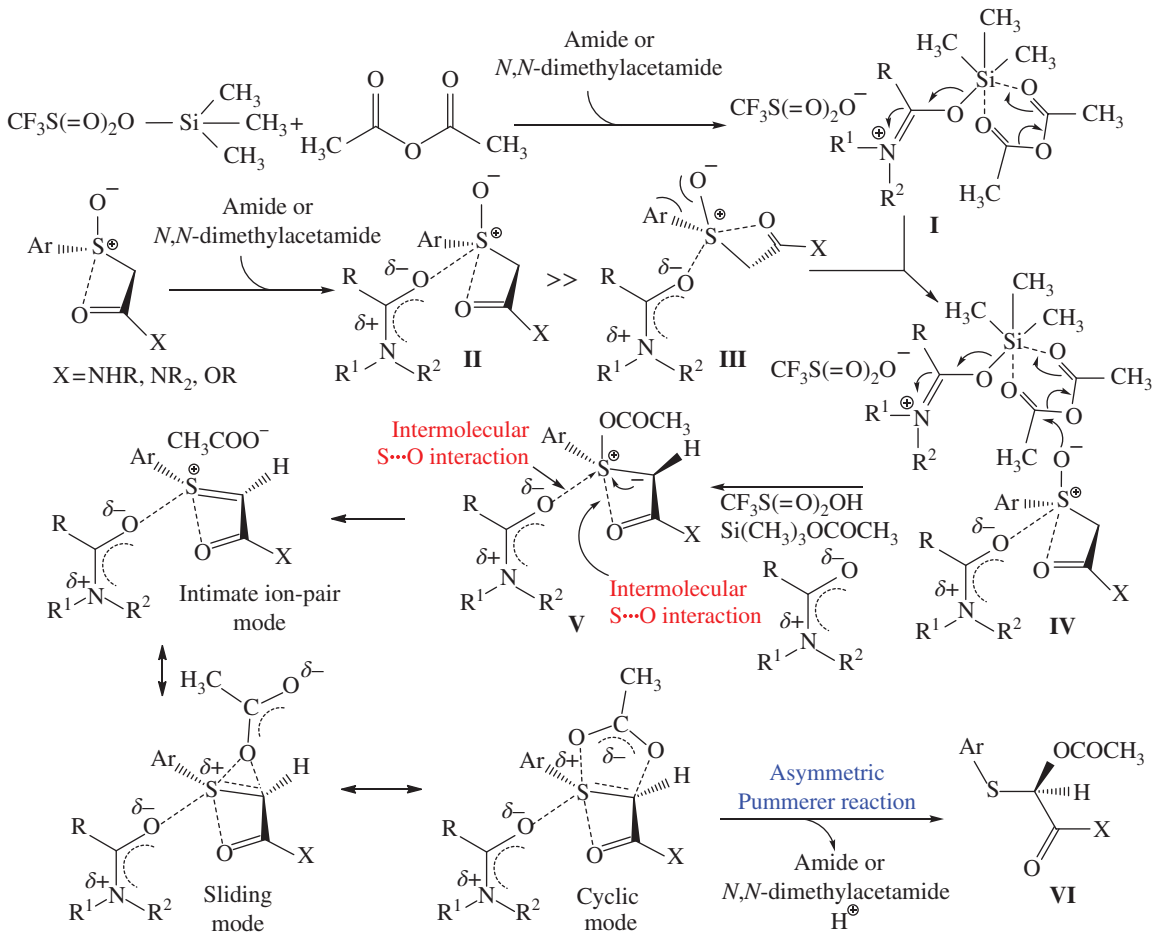
SCHEME 1.29 Synthesis of *N*-benzhydryl acetamide [59].

1.4 OTHER TYPES OF NON-COVALENT INTERACTIONS AND PERSPECTIVES

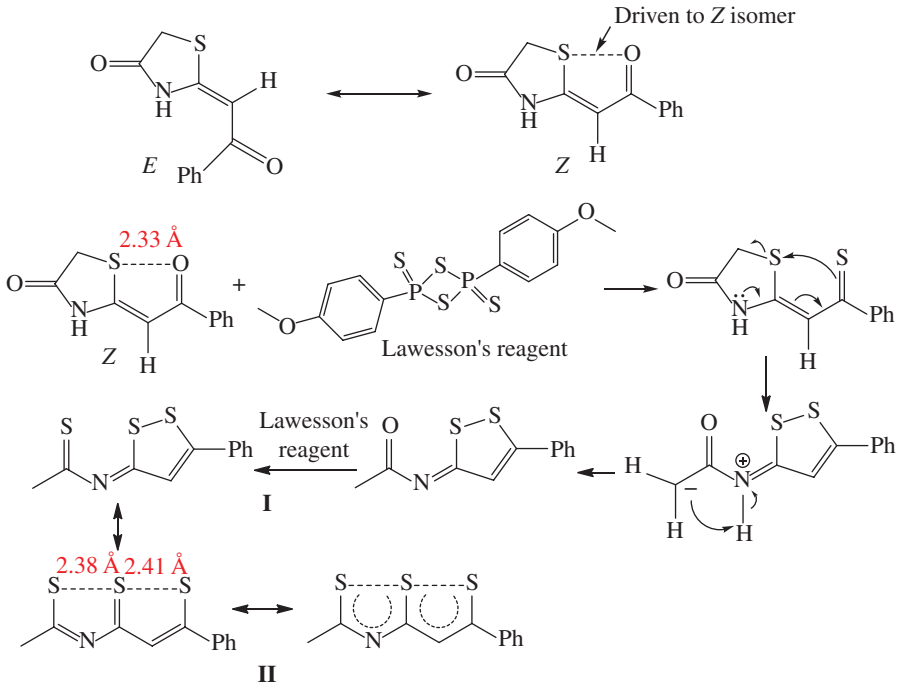
Other non-covalent interactions such as S···O, S···N, P···P, P···N, B···N, and B···O are also important for molecular recognition, biological activity of some compounds [60], and regulation of catalytic functions [61]. Thus, S···O interactions are supposed to play a key role in the synthesis of chiral sulfoxides by the Pummerer reaction (Scheme 1.30) [62]. It is supposed that coordination of acetic anhydride to trimethylsilyl triflate in amide (or lactam) generates an intermediate **I**. In parallel, an interaction of chiral sulfoxide with amide (or lactam) leads to intermediates **II** and **III** bearing the inter- and intramolecular S···O interactions. It appears that structure **II** is more stable than **III** due to the steric repulsion between the aryl group and the carbonyl group in **III**. Subsequently, acetylation of the sulfonyl oxygen atom of **II** with acetic anhydride in the presence of active species **I** affords a chiral sulfurane-type intermediate **IV**. The subsequent abstraction of the methylene α-hydrogen atom by $CF_3S(=O)_2O^-$ from **IV** generates a rigid ylide intermediate **V** supported by both inter- and intramolecular S···O interactions. The stereoselective 1,2-acetoxy transfer in **V** proceeds via three kinds of plausible modes, intimate ion pair, sliding, and cyclic, to furnish the desired chiral Pummerer product.

Intramolecular nonconventional S···X (X = O or S) interactions were found in a large number of organosulfur compounds, such as acetazolamides, thiadiazolines, natural antitumor antibiotic leinamycin, cyclic sulfilimine, or 1,3-dithiole, and have shown to be important in controlling their structural properties and chemical reactivity. For instance, a role of intramolecular S···O interactions in the regiochemical control of the 4-oxothiazolidine → 1,2-dithiole-3-ylidene thione rearrangement (Scheme 1.31) was demonstrated [63, 64]. A ring-opening/ring-closing transformation of selected 4-oxothiazolidine enaminoketones in the presence of Lawesson's reagent produces functionalized 1,2-dithiole-3-ylidene thiones. This reaction is initiated by the directional non-covalent 1,5-type S···O interaction in the 4-oxothiazolidines. The S···S distances, being 2.3374(5) and 2.3408(5)Å in 1,2-dithiole-3-ylidene thiones, are shorter than the sum of the van der Waals radii but relatively long in comparison to a S—S covalent bond (2.08Å) and not exactly of equal length, as the two fused rings differ (see isomerization of 1,2-dithiole-3-ylidene thiones in Scheme 1.31).

Another sort of non-covalent interaction, the pnicogen bond, concerns group 15 elements (N, P, or As, i.e., a pnictogen element) and a Lewis base and has also drawn attention [8]. Different from the hydrogen bond but similar to halogen and chalcogen bonds, a pnicogen bond (X)A(H)···D is formed with the electrons transferred from the Lewis base D to the pnicogen atom A, which acts as a Lewis acid and shows a high degree of anisotropy. X represents substituent group(s) and H is hydrogen atom(s) bonded to A but not directly interacting with D. For instance, B···N, P···N, As···N, S···N, and P···P interactions are recognized [8] but still without respective applications in synthesis.



SCHEME 1.30 Asymmetric Pummerer reaction [62].



SCHEME 1.31 Selective synthesis of (*E*,*Z*)-*N*-(5-phenyl-3H-1,2-dithiol-3-ylidene)ethan-ethioamide (I) and its isomerization (II) [63, 64].

1.5 FINAL COMMENTS

In summary, non-covalent interactions have a rich history, being largely responsible for the properties of condensed phases, solutions, and crystals. Many examples of their use as a tool in activation of covalent bonds and thus in synthesis are reported. Increasing attention has been paid to hydrogen bonds and, to a lower extent, to halogen bond interactions, due to their extensive potential in many fields of catalysis, molecular recognition, and supramolecular, material, and bio-chemistries. Other non-covalent interactions, such as S···O, S···N, P···P, P···N, B···N, B···O, etc., have also been recognized, but still their application in synthesis remains to be developed (mainly the pnictogen bonds, involving a group 15 elements).

The selected examples on the use of non-covalent interactions in synthesis show that these forces determine the fate of many chemical transformations, and in particular, the regio- and stereoselective control of reactions is a current topic of a high prospect.

ACKNOWLEDGMENTS

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REFERENCES

1. P. M. Pihko (Ed.), Hydrogen Bonding in Organic Synthesis, Wiley-VCH, Weinheim, 2009.
2. P. Gilli, G. Gilli, The Nature of the Hydrogen Bond, Oxford University Press, Oxford, 2009.
3. P. Hobza, K. Müller-Dethlefs, Non-covalent Interactions: Theory and Experiment, Royal Society of Chemistry, Cambridge, UK, 2010.
4. P. A. Gale, J. W. Steed (Eds.), Supramolecular Chemistry: From Molecules to Nanomaterials, John Wiley & Sons, Ltd, Chichester, 2012.
5. A. K. Baev, Specific Intermolecular Interactions of Organic Compounds, Springer, Heidelberg, 2012.
6. A. K. Baev, Specific Intermolecular Interactions of Nitrogenated and Bioorganic Compounds, Springer, Heidelberg, 2014.
7. P. Metrangolo, G. Resnati, Halogen Bonding: Fundamentals and Applications (Structure and Bonding); Springer, Heidelberg, 2010.
8. S. Scheiner, *Acc. Chem. Res.* 2013, *46*, 280.
9. C. J. Allpress, L. M. Berreau, *Coord. Chem. Rev.* 2013, *257*, 3005.
10. J.-J. Li, T. D. H. Bugg, *Chem. Commun.* 2005, *5*, 130.
11. J.-J. Li, T. D. H. Bugg, *Org. Biomol. Chem.* 2007, *5*, 507.
12. M. N. Kopylovich, K. T. Mahmudov, M. Haukka, A. J. L. Pombeiro, *New J. Chem.* 2014, *38*, 495.
13. R. Solhnejad, F. S. Aliyeva, A. M. Maharramov, R. A. Aliyeva, F. M. Chyragov, A. V. Gurbanov, K. T. Mahmudov, M. N. Kopylovich, *J. Mol. Struct.* 2013, *1050*, 180.
14. S.-B. Zhao, E. Bilodeau, V. Lemieux, A. M. Beauchemin, *Org. Lett.* 2012, *14*, 5082.
15. N. J. Cooper, D. W. Knight, *Tetrahedron* 2004, *60*, 243.
16. X. Wang, X. Wang, W. He, *Org. Biomol. Chem.* 2014, *12*, 3163.
17. H.-U. Reissig, R. Zimmer, *Chem. Rev.* 2003, *103*, 1151.
18. X.-M. Deng, P. Cai, S. Ye, X.-L. Sun, W.-W. Liao, K. Li, Y. Tang, Y.-D. Wu, L.-X. Dai, *J. Am. Chem. Soc.* 2006, *128*, 9730.
19. R. Chinchilla, C. Najera, *Chem. Rev.* 2014, *114*, 1783.
20. R. Salvio, M. Moliterno, M. Bella, *Asian J. Org. Chem.* 2014, *3*, 340.
21. S. Suzuki, E. Tokunaga, D. S. Reddy, T. Matsumoto, M. Shiro, N. Shibata, *Angew. Chem. Int. Ed.* 2012, *51*, 4131.
22. T. Inokuma, M. Furukawa, Y. Suzuki, T. Kimachi, Y. Kobayashi, Y. Takemoto, *ChemCatChem* 2012, *4*, 983.
23. T. Inokuma, M. Furukawa, T. Uno, Y. Suzuki, K. Yoshida, Y. Yano, K. Matsuzaki, Y. Takemoto, *Chem. Eur. J.* 2011, *17*, 10470.
24. A. Brik, C.-H. Wong, *Org. Biomol. Chem.* 2003, *1*, 5.
25. B. C. M. Fernandes, C. Mateo, C. Kiziak, A. Chmura, W. Wacker, F. Rantwijk, A. Stolz, R. A. Sheldon, *Adv. Synth. Catal.* 2006, *348*, 2597.
26. A. Erkkilä, I. Majander, P. M. Pihko, *Chem. Rev.* 2007, *107*, 5416.
27. S. Kobayashi, Y. Mori, J. S. Fossey, M. M. Salter, *Chem. Rev.* 2011, *111*, 2626.
28. J. Wang, T. Shi, G. Deng, H. Jiang, H. Liu, *J. Org. Chem.* 2008, *73*, 8563.
29. A. Viso, R. Fernández de la Pradillla, A. García, A. Flores, *Chem. Rev.* 2005, *105*, 3167.
30. M. Martjuga, D. Shabashov, S. Belyakov, E. Liepinsh, E. Suna, *J. Org. Chem.* 2010, *75*, 2357.
31. A. Noble, J. C. Anderson, *Chem. Rev.* 2013, *113*, 2887.
32. T. Cheng, S. Meng, Y. Huang, *Org. Lett.* 2013, *15*, 1958.
33. A. Kumar, J. Kaur, S. S. Chimni, A. K. Jassal, *RSC Adv.* 2014, *4*, 24816.
34. V. Y. Kukushkin, A. J. L. Pombeiro, *Chem. Rev.* 2002, *102*, 1771.
35. K. T. Mahmudov, M. N. Kopylovich, A. J. L. Pombeiro, Arylhydrazones of methylene active nitriles as promising ligands and starting materials for organic synthesis, in Ligands: Synthesis, Characterization and Role in Biotechnology, P. Gawryszewska, P. Smoleński (eds.), Nova Science Publishers, New York, 2014, pp. 177–198.
36. M. N. Kopylovich, K. T. Mahmudov, A. Mizar, A. J. L. Pombeiro, *Chem. Commun.* 2011, *47*, 7248.
37. F. Himo, Z. P. Demko, L. Noodleman, K. B. Sharpless, *J. Am. Chem. Soc.* 2002, *124*, 12210.
38. D. Cantillo, B. Gutmann, C. O. Kappe, *J. Am. Chem. Soc.* 2011, *133*, 4465.
39. P. B. Palde, T. F. Jamison, *Angew. Chem. Int. Ed.* 2011, *50*, 3525.

40. N. Nishiwaki, K. Kobiro, S. Hirao, J. Sawayama, K. Saigo, Y. Ise, Y. Okajima, M. Ariga, *Org. Biomol. Chem.* 2011, *9*, 6750.
41. O. T. du Boullay, A. Alba, F. Oukhatar, B. Martin-Vaca, D. Bourissou, *Org. Lett.* 2008, *10*, 4669.
42. R. Ferreira, H. Garcia, A. F. Sousa, M. Guerreiro, F. J. S. Duarte, C. S. R. Freire, M. J. Calhorda, A. J. D. Silvestre, W. Kunz, L. P. N. Rebelo, C. S. Pereira, *RSC Adv.* 2014, *4*, 2993.
43. A. M. R. Smith, K. K. (Mimi) Hii, *Chem. Rev.* 2011, *111*, 1637.
44. M. Yus, J. C. Gonzáez-Gómez, F. Foubelo, *Chem. Rev.* 2013, *113*, 5595.
45. S. Bahmanyar, K. N. Houk, H. J. Martin, B. List, *J. Am. Chem. Soc.* 2003, *125*, 2475.
46. G. G. R. Desiraju, T. Steiner, The Weak Hydrogen Bond in Structural Chemistry and Biology, Oxford University Press, Oxford, 1999.
47. R. C. Johnston, P. H.-Y. Cheong, *Org. Biomol. Chem.* 2013, *11*, 5057.
48. D. Magdziak, S. J. Meek, T. R. R. Pettus, *Chem. Rev.* 2004, *104*, 1383.
49. T. Dohi, Y. Hu, T. Kamitanaka, N. Washimi, Y. Kita, *Org. Lett.* 2011, *13*, 4814.
50. J. M. Berg, J. L. Tymoczko, L. Stryer, Biochemistry, W. H. Freeman, New York, 2002.
51. M. Esseffar, M. El Messaoudi, S. Azzouzi, R. Jalal, J. A. Sáez, L. R. Domingo, J. Latorre, M. Liu-González, *J. Phys. Org. Chem.* 2009, *22*, 31.
52. G. Buemi, *J. Chem. Soc. Faraday Trans.* 1990, *86*, 2813.
53. S. V. Kumar, S. K. Yadav, B. Raghava, B. Saraiah, H. Ila, K. S. Rangappa, A. Hazra, *J. Org. Chem.* 2013, *78*, 4960.
54. A. Priimagi, G. Cavallo, P. Metrangolo, G. Resnati, *Acc. Chem. Res.* 2013, *46*, 2686.
55. S. P. Bew, S. A. Fairhurst, D. L. Hughes, L. Legentil, J. Liddle, P. Pesce, S. Nigudkar, M. A. Wilson, *Org. Lett.* 2009, *11*, 4552.
56. A. Bruckmann, M. A. Pena, C. Bolm, *Synlett* 2008, *6*, 900.
57. S. Dordonne, B. Crousse, D. Bonnet-Delpon, J. Legros, *Chem. Commun.* 2011, *47*, 5855.
58. S. M. Walter, F. Kniep, E. Herdtweck, S. M. Huber, *Angew. Chem. Int. Ed.* 2011, *50*, 7187.
59. S. Zhu, C. Xing, W. Xu, Z. Li, *Tetrahedron Lett.* 2004, *45*, 777.
60. M. Iwaoka, S. Takemoto, M. Okada, S. Tomoda, *Chem. Lett.* 2001, *132*.
61. C. Dugave, L. Demange, *Chem. Rev.* 2003, *103*, 2475.
62. Y. Nagao, S. Miyamoto, M. Miyamoto, H. Takeshige, K. Hayashi, S. Sano, M. Shiro, K. Yamaguchi, Y. Sei, *J. Am. Chem. Soc.* 2006, *128*, 9722.
63. A. Rašović, P. J. Steel, E. Kleinpeter, R. Marković, *Tetrahedron* 2007, *63*, 1937.
64. A. Rašović, A. Koch, E. Kleinpeter, R. Marković, *Tetrahedron* 2013, *69*, 10849.