

# We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900

Open access books available

185,000

International authors and editors

200M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index  
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?  
Contact [book.department@intechopen.com](mailto:book.department@intechopen.com)

Numbers displayed above are based on latest data collected.  
For more information visit [www.intechopen.com](http://www.intechopen.com)



---

# Hydrogen-Bonding Activation in Chiral Organocatalysts

---

Hidetoshi Miyabe

Additional information is available at the end of the chapter

<http://dx.doi.org/10.5772/62459>

---

## Abstract

In a recent decade, various organocatalysts have been developed to be applicable to a wide range of asymmetric reactions. This review briefly summarizes the hydrogen-bonding activation by chiral noncovalent organocatalysts. First, the differences between hydrogen-bonding catalysts and Brønsted acid catalysts are addressed. Next, the effect of hydrogen-bonding interactions on the transition states is discussed. Finally, the hydrogen-bonding activations by the typical noncovalent organocatalysts, such as thiourea, diol, phosphoric acid, Brønsted acid-assisted chiral Brønsted acid, and *N*-triflyl phosphoramidate, are shown.

**Keywords:** hydrogen bond, organocatalyst, enantioselective, Brønsted acid, thiourea, diol, phosphoric acid

---

## 1. Introduction

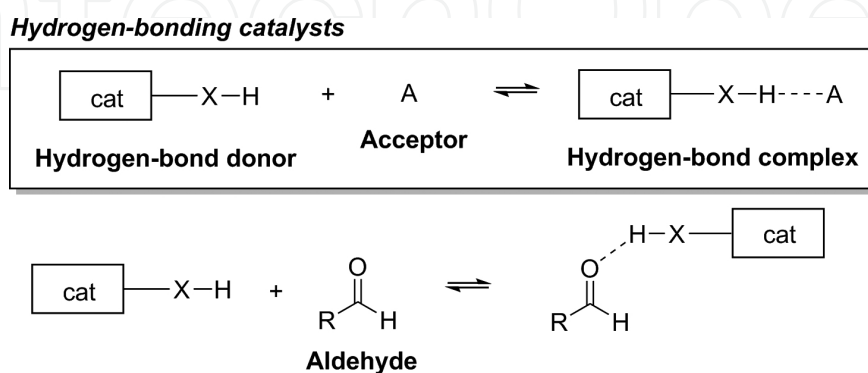
The hydrogen bond is the interaction between a hydrogen atom and an electronegative atom, which plays a central role in biological systems. Recently, the utility of hydrogen bond in organic synthesis has been widely investigated, leading to the discovery of novel chiral organocatalysts for the asymmetric transformations [1–3].

In contrast to the covalent organocatalysts, such as proline derivatives, DMAP derivatives, and *N*-heterocyclic carbene (NHC) catalysts [4–10], the noncovalent organocatalysts have been mainly developed as hydrogen bond donors or proton donors. For examples, thioureas and diols are classified into noncovalent hydrogen-bonding organocatalysts. This chapter highlights the effective and unique hydrogen-bonding activation modes by noncovalent organocatalysts [11–19]. In particular, the various activation mechanisms of nucleophilic additions into C=O and C=N bonds are described.

---

## 2. Noncovalent organocatalysts

In general, noncovalent organocatalysts can be classified into hydrogen-bonding catalysts and Brønsted acid catalysts [20], although these catalysts may rely on other additional noncovalent interactions at the same time. First, the differences between hydrogen-bonding catalysts and Brønsted acid catalysts are addressed.



**Figure 1.** Hydrogen-bonding catalysts.

The hydrogen-bonding catalysts play as a hydrogen bond donor toward an electronegative hydrogen bond acceptor (**Figure 1**). The catalysts forming a hydrogen bond complex are called hydrogen-bonding catalysts. The hydrogen bonds are flexible with regard to bond length and angle. The typical bond length of a hydrogen bond is 1.5 to 2.2 Å. The hydrogen bonds are stronger than a van der Waals interaction but weaker than covalent or ionic bonds. In general, the combination of a neutral electrophile (acceptor) and a weak acid catalyst (donor) leads to hydrogen-bonding catalysis. Therefore, the nucleophilic addition to neutral carbonyl compounds, aldehyde or ketone, takes place via a hydrogen bond complex. In the case of the hydrogen bond-catalyzed reactions, a direct proton transfer from the catalyst (donor) to the electrophile (acceptor) will not occur. In other words, the hydrogen bond-catalyzed nucleophilic addition proceeds without the formation of an ion pair.

Brønsted acid catalysts play as a proton donor toward an electronegative acceptor (**Figure 2**). In general, the catalysts forming an activated ion pair are called Brønsted acid catalysts. When a catalyst (donor) is a stronger acid, the proton transfer to acceptor occurs to give an ion pair via the hydrogen bond complex. In contrast to hydrogen-bonding catalysts, the combination of basic electrophile (acceptor) and stronger acid catalyst (donor) leads to Brønsted acid-catalyzed reactions. Therefore, the nucleophilic addition to basic imine is often assumed to proceed via the formation of ion pair.

These catalysts might be simply distinguished in the point of view of proton transfer from catalysts. However, it is frequently difficult to make a clear distinction between hydrogen-bonding catalysts and Brønsted acid catalysts, because there is the equilibrium between a hydrogen bond complex and an ion pair (**Figure 2**). Moreover, Brønsted acid-catalyzed reactions can be classified into two types based on where proton transfer occurs to the substrate

or to the transition state. Particularly, the Brønsted acid-associated proton transfer in the transition state is closely related to the stabilization of the transition states by hydrogen-bonding catalysts.

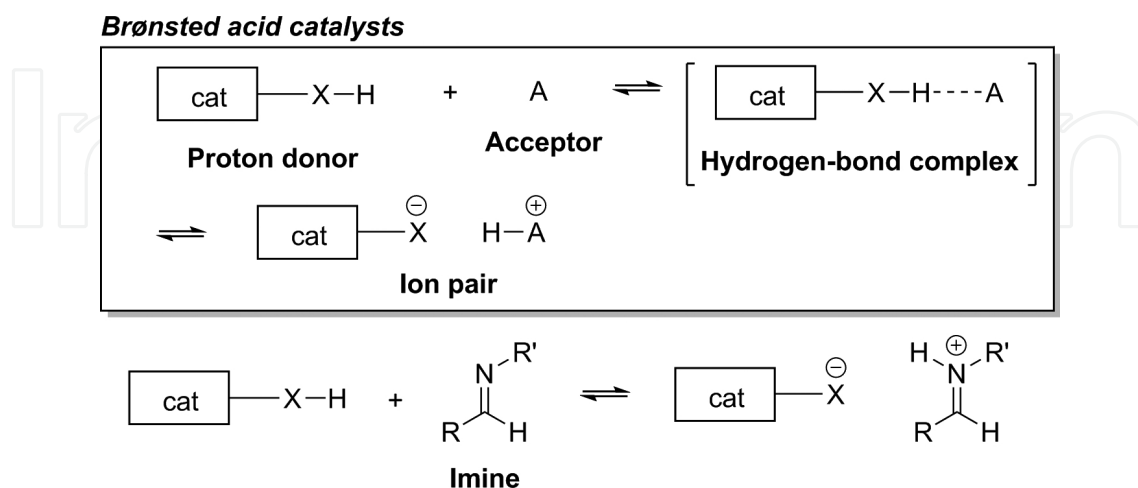


Figure 2. Brønsted acid catalysts.

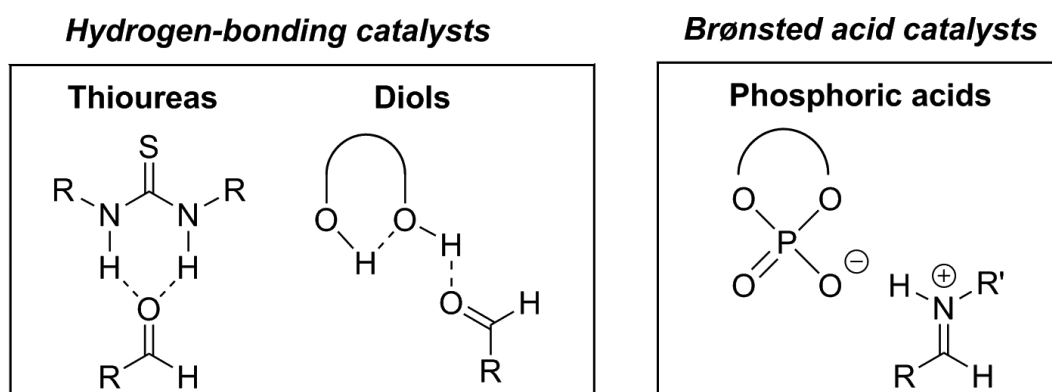


Figure 3. Activation by noncovalent organocatalysts.

Thioureas, diols, phosphoric acids, *N*-oxide, phase-transfer onium salts, etc., are well known as noncovalent organocatalysts [11–19]. Thioureas and diols are classified into hydrogen-bonding catalysts by means of the mode of activation (**Figure 3**). In contrast, phosphoric acids are generally classified into Brønsted acid catalysts.

### 3. Stabilization of transition states by hydrogen bond

The strength of hydrogen bond becomes larger in the charged interaction than the uncharged interaction (**Figure 4**) [21–23]. The hydrogen bond of a water molecule with a hydroxyl anion (negatively charged acceptor) is almost three times stronger than that with another water

molecule (neutral acceptor) in gas phase. The hydrogen bond between a water molecule and a positively charged donor is also strong.

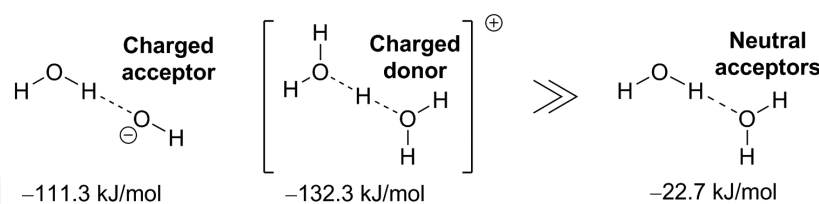


Figure 4. Strength of hydrogen bond.

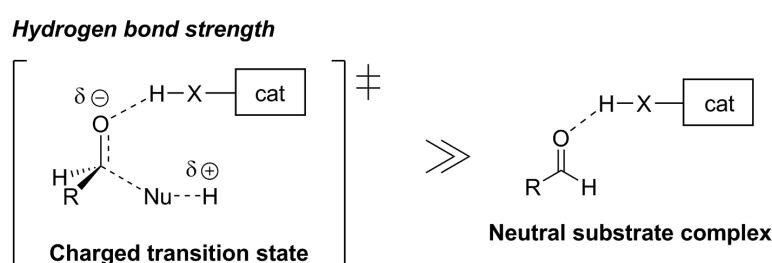


Figure 5. Hydrogen bond strength in charged transition states.

In a hydrogen bond-mediated catalysis, the functions of catalysts are both the activation of substrates and the stabilization of transition states or intermediates. Particularly, the hydrogen bonds effectively stabilize the negative charges in transition states or intermediates [24, 25], because the catalysts are bound more strongly to the charged transition states or intermediates than neutral substrates (**Figure 5**). Therefore, the study on the transition states or the charged intermediates stabilized by hydrogen-bonding interactions is of importance [26, 27], although the catalysts also affect the reaction rates by decreasing the LUMO level of neutral substrates such as carbonyl compounds and imines.

## 4. Hydrogen-bonding catalysts

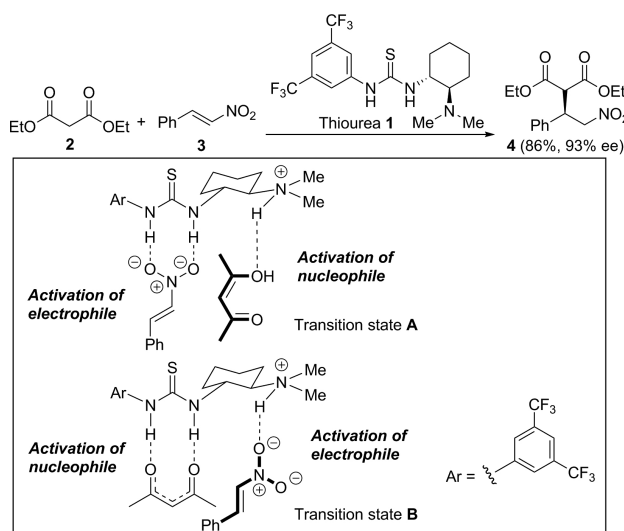
Thioureas and diols are recognized as the typical hydrogen-bonding organocatalysts. This section highlights the hydrogen-bonding activation models and the mechanical investigations using hydrogen-bonding catalysts.

### 4.1. Thiourea derivatives

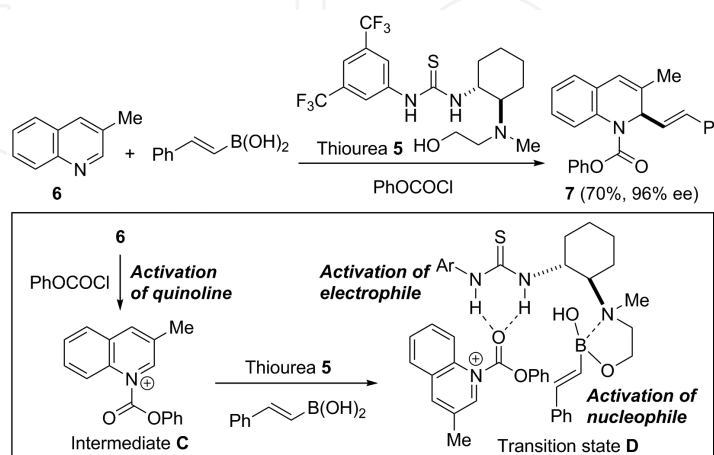
In 1990, the formation of crystals of diaryl ureas with carbonyl compounds as a hydrogen bond acceptor was reported by Etter's group [28]. Later, this study inspired the impressive development of thiourea catalysts. The chiral bifunctional thiourea catalyst **1** was developed by Takemoto's group (**Figure 6**) [29, 30]. Thiourea catalyst **1** catalyzed the enantioselective

Michael addition of 1,3-dicarbonyl compound **2** to nitroolefin **3**. The mechanism of this reaction was investigated through density functional theory (DFT) calculations by Pápai's group [31]. Between two transition states **A** and **B**, the reaction would proceed predominantly via transition state **B** due to the lower activation barrier.

Takemoto's group developed the new chiral bifunctional thiourea **5** for catalyzing the enantioselective Petasis-type reaction using organoboronic acids (**Figure 7**) [32]. In the presence of catalyst **5** and PhOCOCl, the reaction of quinoline **6** with vinyl boronic acid gave the adduct **7** in 96% ee. In this reaction, electrophilic quinoline **6** is activated as a reactive *N*-phenoxy-carbonyl quinolinium salt **C**. Moreover, the chiral chelating aminoalcohol group of catalyst **5** activates the vinyl boronic acid by coordinating with the boron atom and directs the stereochemical outcome of the reaction as shown in transition state **D**.

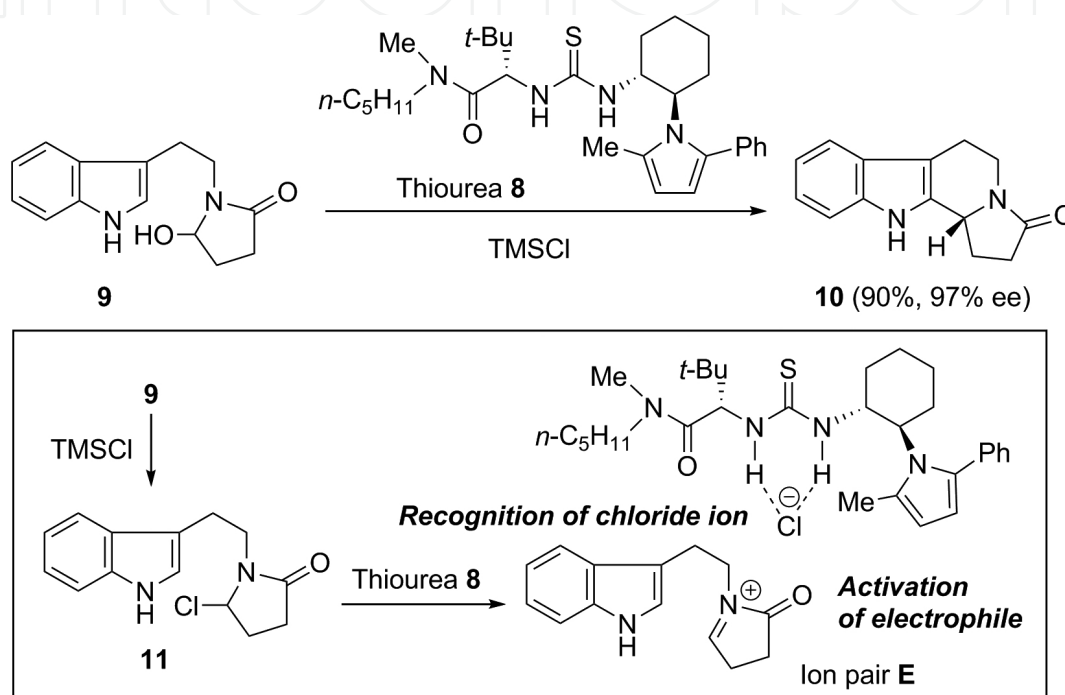


**Figure 6.** Thiourea-catalyzed Michael addition reaction.



**Figure 7.** Thiourea-catalyzed Petasis-type reaction.

Thiourea catalyst can recognize the *in situ* generated counteranion by hydrogen bond to give the ion pair. Jacobsen's group studied the thiourea-catalyzed Pictet-Spengler-type cyclization reaction (**Figure 8**) [33, 34]. In the presence of thiourea **8**, the cyclization of indolylethyl hydroxylactam **9** gave the cyclic product **10** with good enantioselectivity. In this process, electrophile is activated as an iminium ion [35]. The thiourea catalyst **8** would promote the cyclization of **9** by abstracting a chloride on the *in situ*-generated intermediate **11**. In this proposal mechanism, thiourea **8** works as an anion receptor to form the chiral ion pair **E** involving the activated *N*-acyliminium.



**Figure 8.** Thiourea-catalyzed Pictet-Spengler-type cyclization reaction.

#### 4.2. Diol derivatives

Diols, such as  $\alpha,\alpha',\alpha'$ -tetraaryl-1,3-dioxolan-4,5-dimethanol (TADDOL), form an intramolecular hydrogen bond. (*R,R*)-1-Np-TADDOL **12** catalyzed the hetero-Diels-Alder reaction between benzaldehyde **13** and Danishefsky's diene **14** (**Figure 9**). Although the single hydrogen-bond complex **F** and the double hydrogen-bond complex **G** are the possible starting complexes, Ding's group reported that the complex **F** activated by a single hydrogen bond was supported by computational structure optimization [36].

The study on  $pK_a$  values of TADDOL analogues show that the intramolecular hydrogen bond in TADDOL analogues enhances the polarity of the second hydroxyl group and stabilizes the anion resulting from deprotonation [37]. In other words, the formation of the single hydrogen-bond complexes such as complex **F** is favored, because the increase in acidity of the second hydroxyl group on TADDOL is induced by an intramolecular hydrogen bond.

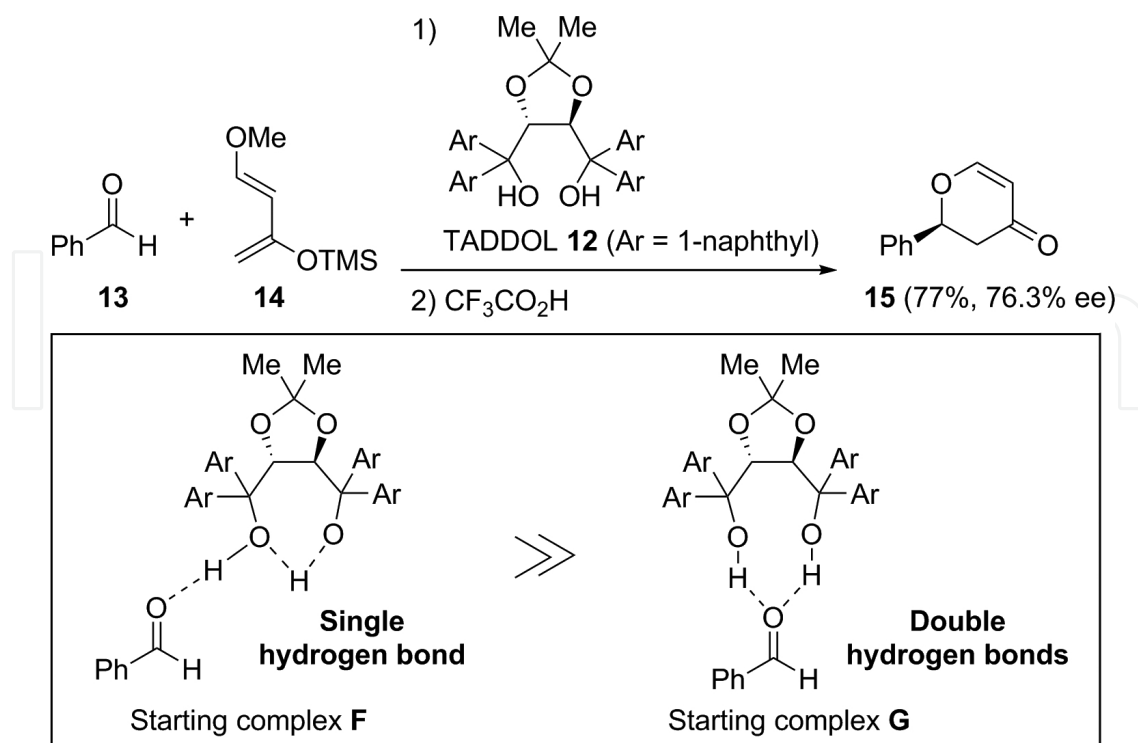


Figure 9. TADDOL-catalyzed hetero-Diels-Alder reaction.

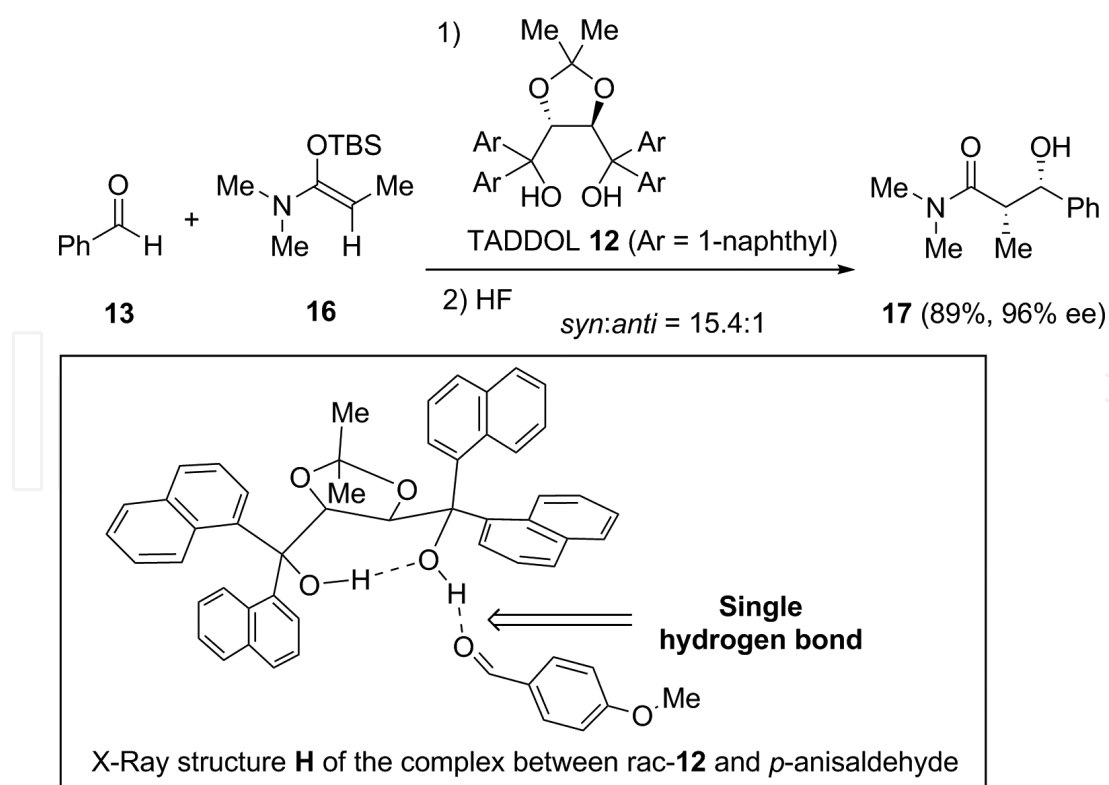


Figure 10. TADDOL-catalyzed Mukaiyama aldol reaction.



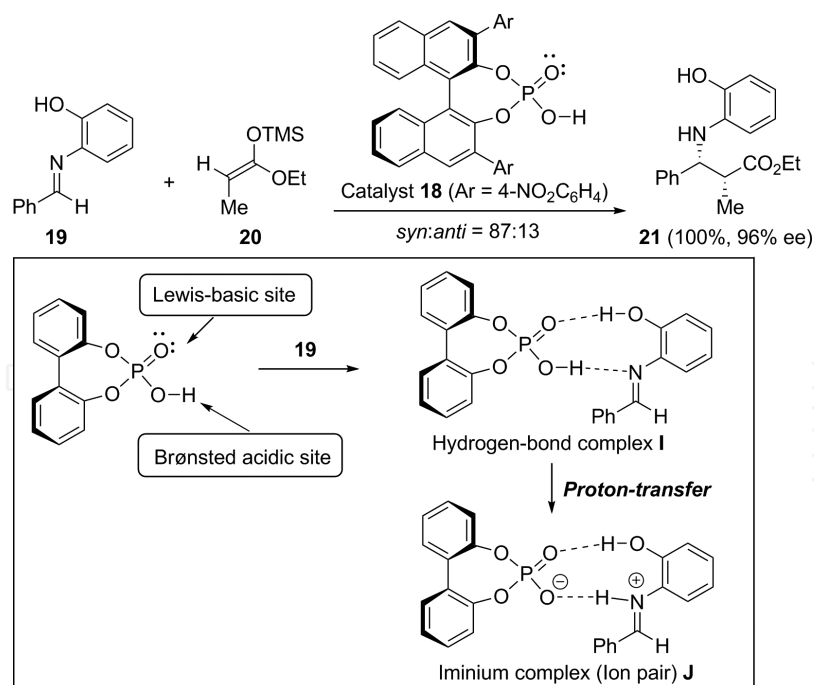
Rawal's group studied the Mukaiyama aldol reaction using TADDOL derivatives (**Figure 10**) [38]. In the presence of chiral TADDOL **12**, the reaction of benzaldehyde **13** with *O*-silyl-*N,O*-acetal **16** gave the product **17** in 96% ee. In this study, they succeeded the X-ray analysis of the complex **H** forming between racemic TADDOL **12** and *p*-anisaldehyde. The X-ray structure clearly supports the formation of the single hydrogen bond on the oxygen atom of *p*-anisaldehyde and the intramolecular hydrogen bond in TADDOL **12**.

## 5. Brønsted acid catalysts

The stronger acids are suitable for catalyzing the nucleophilic addition to basic imines as a Brønsted acid catalyst. This section highlights the activation by Brønsted acid catalyst and the investigations into Brønsted acid-associated proton transfers.

### 5.1. Phosphoric acid derivatives

In general, phosphoric acid derivatives are classified into Brønsted acid catalysts. The chiral BINOL-based phosphoric acid catalysts, independently developed by Akiyama's group and Terada's group, are bearing both Brønsted acidic site and Lewis basic site [39, 40]. In some cases, the bifunctional interaction of electrophilic and nucleophilic components plays a crucial role in the transition state of a rate-determining step.

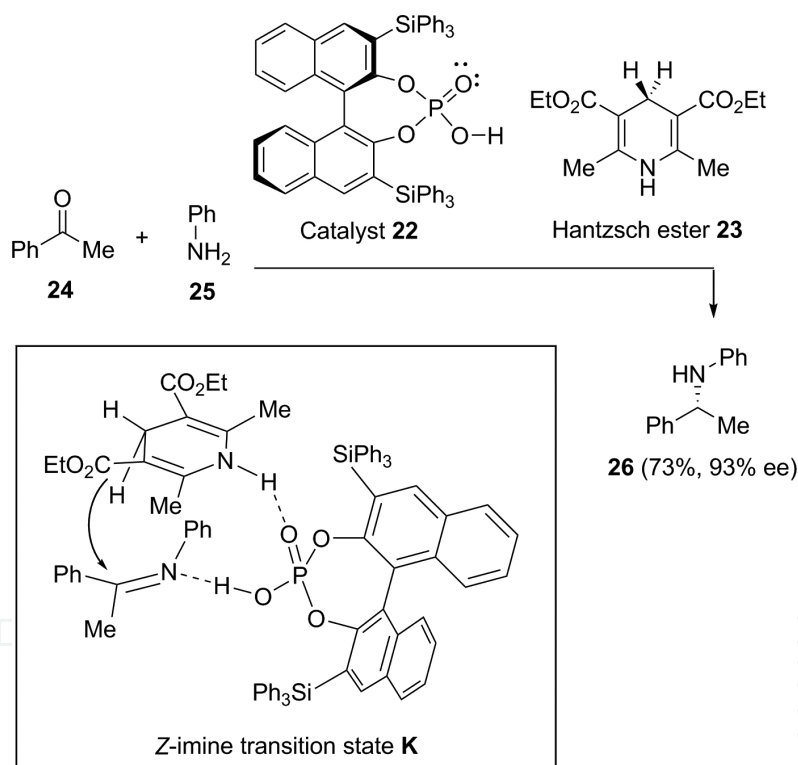


**Figure 11.** Phosphoric acid-catalyzed Mannich-type reaction.

Akiyama's group reported the enantioselective Mannich-type reaction using chiral phosphoric acids (**Figure 11**) [39]. In the presence of phosphoric acid **18**, the reaction of aldimine **19** with

ketene silyl acetal **20** gave the adduct **21** in 96% ee. The theoretical investigation was performed using an analogous simple phosphoric acid [41]. The computational analysis supports that a double hydrogen-bonding complex **I** is the favored starting complex over a single hydrogen-bonding complex. Moreover, the calculation supports that the proton transfer from phosphoric acid to the nitrogen atom of aldimine **19** occurs to give the iminium complex **J** as a stable ion pair.

The reductions of imines with Hantzsch ester **23** have been widely investigated by the use of various chiral phosphoric acids. MacMillan's group reported that the phosphoric acid **22**-catalyzed reduction of imine, generated from ketone **24** and aniline **25**, proceeded with a good enantioselectivity [42]. In his paper, the single bonding complex between imine and Brønsted acid catalyst **22** was proposed. More recently, Goodman's group performed the DFT calculation study, which indicates that the ternary complex between imine, catalyst **22**, and Hantzsch ester **23** is important to stereochemical course [43]. The *Z*-imine transition state **K** is on the lowest energy route to the product (**Figure 12**).



**Figure 12.** Phosphoric acid-catalyzed reduction using Hantzsch ester.

## 5.2. Brønsted acid-assisted chiral Brønsted acid

Ishihara's group developed Brønsted acid-assisted chiral Brønsted acid catalyst **27** (**Figure 13**) [44]. In the presence of catalyst **22**, Mannich-type reaction of aldimine **28** with ketene silyl acetal **29** enantioselectively proceeded to give the adduct **30** in 77% ee. The X-ray analysis of catalyst **27** indicates the acidity of bis(triflyl)methyl proton of **27** increases by intramolec-

ular hydrogen bond between phenolic hydroxy group and oxygen atom of triflyl group, which is 2.305 Å. Therefore, the activation of aldimine **28** by the acidic bis(triflyl)methyl proton of **27** should be important.

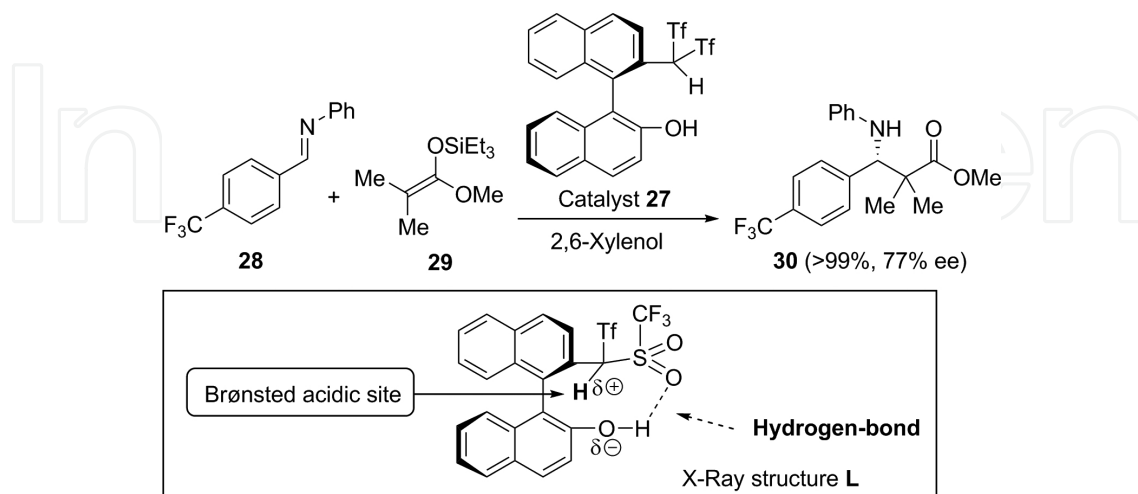


Figure 13. Catalyst **22**-catalyzed Mannich-type reaction.

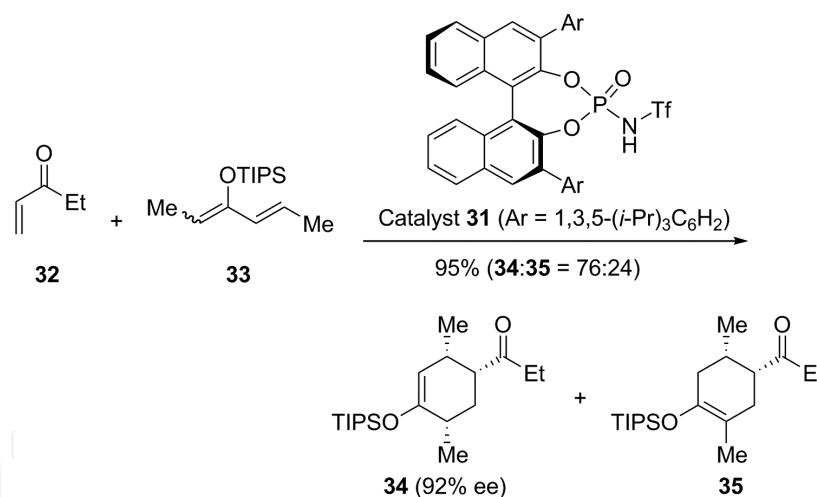


Figure 14. *N*-triflyl phosphoramidate-catalyzed Diels-Alder reaction.

### 5.3. *N*-triflyl phosphoramidate

Yamamoto's group studied the Diels-Alder reaction using chiral *N*-triflyl phosphoramidates (Figure 14) [45]. *N*-triflyl phosphoramidates are strong Brønsted acids due to a strong electron-withdrawing triflyl group. In the presence of *N*-triflyl phosphoramidate **31**, the reaction of ethyl vinyl ketone **32** with diene **33** effectively proceeded to give the cyclic adduct **34** in 92% ee, accompanied by the isomeric adduct **35**. The bulky 1,3,5-*i*-Pr<sub>3</sub>C<sub>6</sub>H<sub>2</sub> groups on catalyst **31** are essential to achieve the reaction with good chemical efficiencies.

## 6. Concluding remarks

The utilization of organocatalysts in organic synthesis has become a subject of recent research. Particularly, chiral hydrogen-bonding catalysts and chiral Brønsted acid catalysts have developed as the highly efficient noncovalent organocatalysts for a broad spectrum of asymmetric transformations. One of the most important features of noncovalent organocatalysts is that we can use the hydrogen bond for the stabilization of transition states or intermediates as well as the activation of C=O bond in carbonyl compounds or C=N bond in imines. Because the use of organocatalysts has many advantages in organic synthesis from both economical and environmental points of view, the research into organocatalysts continues to blossom and grow.

## Author details

Hideto Miyabe

Address all correspondence to: [miyabe@huhs.ac.jp](mailto:miyabe@huhs.ac.jp)

School of Pharmacy, Hyogo University of Health Sciences, Minatojima, Chuo-ku, Japan

## References

- [1] List B, editor (2012) *Asymmetric Organocatalysis 1—Workbench Edition: Lewis Base and Acid Catalysts in Science of Synthesis*. Stuttgart: Thieme.
- [2] Maruoka K, editor (2012) *Asymmetric Organocatalysis 2—Workbench Edition: Brønsted Base and Acid Catalysts, and Additional Topics in Science of Synthesis*. Stuttgart: Thieme.
- [3] Dalko PI, editor (2007) *Enantioselective Organocatalysis*. Weinheim: Wiley-VCH.
- [4] Lelais G, MacMillan DWD (2006) Modern Strategies in Organic Catalysis: The Advent and Development of Iminium Activation. *Aldrichima Acta* 39: 79–87.
- [5] Erkkilä A, Majander I, Pihko PM (2007) Iminium catalysis. *Chem. Rev.* 107: 5416–5470.
- [6] Mukherjee S, Yang JW, Hoffmann S, List B (2007) Asymmetric enamine catalysis. *Chem. Rev.* 107: 5471–5569.
- [7] Gaunt MJ, Johansson CCC (2007) Recent developments in the use of catalytic asymmetric ammonium enolates in chemical synthesis. *Chem. Rev.* 107: 5596–5605.
- [8] Wurz RP (2007) Chiral dialkylaminopyridine catalysts in asymmetric synthesis. *Chem. Rev.* 107: 5570–5595.

- [9] Enders D, Niemeier O, Henseler A (2007) Organocatalysis by *N*-heterocyclic carbenes. *Chem. Rev.* 107: 5606–5655.
- [10] Bugaut X, Glorius F (2012) Organocatalytic umpolung: *N*-heterocyclic carbenes and beyond. *Chem. Soc. Rev.* 41: 3511–3522.
- [11] Sohtome Y, Nagasawa K (2012) Dynamic asymmetric organocatalysis: cooperative effects of weak interactions and conformational flexibility in asymmetric organocatalysts. *Chem. Commun.* 48: 7777–7789.
- [12] Maruoka K (2010) Highly practical amino acid and alkaloid synthesis using designer chiral phase transfer catalysts as high-performance organocatalysts. *Chem. Rec.* 10: 254–259.
- [13] Miyabe H, Takemoto Y (2008) Discovery and application of asymmetric reaction by multi-functional thioureas. *Bull. Chem. Soc. Jpn.* 81: 785–795.
- [14] Hashimoto T, Maruoka K (2007) Recent development and application of chiral phase-transfer catalysts. *Chem. Rev.* 107: 5656–5682.
- [15] Doyle AG, Jacobsen EN (2007) Small-molecule H-bond donors in asymmetric catalysis. *Chem. Rev.* 107: 5713–5743.
- [16] Schreiner PR (2003) Metal-free organocatalysis through explicit hydrogen bonding interactions. *Chem. Soc. Rev.* 32: 289–296.
- [17] Akiyama T (2007) Stronger Brønsted acids. *Chem. Rev.* 107: 5744–5758.
- [18] Terada M (2010) Chiral phosphoric acids as versatile catalysts for enantioselective transformations. *Synthesis* 42: 1929–1982.
- [19] Yu J, Shi F, Gong LZ (2011) Brønsted-acid-catalyzed asymmetric multicomponent reactions for the facile synthesis of highly enantioenriched structurally diverse nitrogenous heterocycles. *Acc. Chem. Res.* 44: 1156–1171.
- [20] Akiyama T (2009) Hydrogen-bond catalysis or Brønsted acid catalysis? General considerations. In: Pihko PM, editor. *Hydrogen Bonding in Organic Synthesis*. Weinheim: Wiley-VCH. pp. 5–14.
- [21] Curtiss LA, Frurip DJ, Blander M (1979) Studies of molecular association in H<sub>2</sub>O and D<sub>2</sub>O vapors by measurement of thermal conductivity. *J. Chem. Phys.* 71: 2703–2711.
- [22] Xie Y, Remington RB, Schaefer HFIII (1994) The protonated water dimer: extensive theoretical studies of H<sub>5</sub>O<sup>+</sup>. *J. Chem. Phys.* 101: 4878–4884.
- [23] Pudzianowsk AT (1995) MP2/6-311++G(d,p) study of ten ionic hydrogen-bonded binary systems: structures, normal modes, thermodynamics, and counterpoise energies. *J. Chem. Phys.* 102: 8029–8039.
- [24] Jencks WP (1976) Enforced general acid-base catalysis of complex reactions and its limitations. *Acc. Chem. Rev.* 9: 425–432.

- [25] Jencks WP (1980) When is an intermediate not an intermediate? Enforced mechanisms of general acid-base, catalyzed, carbocation, carbanion, and ligand exchange reaction. *Acc. Chem. Rev.* 13: 161–169.
- [26] Cheong PHY, Legault CY, Um JM, Çelebi-Ölçüm N, Houk KN (2011) Quantum mechanical investigations of organocatalysis: mechanisms, reactivities, and selectivities. *Chem. Rev.* 111: 5042–5137.
- [27] Berkessel A, Etzenbach-Effers K (2009) Computational studies of organocatalytic processes based on hydrogen bonding. In: Pihko PM, editor. *Hydrogen Bonding in Organic Synthesis*. Weinheim: Wiley-VCH. pp. 15–42.
- [28] Etter MC, Urbańczyk-Lipkowska Z, Zia-Ebrahimi M, Panunto TW (1990) Hydrogen bond-directed cocrystallization and molecular recognition properties of diarylureas. *J. Am. Chem. Soc.* 112: 8415–8426.
- [29] Okino T, Hoashi Y, Takemoto Y (2003) Enantioselective Michael reaction of malonates to nitroolefins catalyzed by bifunctional organocatalysts. *J. Am. Chem. Soc.* 125: 12672–12673.
- [30] Xu X, Furukawa T, Okino T, Hoashi Y, Miyabe H, Takemoto Y (2006) Bifunctional-thiourea-catalyzed diastereo- and enantioselective Aza-Henry reaction. *Chem. Eur. J.* 12: 466–476.
- [31] Hamza A, Schubert G, Soós T, Pápai I (2006) Theoretical studies on the bifunctionality of chiral thiourea-based organocatalysts: competing routes to C-C bond formation. *J. Am. Chem. Soc.* 128: 13151–13160.
- [32] Yamaoka Y, Miyabe H, Takemoto Y (2007) Catalytic enantioselective petasis-type reaction of quinolines catalyzed by a newly designed thiourea catalyst. *J. Am. Chem. Soc.* 129: 6686–6687.
- [33] Taylor MS, Jacobsen EN (2004) Highly enantioselective catalytic acyl-Pictet-Spengler reactions. *J. Am. Chem. Soc.* 126: 10558–10559.
- [34] Raheem IT, Thiara PS, Peterson EA, Jacobsen EN (2007) Enantioselective Pictet-Spengler-type cyclizations of hydroxylactams: H-bond donor catalysis by anion binding. *J. Am. Chem. Soc.* 129: 13404–13405.
- [35] Brière JF, Oudeyer S, Dalla V, Levacher V (2012) Recent advances in cooperative ion pairing in asymmetric organocatalysis. *Chem. Soc. Rev.* 41: 1696–1707.
- [36] Zhang X, Du H, Wang Z, Wu YD, Ding K (2006) Experimental and theoretical studies on the hydrogen-bond-promoted enantioselective hetero-Diels-Alder reaction of Danishefsky's diene with benzaldehyde. *J. Org. Chem.* 71: 2862–2869.
- [37] Christ P, Lindsay AG, Vormittag SS, Neudörfl JM, Berkessel A, O'Donoghue AC (2011)  $pK_a$  values of chiral Brønsted acid catalysts: phosphoric acids/amides, sulfonyl/sulfuryl imides, and perfluorinated TADDOLs (TEFDDOLs). *Chem. Eur. J.* 17: 8524–8528.



- [38] McGilvra JD, Unni AK, Modi K, Rawal VH (2006) Highly diastereo- and enantioselective Mukaiyama aldol reactions catalyzed by hydrogen bonding. *Angew. Chem. Int. Ed.* 45: 6130–6133.
- [39] Akiyama T, Itoh J, Yokota K, Fuchibe K (2004) Enantioselective Mannich-type reaction catalyzed by a chiral Brønsted acid. *Angew. Chem. Int. Ed.* 43: 1566–1568.
- [40] Uraguchi D, Terada M (2004) Chiral Brønsted acid-catalyzed direct Mannich reactions via electrophilic activation. *J. Am. Chem. Soc.* 126: 5356–5357.
- [41] Yamanaka M, Itoh J, Fuchibe K, Akiyama T (2007) Chiral Brønsted acid catalyzed enantioselective Mannich-type reaction. *J. Am. Chem. Soc.* 129: 6756–6764.
- [42] Storer RI, Carrera DE, Ni Y, MacMillan DWC (2006) Enantioselective organocatalytic reductive amination. *J. Am. Chem. Soc.* 128: 84–86.
- [43] Simón L, Goodman JM (2008) Theoretical study of the mechanism of Hantzsch ester hydrogenation of imines catalyzed by chiral BINOL-phosphoric acids. *J. Am. Chem. Soc.* 130: 8741–8747.
- [44] Hasegawa A, Naganawa Y, Fushimi M, Ishihara K, Yamamoto H (2006) Design of Brønsted acid-assisted chiral Brønsted acid catalyst bearing a bis(triflyl)methyl group for a Mannich-type reaction. *Org. Lett.* 8: 3175–3178.
- [45] Nakashima D, Yamamoto H (2006) Design of chiral *N*-triflyl phosphoramidate as a strong chiral Brønsted acid and its application to asymmetric Diels-Alder reaction. *J. Am. Chem. Soc.* 128: 9626–9627.

IntechOpen