DOI: 10.1002/adsc.200606074

Recent Progress in Chiral Brønsted Acid Catalysis

Takahiko Akiyama,[a,*] Junji Itoh,[a] and Kohei Fuchibe[a]

[a] Department of Chemistry, Faculty of Science, Gakushuin University, 1-5-1 Mejiro, Toshima-ku, Tokyo 171-8588, Japan
Fax: (+81)-3-5992-1029; e-mail: takahiko.akiyama@gakushuin.ac.jp

Received: March 1, 2006; Accepted: May 9, 2006

Abstract: Hydrogen bond catalysis and Brønsted acid catalysis are rapidly growing areas in organocatalysis. A number of chiral acid catalysts has been developed recently. Recent progress in the chiral Brønsted acid catalysis has been reviewed with a focus being placed on thiourea, TADDOL, and phosphoric acids.

1 Introduction
2 Hydrogen Bond Catalysis
2.1 Monofunctional Thiourea Catalysts
2.2 Bifunctional Thiourea Catalysts
2.3 TADDOL Derivatives
2.4 BINOL Derivatives
3 Brønsted Acid Catalysis
3.1 Ammonium Salts
3.2 Phosphoric Acids
4 Conclusion

Keywords: asymmetric synthesis; chiral Brønsted acids; hydrogen bonding; organocatalysis; phosphoric acid

1 Introduction

Metal-centered Lewis acid catalysts have been recognized as efficient electrophilic activators of carbonyl compounds. The combination of a metal-centered Lewis acid catalyst and a chiral ligand will result in the formation of a chiral Lewis acid catalyst, which is usually generated *in situ* and employed directly. A range of metals has been investigated as the center element.[1] Hydrogen is the smallest kind of center element. Recently, hydrogen bonding activation and/or Brønsted acid activation of carbonyl compounds and/or imines have attracted much attention as chiral catalysts.[2] Brønsted acid catalysis is a rapidly growing area of organocatalysis.[3]

There are three modes of activation of carbonyl compounds and/or imines (Figure 1); (1) double hydrogen bonding, (2) single hydrogen bonding, (3) Brønsted acid catalysis. There is no clear borderline between hydrogen bond catalysis and Brønsted acid catalysis.

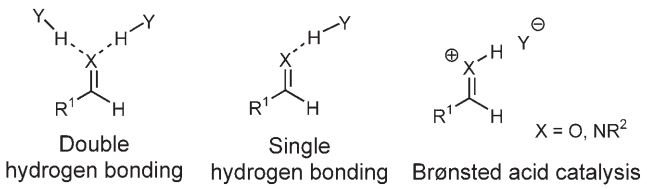


Figure 1. The modes of activation.

In this review, the Brønsted acid catalysis will be classified based on the type of the catalysts employed in the order: hydrogen bond catalysis; monofunctional thiourea catalysts; bifunctional thiourea catalysts; TADDOL derivatives; BINOL derivatives; Brønsted acid catalysis; ammonium salts; and phosphoric acids.

Thiourea and TADDOL, being neutral compounds, activate carbonyl compounds by hydrogen bond, whereas strong acids such as phosphoric acid activate carbonyl compounds by way of protonation. Therefore, thiourea and TADDOL are examples of general acid catalysis. In contrast, phosphoric acid is an example of specific acid catalysis (Figure 2).[4]

Since several review articles have appeared on Brønsted acid catalysis,[2] reports published after 2004 through the beginning of 2006 will chiefly be reviewed with the main focus on thiourea, TADDOL, and phosphoric acids. Although it is established that hydrogen bonding plays an important role in proline

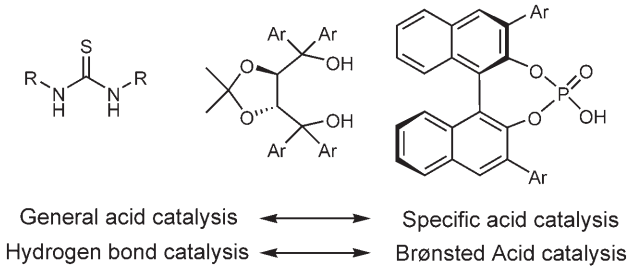


Figure 2. Types of catalysis.

Takahiko Akiyama was born in 1958 in Kurashiki (Japan). He received his Ph.D. degree in 1985 from the University of Tokyo under the direction of Professor T. Mukaiyama. Immediately thereafter he joined Shionogi Research Laboratories (Osaka, Japan) as a research chemist. In 1988 he was appointed Assistant Professor at Ehime University. He joined Professor B. M. Trost's group at Stanford University in 1992 as a post-doctoral fellow. He was appointed Associate Professor at Gakushuin University in 1994. Since 1997 he has been Full Professor at Gakushuin University. His research interest centers around thedevelopment of novel synthetic methods in particular focused on asymmetric synthesis using organocatalysts as well as metal catalysts.

Kohei Fuchibe was born in 1974 in Fukui (Japan). He received his Ph.D. degree from the University of Tokyo in 2002. He joined Professor Akiyama's group as Research Associate in 2002. His research interests are in the development of novel organic reactions by use of organometallics.

Junji Itoh was born in 1978 in Chiba (Japan). He graduated from Gakushuin University in 2002, and is now a graduate student of Gakushuin University. In 2005, he was selected as a Research Fellow of the Japan Society for the Promotion of Science. His current research is the development of novel asymmetric reactions by organocatalyst.

catalysis, the proline-catalyzed reactions are beyond the scope of this review.[5,6]

2 Hydrogen Bond Catalysis

2.1 Monofunctional Thiourea Catalysts

Thioures have been extensively investigated in the area of molecular recognition due to their ability to form hydrogen bonds.[7] Curran et al. observed the alteration of the stereoselectivity by use of a urea derivative in 1994.[8] Its application to asymmetric catalysis dates back to 1998, when Jacobsen et al. described a parallel-library approach to the discovery of catalysts for the asymmetric hydrocyanation of imines (the Strecker reaction).[9] Through a combination of empirical and structure-based optimization studies, thiourea derivative **1a** (Figure 3) and closely related ana-

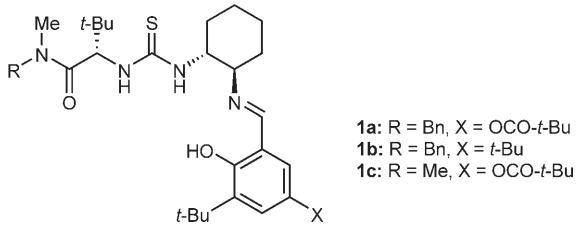
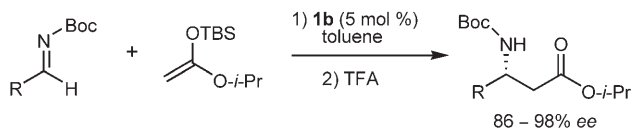


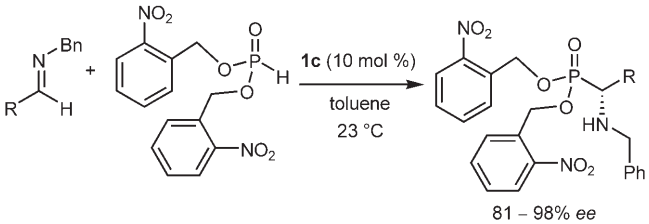
Figure 3.

logues were identified as highly general and effective catalysts for the asymmetric hydrocyanation of *N*-allyl- or *N*-benzylaldimines.[10] A similar catalyst **1b** is applicable to the asymmetric Mannich-type reaction of *N*-Boc-aldimines with silylketene acetals. The corresponding β-amino esters were obtained in 86–98% *ee* (Scheme 1).[11] Hydrophosphonylation of imines with bis(2-nitrobenzyl) phosphite proceeded by means of **1c** to give α-aminophosphonates highly enantioselectively (Scheme 2).[12]

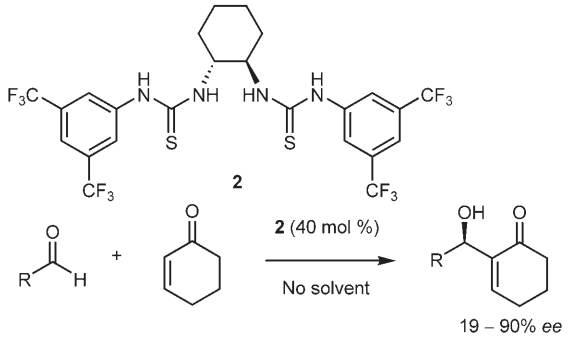
Nagasawa et al. reported that a chiral urea promoted the Michael reaction of pyrrolidine to an α,β-unsa-



Scheme 1.



Scheme 2.

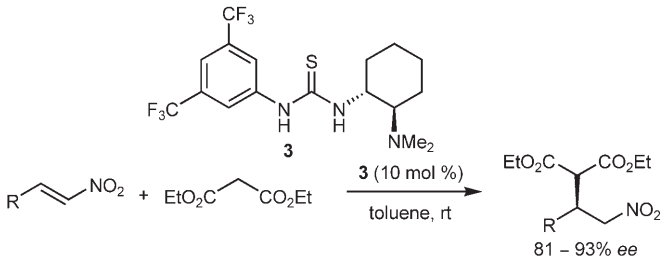


Scheme 3.

turated γ-lactone with moderate *ee*.[13] They also found that bis-thiourea **2** catalyzed the Baylis–Hillman reaction with high *ee* (Scheme 3).[14]

2.2 Bifunctional Thiourea Catalysts

Takemoto et al. developed a novel bifunctional thiourea **3**, bearing a tertiary amine moiety, and demonstrated its catalytic activity in the Michael reaction of malonates to nitroolefins (Scheme 4).[15] The Michael



Scheme 4.

adducts were obtained in good yields with high *ee*s. The presence of both thiourea and tertiary amine moiety in the molecule is crucial for the high yield and high stereoselectivity. The authors have proposed that the bifunctional thiourea catalyst interacts with a nitro group of the nitroolefin and this enhances the electrophilicity of nitroolefin, at the same time the

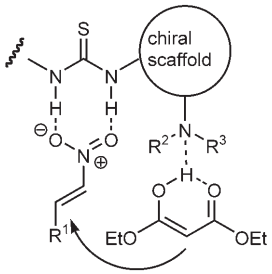


Figure 4.

amine forms hydrogen bonding with nucleophile to enhance the nucleophilicity, thereby controlling the approach of the nucleophiles to the nitroolefin (Figure 4). They screened the Michael acceptor and found that an α,β-unsaturated imide is a suitable structure for the hydrogen bond activation (Figure 5, Scheme 5).[16]

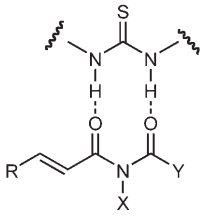
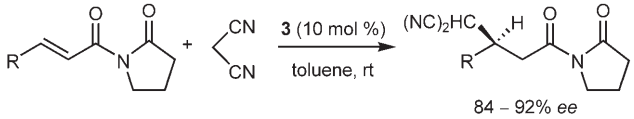
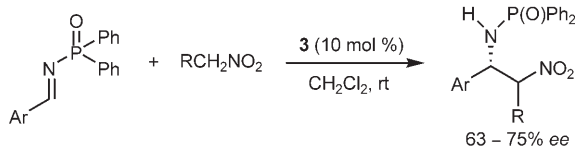


Figure 5.



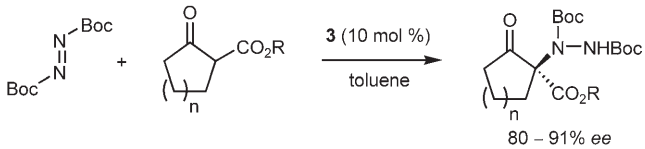
Scheme 5.

They employed **3** for the aza-Henry reaction, the nucleophilic addition of nitroalkanes to imines.[17] β-Nitroamine derivatives were obtained in good to high *ee*s (Scheme 6). The thiourea activated the nitro



Scheme 6.

group and facilitated the formation of the nucleophilic nitronate anion. Asymmetric hydrazination of 1,3-dicarbonyl compounds also proceeded highly enantioselectively to afford α,α-disubstituted α-amino acid derivatives in up to 91% *ee* (Scheme 7).[18]

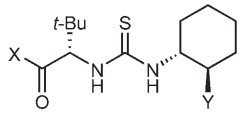


Scheme 7.

Takemoto's catalyst **3** turned out to be effective for the asymmetric addition of arylthiols to α,β-unsaturat-

ed carbonyl compounds.[19] β-Arylthio ketones were obtained in up to 85% *ee*.

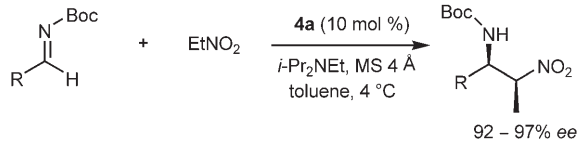
Since Takemoto's finding that the bifunctional thiourea catalyst is quite effective, a number of bifunctional catalysts bearing a thiourea moiety have appeared (Figure 6).



4a: X = NMe_2, Y = NHAc
4b: X = $N(i\text{-}Bu)_2$, Y = 2-methyl-5-phenyl-1-pyrrolyl
4c: X = NHMe, Y = $N(n\text{-}Bu)_2$
4d: X = NMeBn, Y = NMe_2

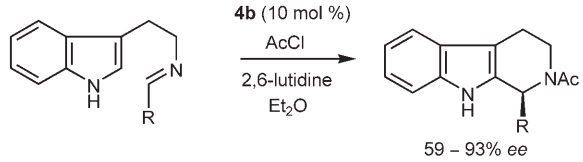
Figure 6.

Jacobsen et al. reported a nitro-Mannich reaction catalyzed by thiourea **4a** to give the β-nitro amine with excellent enantioselectivity (Scheme 8).[20]

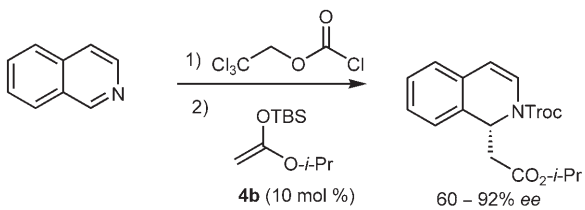


Scheme 8.

A catalytic acyl-Pictet–Spengler reaction was promoted by **4b** to give indole derivatives highly enantioselectively (Scheme 9).[21] Enantioselective acyl-Mannich reactions of isoquinolines were successfully achieved by using the same catalyst (Scheme 10).[22] A thiourea derivative **4b** was found to be a good activator of the weakly Lewis basic *N*-acyliminium ion.

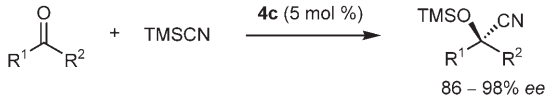


Scheme 9.



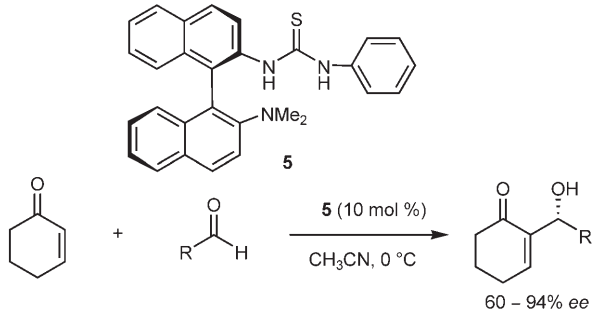
Scheme 10.

Jacobsen et al. found that the bifunctional catalyst **4c** is effective for the hydrocyanation of ketones to afford cycanohydrin trimethylsilyl ether with high *ee*s (Scheme 11).[23]

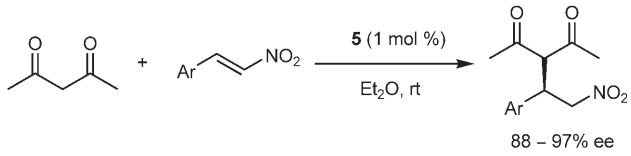


Scheme 11.

Wang et al. developed the bifunctional thiourea **5**, bearing a binaphthyl backbone and an amine moiety, which catalyzed the Morita–Baylis–Hillman reaction of cyclohexenone with a wide range of aldehydes (Scheme 12).[24] The same catalyst promoted the asymmetric Michael addition of acetylacetone to nitroolefins (Scheme 13).[25]



Scheme 12.

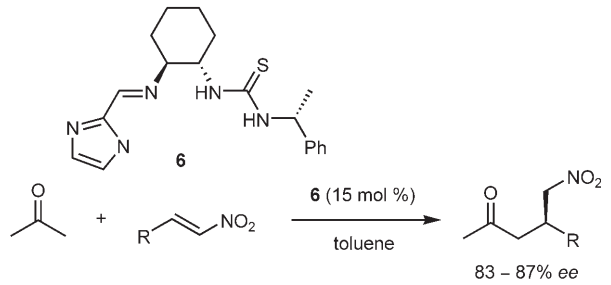


Scheme 13.

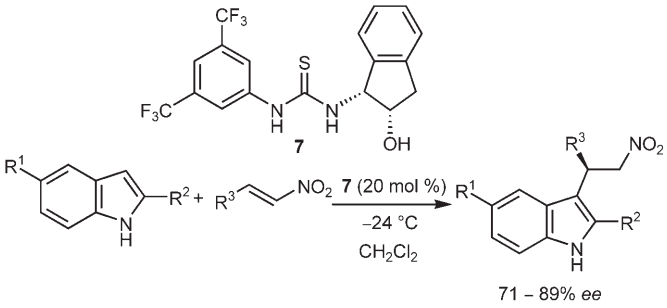
Tsogoeva et al. synthesized a novel bifunctional organocatalyst **6**, bearing both a thiourea moiety and an imidazole group on a chiral scaffold, and applied it to the Strecker synthesis and nitro-Michael reaction (Scheme 14).[26]

Ricci et al. developed the Friedel–Crafts alkylation of aromatic and heteroaromatic compounds with nitroalkenes catalyzed by a thiourea derivative.[27] They extended the chemistry to asymmetric thiourea **7**-catalyzed Michael addition reactions (Scheme 15).[28]

Cinchona alkaloid-thiourea bifunctional catalysts have been developed (Figure 7). After screening a range of bifunctional thiourea catalysts, Soos et al. found that *Cinchona* alkaloid **8a** is quite effective in the 1,4-addition reaction of nitromethane to chalcone



Scheme 14.



Scheme 15.

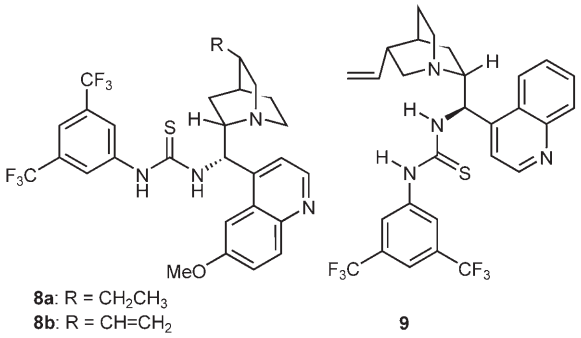
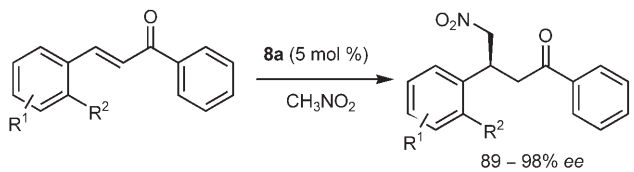


Figure 7.

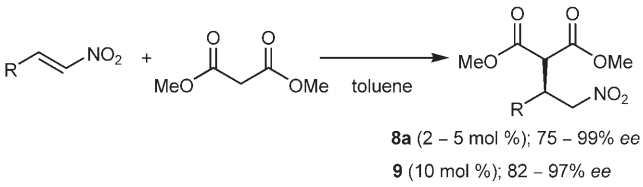
derivatives.[29,30] Conjugate addition products were obtained with high enantioselectivity (Scheme 16).

Connon et al.[31] and Dixon et al.[32] independently reported the Michael reactions of malonates to nitroolefins to give 1,4-adducts were highly enantioselectively. Connon employed **8a** as an organocatalyst, whereas Dixon used **9** (Scheme 17).

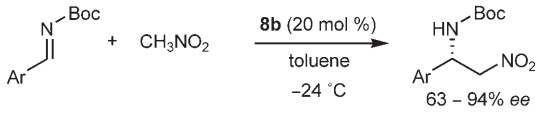
An aza-Henry reaction was also successfully achieved by Ricci et al. by means of **8b** (Scheme 18).[33]



Scheme 16.

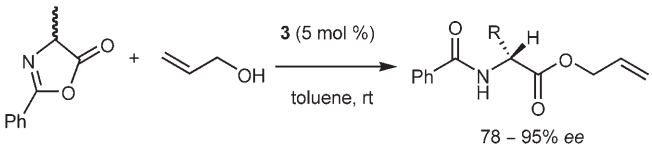


Scheme 17.



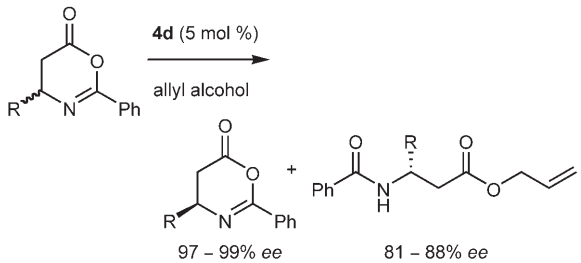
Scheme 18.

Thiourea catalysts are also effective for the kinetic resolution: Berkessel et al. employed **3** for the enantioselective dynamic kinetic resolutions of azlactones leading to natural and unnatural amino acid derivatives.[34] Treatment of an azlactone with allyl alcohol in the presence of 5 mol% of the catalyst resulted in ring opening and the corresponding ester was obtained in 78–95% *ee* (Scheme 19). They later found a



Scheme 19.

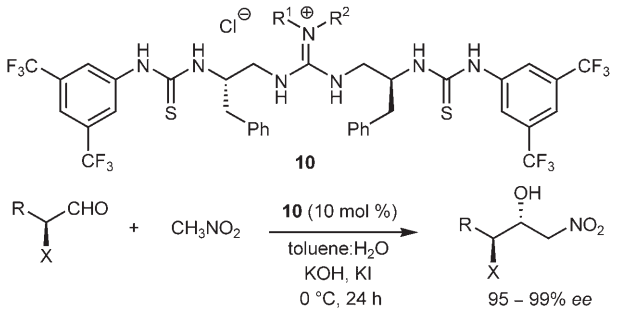
more effective thiourea derivative **4d**[35] and employed it in the kinetic resolution of oxazinones whereby β-amino acid derivatives were obtained with high enantioselectivity (Scheme 20).[36]



Scheme 20.

Nagasawa et al. designed a novel bifunctional catalyst having guanidine and thiourea functional groups **10**, which effectively promoted the Henry reaction with aliphatic cyclic aldehydes and branched aldehydes in the presence of KI as an additive to afford β-

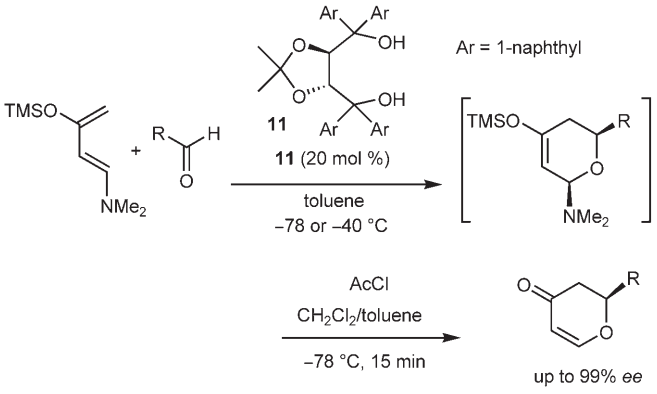
nitroamines in 82–90% *ee*.[37] They subsequently found that use of α-substituted aldehydes improved the enantioselectivity to 95–99% *ee* (Scheme 21).[38]



Scheme 21.

2.3 TADDOL Derivatives

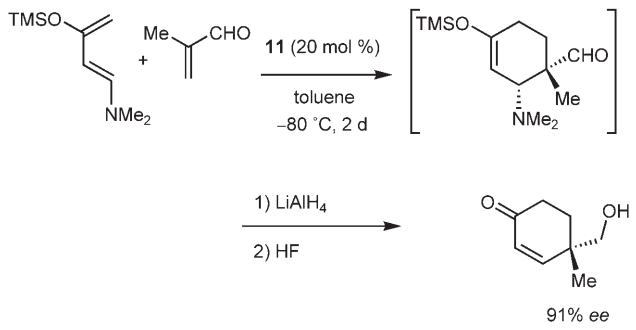
Rawal et al. reported the hydrogen bond-promoted hetero-Diels–Alder reaction of non-activated aldehydes and aminodiene.[39,40] They subsequently found that the simple diol **11** (TADDOL) is highly effective as a chiral catalyst for the herero-Diels–Alder reaction. On treatment of aminosiloxydiene with aldehyde in the presence of 20 mol% of **11**,[41] the hetero-Diels–Alder reaction proceeded smoothly to furnish the cycloadducts highly enantioselectively after treatment with AcCl (Scheme 22).



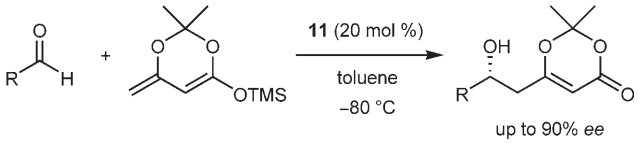
Scheme 22.

A Diels–Alder reaction of the aminosiloxydiene with α,β-unsaturated aldehydes also took place highly enantioselectively by means of **11** to afford cyclohexenone derivatives (Scheme 23).[42]

The TADDOL catalyst **11** proved to be effective for the vinylogous Mukaiyama aldol reaction to give the corresponding aldol products highly enantioselectively (Scheme 24). The aldol products should be useful for the preparation of polyketides.[43]

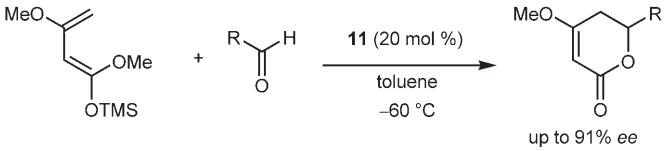


Scheme 23.



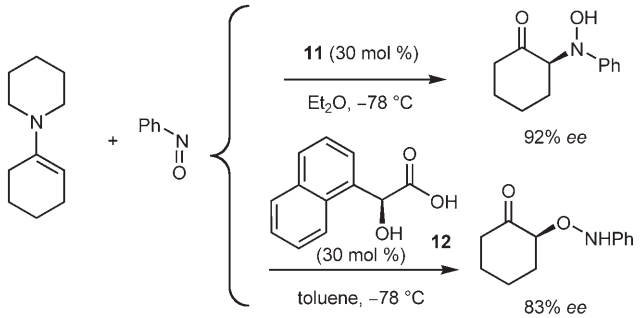
Scheme 24.

Ding et al. reported the hetero-Diels–Alder reaction of an aldehyde with Brassard's diene by means of **11** to afford δ-lactone derivatives highly enantioselectively (Scheme 25).[44]



Scheme 25.

Yamamoto et al. extended his nitrosobenzene chemistry to the reaction with enamines.[45] The proper choice of catalyst resulted in a regio- and enantioselective nitroso aldol reaction: use of the TADDOL catalyst **11** gave *N*-nitroso aldol products in 77–91% *ee*. In striking contrast, the glycolic acid derivative **12** furnished *O*-nitroso aldol products in 70–93% *ee* (Scheme 26).



Scheme 26.

Yamamoto and Rawal have found that the axially chiral 1,1′-biaryl-2,2′-dimethanol (Figure 8, **13**, BAMOL) scaffold is highly effective as a catalyst for

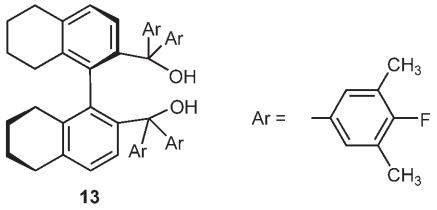


Figure 8.

the hetero-Diels–Alder reactions of a wide range of aliphatic and aromatic aldehydes with aminosiloxydienes to give the cycloadducts in 84–99 % *ee*.[46] They have succeeded in obtaining an X-ray structure of an inclusion complex of 2,2-bis(diphenylhydroxymethyl)-binaphthylene, a simple member of the BAMOL family of catalysts, and benzaldehyde. The structure not only shows a 1:1 association between BAMOL and benzaldehyde, but also reveals the presence of an *intra*molecular hydrogen bond between the two hydroxy groups and an *inter*molecular hydrogen bond to the carbonyl oxygen of benzaldehyde. The above complex suggests that carbonyl activation is through a single-point hydrogen bond, as was postulated for TADDOL catalysis (Figure 9).

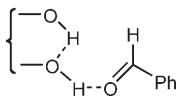
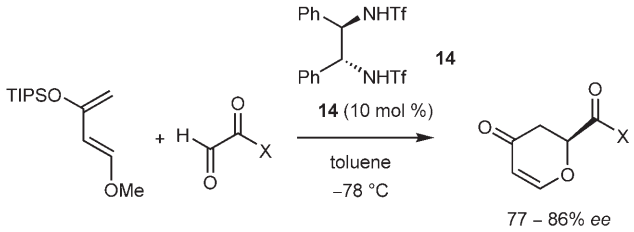


Figure 9.

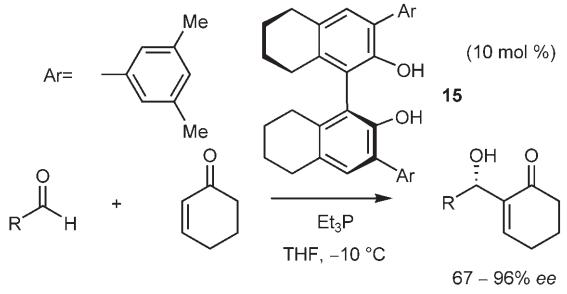
Mikami et al. reported that the bis-sulfonamide derived from 1,2-diamino-1,2-diphenylethane **14** proved to be effective as a catalyst for the hetero-Diels–Alder reaction of Danishefsky's diene with glyoxylate (Scheme 27).[47]



Scheme 27.

2.4 BINOL Derivatives

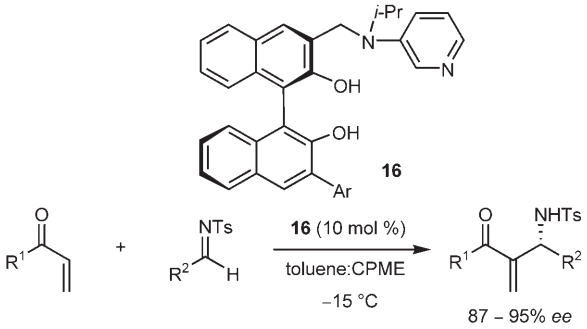
Schaus et al. reported asymmetric Morita–Baylis–Hillman reactions catalyzed by a chiral Brønsted acid **15**, which was derived from BINOL, in the presence of a stoichiometric amount of PEt_3 (Scheme 28).[48,49] Sat-



Scheme 28.

uration of the BINOL derivative and introduction of bulky substituents on the 3,3′-positions are essential for the excellent enantioselectivity. They proposed that the phosphonium enolate of cyclohexanone is stabilized *via* a hydrogen bond with the binaphthol-derived Brønsted acid, creating a chiral nucleophile.

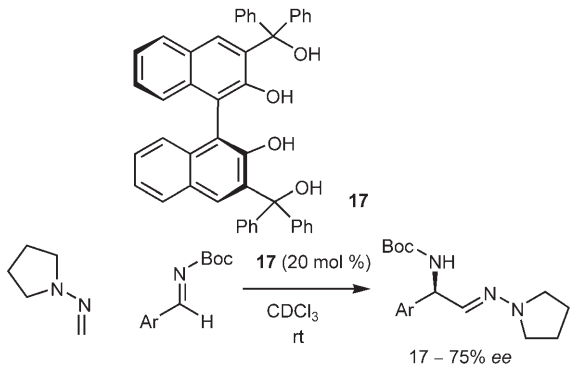
Sasai et al. reported an aza-Morita–Baylis–Hillman reaction catalyzed by the bifunctional organocatalyst



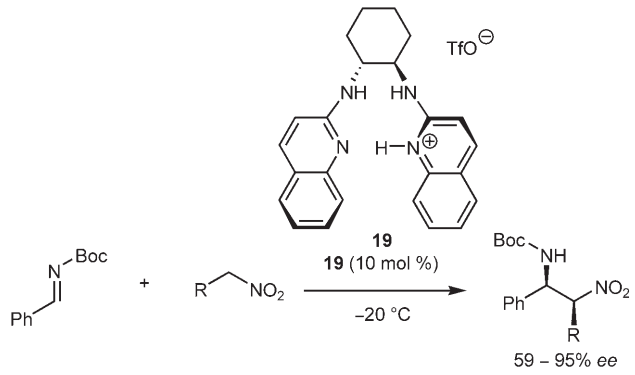
Scheme 29.

16 (Scheme 29).[50] The pyridyl moiety plays as the role of a Lewis base unit and the diol moiety acts as a Brønsted acid site.[51] Interestingly, only the 3-pyridyl-aminomethyl moiety at the 3-position turned out to be quite effective with respect to both enantioselectivity and reactivity.

Dixon et al. reported that a tetraol **17** catalyzes the addition reaction of methyleneaminopyrrolidine to imines to give α-aminohydrazolones in 17–75 % *ee* (Scheme 30).[52]



Scheme 30.

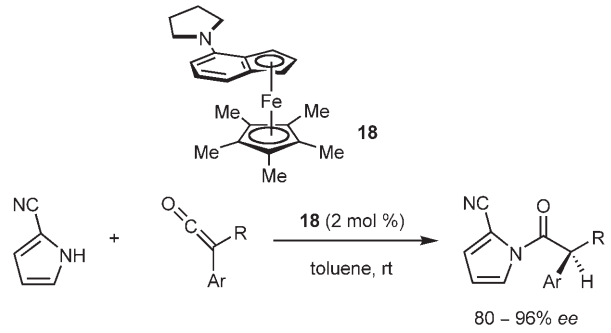


Scheme 32.

3 Brønsted Acid Catalysis

3.1 Ammonium Salts

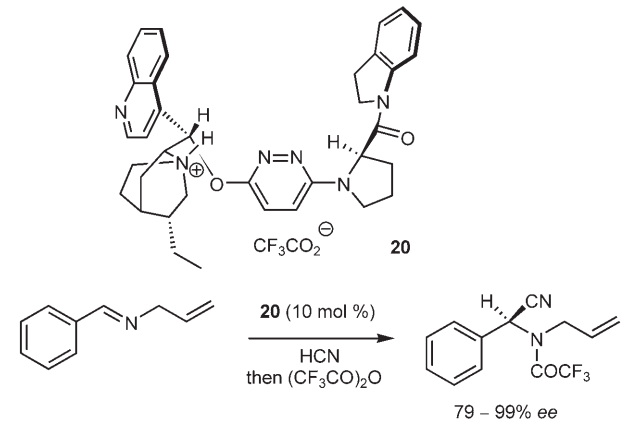
Fu et al. reported in 2002 the enantioselective addition of amines to ketenes catalyzed by a planar-chiral 4-(pyrrolidino)pyridine derivative **18**, giving rise to acylpyrroles, wherein they proposed the intervention of chiral Brønsted acid catalysis (Scheme 31).[53,54] Recently, they employed **18** as a catalyst for the enantioselective synthesis of esters from ketenes.[55]



Scheme 31.

Johnston et al. reported the aza-Henry reaction by means of an ammonium salt **19**, derived from cyclohexane diamine and quinoline.[56] β-Nitroamines were obtained with high diastereoselectivity and enantioselectivity (Scheme 32). They measured the pK_a value of the ammonium salt by Perrin titration method and estimated it to be 5.78,[57] which indicates that the ammonium salt is not strong enough to protonate the imine.

Corey et al. investigated the use of the chiral *Cinchona* alkaloid-based ammonium salt **20** as a catalyst for the enantioselective Strecker reaction (Scheme 33).[58] They proposed that the acid could be used to hold the aldehyde-derived part of an aldimine, which was activated by hydrogen bonding with the protonated quinuclidine moiety.

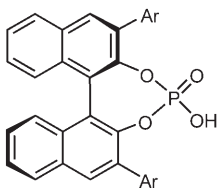


Scheme 33.

3.2 Phosphoric Acids

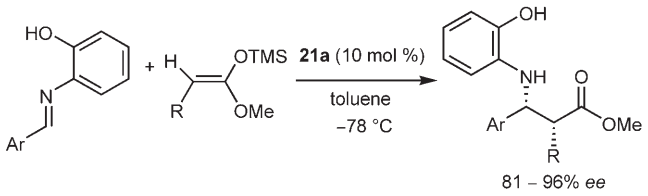
The Brønsted acids so far studied are rather weak acids. Fairly strong Brønsted acid catalysis has been developed recently (Figure 10).

Akiyama et al. synthesized chiral cyclic phosphoric acid diester **21a**, starting from (*R*)-BINOL, and demonstrated its catalytic activity in the Mannich-type reaction of ketene silyl acetal with the aldimine derived from 2-hydroxyaniline (Scheme 34).[59] The introduction of substituted aryl groups onto the 3,3′-positions



21a: Ar = 4-$NO_2C_6H_4$
21b: Ar = 3,5-$(CF_3)_2C_6H_3$
21c: Ar = 2,4,6-(*i*-Pr)$_3C_6H_2$
21d: Ar = 4-β-naphthyl-C_6H_4
21e: Ar = 3,5-dimesitylphenyl
21f: 9-anthryl
21g; $SiPh_3$

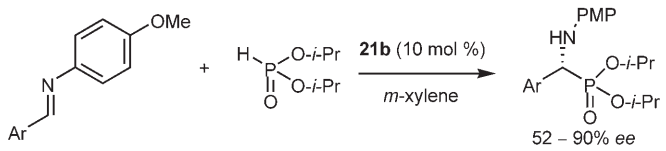
Figure 10.



Scheme 34.

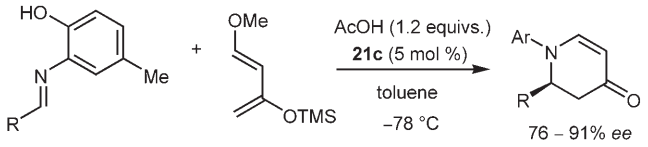
is essential for the excellent enantioselectivity; a phosphoric acid **21a**, bearing a 4-nitrophenyl group, gave the best result in terms of both reactivity and enantioselectivity. β-Amino esters were obtained with high *syn* selectivity and the *ee* of the *syn* isomer reached as much as 96%. The presence of an *o*-hydroxy functionality on the *N*-aryl group is essential for the excellent enantioselectivity.

The hydrophosphonylation of aldimines with dialkyl phosphite was catalyzed by **21b** to give α-amino phosphonates with good to high enantioselectivity. The use of aldimines derived from *p*-anisidine gave the best results (Scheme 35).[60]



Scheme 35.

The aza-Diels–Alder reaction of aldimines with Danishefsky's diene also proceeded highly enantioselectivity by means of **21c**. Interestingly, the addition of acetic acid gave beneficial effects both on the enantioselectivity and chemical yield (Scheme 36).[61]



Scheme 36.

Because the use of the *N*-(2-HOC_6H_4) moiety is essential for the Mannich-type reaction and aza-Diels–Alder reaction, a 9-membered cyclic transition state model, derived from the aldimine and the acid, has been proposed (Figure 11). In contrast, the hydrophosphonylation reaction has been proposed to proceed *via* the 9-membered cyclic transition state derived from the aldimine, acid, and dialkyl phosphite, wherein the phosphoryl oxygen activates the nucleophile by coordinating with the hydrogen of the phosphite as a Brønsted base (Figure 12).

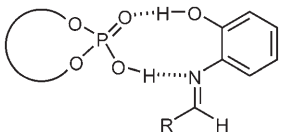


Figure 11.

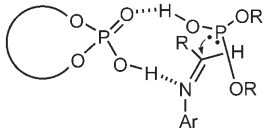
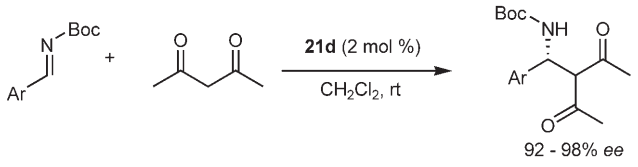
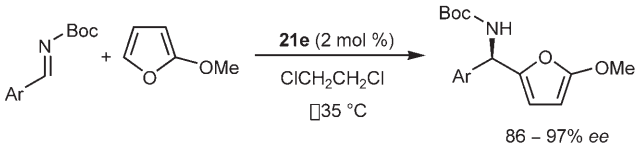


Figure 12.

Terada et al. reported direct the Mannich reaction of 1,3-diketone to aldimines, bearing an *N*-Boc group, catalyzed by **21d** (2 mol%) (Scheme 37).[62] The Friedel–Crafts type addition of electron-rich aromatics also proceeded highly enantioselectively by means of 2 mol% of **21e** (Scheme 38).[63] The addition of a

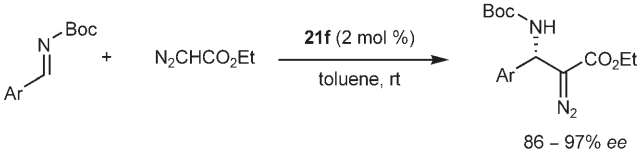


Scheme 37.



Scheme 38.

diazo ester was catalyzed by **21f** to give an α-diazo ester with up to 97% *ee* (Scheme 39), in which the phosphoryl oxygen acted as an intramolecular basic site (Figure 13).[64]



Scheme 39.

The reductive amination reaction provides a rapid and general access to stereogenic C–C–N bonds. A

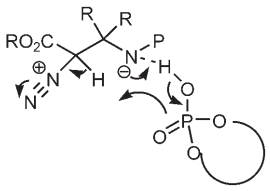
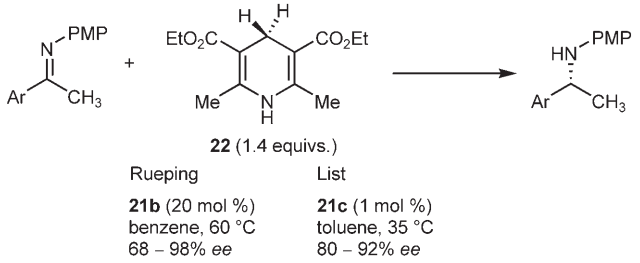


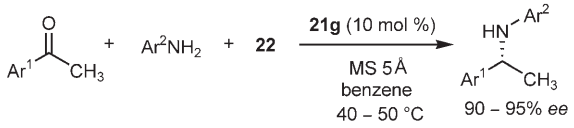
Figure 13.

biomimetic approach has been successfully achieved and reported by Rueping,[65] List,[66] and MacMillan[67] successively. They used the Hantzsch ester **22** as an NADH model reducing agent. Rueping et al. employed **21b** (20 mol%) as a catalyst, whereas List et al. utilized **21c** (1 mol%) as a catalyst (Scheme 40).



Scheme 40.

MacMillan found that the reductive amination starting from aldehyde, amine, and Hantzsch ester **22** also proceeded smoothly by means of **21g** (10 mol%) in the presence of MS 5 Å to afford benzylic amines in 83–97% *ee* (Scheme 41). It is noted that dialkyl ketones as well as alkyl aryl ketones proved to be good substrates and even methyl ethyl ketone is reductively aminated in 88% *ee*. MacMillan et al. reported the single-crystal X-ray structure of a catalyst-bound arylimine **23** (Figure 14). The structure exhibited a remarkable correlation to MM3 calculations in terms of both hydrogen bond orientation and the specific architectural elements that dictate iminium enantiofacial discrimination.



Scheme 41.

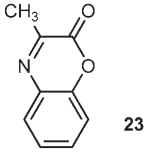
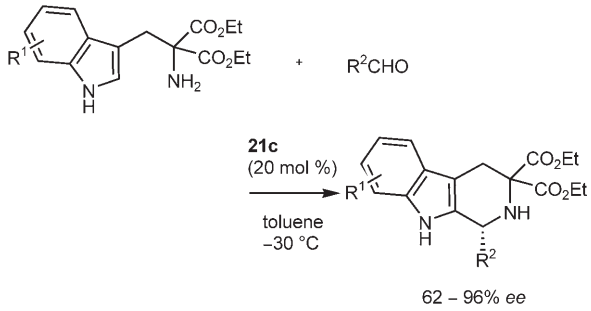


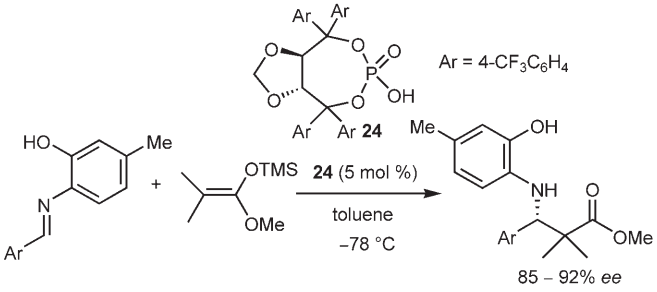
Figure 14.

List et al. has recently reported the Pictet–Spengler reaction.[68] On treatment of an aldehyde and an amine bearing an indole moiety with **21c** (20 mol%), in situ generation of aldimine and subsequent enantioselective addition of indole to aldimine took place to afford the cyclized product in 62–96% *ee* (Scheme 42). The presence of a geminal diester functionality is essential for the cyclization reaction to proceed.



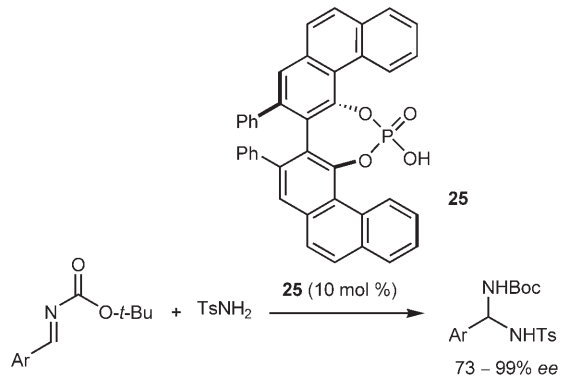
Scheme 42.

Chiral phosphoric acids are not restricted to those originating from BINOL. A TADDOL-based phosphoric acid diester **24** was developed by Akiyama et al. and applied to the Mannich-type reaction (Scheme 43).[69] Interestingly, the aryl substituents of TADDOL strongly affected both the chemical yield and the enantioselectivity. Use of the 4-$CF_3C_6H_4$ group on the TADDOL moiety is essential.



Scheme 43.

Antilla et al. synthesized a novel phosphoric acid derivative **25**, starting from (*S*)-VAPOL, and demonstrated its catalytic activity in the addition of sulfonamides to imines, giving rise to protected aminals, which have been incorporated into peptide chains as retro-inverso peptide mimics (Scheme 44).[70]



Scheme 44.

4 Conclusion

Dalko and Moisan wrote a review article entitled "In the Golden Age of Organocatalysis" in 2004. Since then, a large number of papers concerning chiral Brønsted acid catalysis have been reported. Now we are in the middle of a golden age of the Brønsted acid catalysis.

In contrast to the chiral Lewis acid catalysts, which are normally generated in situ and employed directly, chiral Brønsted acids acts as catalysts by themselves. They are normally stable toward water and oxygen, furthermore, they are potentially recoverable and recyclable.

One of the deficiencies of the chiral Brønsted acids is catalyst loading: 5–10 mol% of the catalysts are usually required. More efficient chiral Brønsted acids will probably be developed and applied in industry in the near future.

Acknowledgements

Partial financial support by a Grant-in Aid for Scientific Research from the Ministry of Education, Science, Sports, Culture, and Technology, Japan is appreciated. J. I. thanks the JSPS Research Fellowships for Young Scientists.

References

[1] H. Yamamoto (Ed.), *Lewis Acids in Organic Synthesis* Vols. 1 and 2, Wiley-VCH, Weinheim, **2000**.
[2] P. R. Schreiner, *Chem. Soc., Rev.* **2003**, 28; Pihko, P. M. *Lett. Org. Chem.* **2004**, *2*, 398; P. M. Pihko, *Angew. Chem. Int. Ed.* **2004**, *43*, 2062; C. Bolm, T. Rantanen, I. Schiffers, L. Zani, *Angew. Chem. Int. Ed.* **2005**, *44*, 1758.
[3] For reviews on organocatalysis, see: P. I. Dalko, L. Moisan, *Angew. Chem. Int. Ed.* **2001**, *40*, 3726; P. I. Dalko, L. Moisan, *Angew. Chem. Int. Ed.* **2004**, *43*, 5138; J. Seayad, B. List, *Org. Biomol. Chem.* **2005**, *3*, 719; A. Berkessel, H. Gröger, (Eds.), *Asymmetric Organocatalysis*, Wiley-VCH, Weinheim, **2005**.
[4] W. P. Jencks, *Acc. Chem. Res.* **1976**, *9*, 425.
[5] For reviews on proline catalysis, see: B. List, *Synlett* **2001**, 1675; B. List, *Tetrahedron* **2002**, *58*, 5573; W. Notz, F. Tanaka, C. F. Barbas, *Acc. Chem. Res.* **2004**, *37*, 580; B. List, *Acc. Chem. Res.* **2004**, *37*, 548.
[6] For a review on Brønsted acid and base combined systems, see: H. Yamamoto, K. Futatsugi, *Angew. Chem. Int. Ed.* **2005**, *44*, 1924.
[7] B. R. Linton, M. S. Goodman, A. D. Hamilton, *Chem. Eur. J.* **2000**, *6*, 2449 and references cited therein.
[8] D. P. Curran, L. H. Kuo, *J. Org. Chem.* **1994**, *59*, 3259.
[9] M. S. Sigman, E. N. Jacobsen, *J. Am. Chem. Soc.* **1998**, *120*, 4901; P. Vachal, E. N. Jacobsen, *Org. Lett.* **2000**, *2*, 867; M. S. Sigman, P. Vachal, E. N. Jacobsen, *Angew. Chem. Int. Ed.* **2000**, *39*, 1279; P. Vachal, E. N. Jacobsen, *J. Am. Chem. Soc.* **2002**, *124*, 10012.
[10] A. G. Wenzel, M. P. Lalonde, E. N. Jacobsen, *Synlett* **2003**, 1919.
[11] A. G. Wenzel, E. N. Jacobsen, *J. Am. Chem. Soc.* **2002**, *124*, 12964.
[12] G. D. Joly, E. N. Jacobsen, *J. Am. Chem. Soc.* **2004**, *126*, 4102.
[13] Y. Sohtome, A. Tanatani, Y. Hashimoto, K. Nagasawa, *Chem. Pharm. Bull.* **2004**, *52*, 477.
[14] Y. Sohtome, A. Tanatani, Y. Hashimoto, K. Nagasawa, *Tetrahedron Lett.* **2004**, *45*, 5589.
[15] T. Okino, Y. Hoashi, Y. Takemoto, *J. Am. Chem. Soc.* **2003**, *125*, 12672; Y. Hoashi, T. Yabuta, Y. Takemoto, *Tetrahedron Lett.* **2004**, *45*, 9185; T. Okino, Y. Hoashi, T. Furukawa, X. Xu, Y. Takemoto, *J. Am. Chem. Soc.* **2005**, *127*, 119.
[16] Y. Hoashi, T. Okino, Y. Takemoto, *Angew. Chem. Int. Ed.* **2005**, *44*, 4032.
[17] T. Okino, S. Nakamura, T. Furukawa, Y. Takemoto, *Org. Lett.* **2004**, *6*, 625.
[18] X. Xu, T. Yabuta, P. Yuan, Y. Takemoto, *Synlett* **2006**, 137.
[19] B.-J. Li, L. Jiang, M. Liu, Y.-C. Chen, L.-S. Ding, Y. Wu, *Synlett* **2005**, 603.
[20] T. P. Yoon, E. N. Jacobsen, *Angew. Chem. Int. Ed.* **2005**, *44*, 466.
[21] M. S. Taylor, E. N. Jacobsen, *J. Am. Chem. Soc.* **2004**, *126*, 10558.
[22] T. P. Yoon, E. N. Jacobsen, *Angew. Chem. Int. Ed.* **2005**, *44*, 466.
[23] D. E. Fuerst, E. N. Jacobsen, *J. Am. Chem. Soc.* **2005**, *127*, 8964.
[24] J. Wang, H. Li, X. Yu, L. Zu, W. Wang, *Org. Lett.* **2005**, *7*, 4293.
[25] J. Wang, H. Li, W. Duan, L. Zu, W. Wang, *Org. Lett.* **2005**, *7*, 4713.
[26] S. B. Tsogoeva, D. A. Yalalov, M. J. Hateley, C. Weckbecker, K. Huthmacher, *Eur. J. Org. Chem.* **2005**, 4995.
[27] G. Dessolea, R. P. Herrera, A. Ricci, *Synlett* **2004**, 2374.
[28] R. P. Herrera, V. Sgarzani, L. Bernardi, A. Ricci, *Angew. Chem. Int. Ed.* **2005**, *44*, 6576.
[29] B. Vakulya, S. Varga, A. Csámpai, T. Soós, *Org. Lett.* **2005**, *7*, 1967.

[30] For a review on *Cinchona* alkaloids, see: S.-K. Tian, Y. Chen, J. Hang, L. Tang, P. McDaid, L. Deng, *Acc. Chem. Res.* **2004**, 37, 621.
[31] S. H. McCooey, S. J. Connon, *Angew. Chem. Int. Ed.* **2005**, *44*, 6367.
[32] J. Ye, D. J. Dixon, P. S. Hynes, *Chem. Commun.* **2005**, 4481.
[33] L. Bernardi, F. Fini, R. P. Herrera, A. Ricci, V. Sgarzani, *Tetrahedron* **2006**, *62*, 375.
[34] A. Berkessel, F. Cleemann, S. Mukherjee, T. N. Müller, J. Lex, *Angew. Chem. Int. Ed.* **2005**, *44*, 807.
[35] A. Berkessel, S. Mukherjee, F. Cleemann, T. N. Müller, J. Lex, *Chem. Commun.* **2005**, 1898.
[36] A. Berkessel, F. Cleemann, S. Mukherjee, *Angew. Chem. Int. Ed.* **2005**, *44*, 7466.
[37] Y. Sohtome, Y. Hashimoto, K. Nagasawa, *Adv. Synth. Catal.* **2005**, *347*, 1643.
[38] Y. Sohtome, N. Takemura, T. Iguchi, Y. Hashimoto, K. Nagasawa, *Synlett* **2006**, 144.
[39] Y. Huang, V. H. Rawal, *J. Am. Chem. Soc.* **2002**, *124*, 9662.
[40] For a computational study on the enhancing reactivity of carbonyl compounds *via* hydrogen-bonding, see: L. R. Domingo, J. Andrés, *J. Org. Chem.* **2003**, 68, 8662.
[41] Y. Huang, A. K. Unni, A. N. Thadani, V. H. Rawal, *Nature* **2003**, *424*, 146.
[42] A. N. Thadani, A. R. Stankovic, V. H. Rawal, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5846.
[43] V. B. Gondi, M. Gravel, V. H. Rawal, *Org. Lett.* **2005**, *7*, 5657.
[44] H. Du, D. Zhao, K. Ding, *Chem. Eur. J.* **2004**, *10*, 5964.
[45] N. Momiyama, H. Yamamoto, *J. Am. Chem. Soc.* **2005**, *127*, 1080.
[46] A. K. Unni, N. Takenaka, H. Yamamoto, V. H. Rawal, *J. Am. Chem. Soc.* **2005**, *127*, 1336.
[47] T. Tonoi, K. Mikami, *Tetrahedron Lett.* **2005**, *46*, 6355.
[48] N. T. McDougal, S. E. Schaus, *J. Am. Chem. Soc.* **2003**, *125*, 12094.
[49] N. T. McDougal, W. L. Trevellini, S. A. Rodgen, L. T. Kliman, S. E. Schaus, *Adv. Synth. Catal.* **2004**, *346*, 1231.
[50] K. Matsui, S. Takizawa, H. Sasai, *J. Am. Chem. Soc.* **2005**, *127*, 3680.
[51] For the aza-Morita–Baylis–Hillman reaction catalyzed by chiral phosphinyl BINOL, see: M. Shi, L.-H. Chen, *Chem. Commun.* **2003**, 1310.
[52] D. J. Dixon, A. L. Tillman, *Synlett* **2005**, 2635.
[53] B. L. Hodous, G. C. Fu, *J. Am. Chem. Soc.* **2002**, *124*, 10006.
[54] For asymmetric protonation, see: A. Yanagisawa, H. Yamamoto, in: *Comprehensive Asymmetric Caalysis*, (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Berlin, Heidelberg, NewYork, **1999**, Chapter 34.2.
[55] S. L. Wiskur, G. C. Fu, *J. Am. Chem. Soc.* **2005**, *127*, 6176.
[56] B. M. Nugent, R. A. Yoder, J. N. Johnston, *J. Am. Chem. Soc.* **2004**, *126*, 3418.
[57] A. S. Hess, R. A. Yoder, J. N. Johnston, *Synlett* **2006**, 147.
[58] J. Huang, E. J. Corey, *Org. Lett.* **2004**, *##6###3*, 5027.
[59] T. Akiyama, J. Itoh, K. Yokota, K. Fuchibe, *Angew. Chem. Int. Ed.* **2004**, *43*, 1566.
[60] T. Akiyama, H. Morita, J. Itoh, K. Fuchibe, *Org. Lett.* **2005**, *7*, 2583.
[61] T. Akiyama, Y. Tamura, J. Itoh, H. Morita, K. Fuchibe, *Synlett* **2006**, 141.
[62] D. Uraguchi, M. Terada, *J. Am. Chem. Soc.* **2004**, *126*, 5356.
[63] D. Uraguchi, K. Sorimachi, M. Terada, *J. Am. Chem. Soc.* **2004**, *126*, 11804.
[64] D. Uraguchi, K. Sorimachi, M. Terada, *J. Am. Chem. Soc.* **2005**, *127*, 9360.
[65] M. Rueping, E. Sugiono, C. Azap, T. Theissmann, M. Bolte, *Org. Lett.* **2005**, *7*, 3781.
[66] S. Hoffmann, A. M. Seayad, B. List, *Angew. Chem. Int. Ed.* **2005**, *44*, 7424.
[67] R. I. Storer, D. E. Carrera, Y. Ni, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2006**, *128*, 84.
[68] J. Seayad, A. M. Seayad, B. List, *J. Am. Chem. Soc.* **2006**, *128*, 1086.
[69] T. Akiyama, Y. Saitoh, H. Morita, K. Fuchibe, *Adv. Synth. Catal.* **2005**, *347*, 1523.
[70] G. B. Rowland, H. Zhang, E. B. Rowland, S. Chennamadhavuni, Y. Wang, J. C. Antilla, *J. Am. Chem. Soc.* **2005**, *127*, 15696.

