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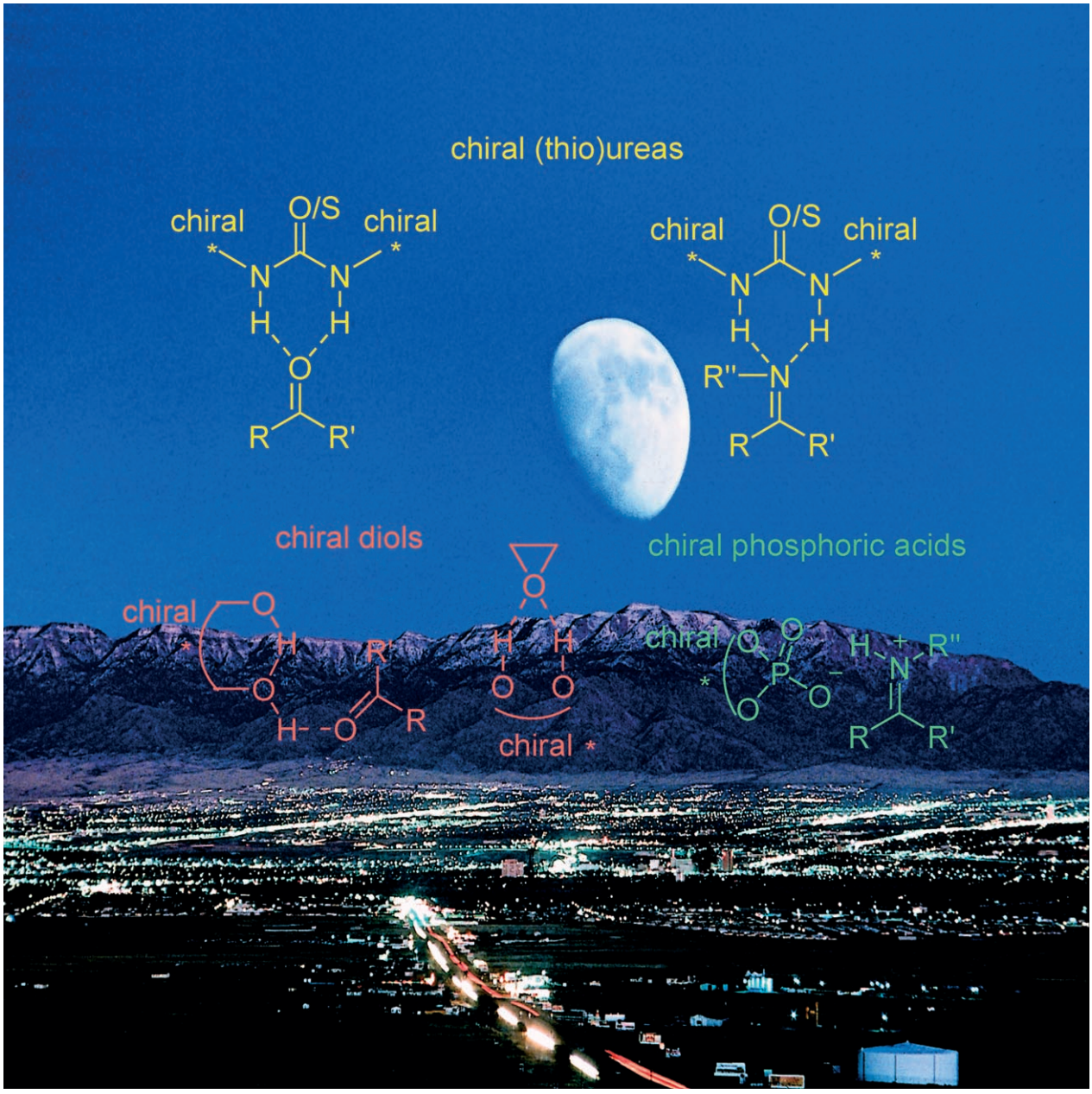
Hydrogen-Bond-Mediated Asymmetric Catalysis

Xinhong Yu[b] and Wei Wang*[a, b]



Abstract: The utilization of hydrogen bonding as an activation force has become a powerful tool in asymmetric organocatalysis. Significant advances have been made in the recent past in this emerging field. Due to space constraints, this Focus Review summarizes only the key aspects with an emphasis on catalysis based on chiral ureas and thioureas, diols, and phosphoric acids. The examples provided neatly demonstrate that chiral ureas and thioureas, diols, and phosphoric acids display effective and unique activation modes of catalysis for a broad spectrum of asymmetric organic transformations, including single-step and multiple-step cascade reactions. These functionalities, which have the ability to afford efficient H-bond activation of electrophiles including C=O, C=N, aziridines, and epoxides, have established their status as "privileged" functional groups in the design of organocatalysts.

Keywords: asymmetric catalysis · diols · hydrogen bonds · phosphoric acids · ureas

1. Introduction

Hydrogen bonding is one of the most dominant forces in molecular interaction and recognition in biological systems.[1] It plays a central role in biocatalysis. However, the design of small molecules that mimic the catalytic activities of enzymes presents a formidable challenge as small organic molecules often lack the nearly rigid and dynamic three-dimensional structures and multiple functional groups that are present in the active sites of enzymes. Therefore, prior to the late 1960s, the prevailing dogma was that only complex supramolecular structures that matched the molecular sophistication of enzymes were capable of catalyzing enantioselective transformations. The dominant strategy mainly employed nowadays by synthetic organic chemists to bring about asymmetric catalysis relies on the use of metal-centered, chiral Lewis acids that often form tight complexes with organic substrates.[2] Nevertheless, the development of chiral Brønsted acids as activation forces is a highly challenging task in asymmetric catalysis, presumably because much weaker hydrogen-bonding interactions between the promoter and substrates would be the source of stereochemical control.

This perception has delayed the advancement of this area. Recently, chemists have begun to appreciate the potential offered by hydrogen bonding as a force for electrophile activation in small-molecule-based catalysis.[3] In particular, the utilization of chiral hydrogen-bond donors as promoters has been the subject of intense research, as evidenced by the number of research papers that have appeared.[4] In a similar manner to enzymatic catalysis, in which H bonding to a transition state occurs, the type of catalysis can be described as general acid catalysis in many cases. In this Focus Review, only key developments in this field will be discussed as several excellent reviews have summarized the discoveries in detail.[4] Furthermore, because of space constraints, we will focus only on major achievements in the areas of chiral (thio)urea, diol, and phosphoric acid catalysis.

2. Enantioselective Reactions Promoted by Chiral Urea and Thiourea Catalysts

2.1. Monofunctional Urea and Thiourea Catalysts

Despite the fact that the conceptual basis of urea- and thiourea-based catalysis was established about 25 years ago as pioneered by Curran and Kuo,[5] true attention paid to the utilization of ureas and thioureas as a viable strategy in catalysis came from the landmark works by Taylor and Jacobsen.[4e] They developed a series of urea- and thiourea-containing Schiff bases, which were originally designed as potential ligands for organometallic catalysis, as organocatalysts (Scheme 1). This strategy turned out to be a great success. In the initial exploration, thiourea **1a** was found to be an optimal promoter for the highly enantioselective Strecker

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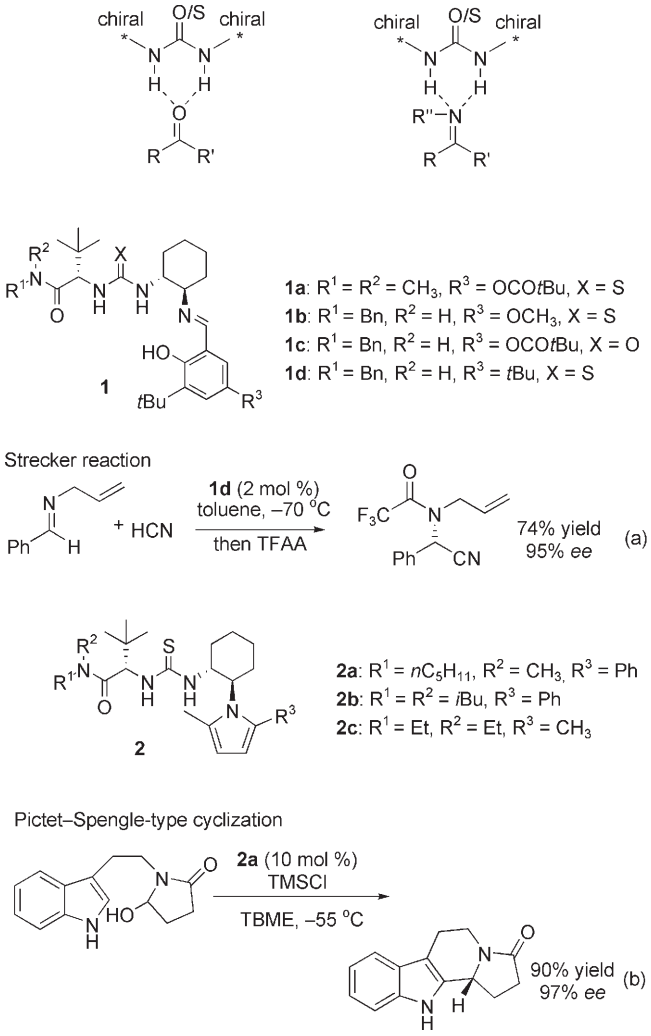
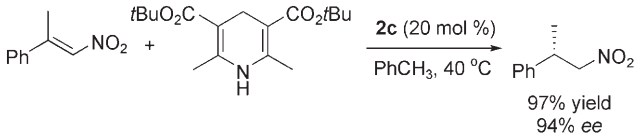


Scheme 1. Asymmetric reactions catalyzed by the Jacobsen urea and thiourea catalysts. Bn = benzyl, TBME = *tert*-butyl methyl ether, TFAA = trifluoroacetic anhydride, TMS = trimethylsilyl.

reaction of aldimines and methylketoimines with HCN (Scheme 1, reaction a).[6a,b] A mechanistic study revealed that the high catalytic activity can be attributed to the capacity of the thiourea to activate the electrophile (e.g., imine) efficiently by double H bonding for nucleophilic attack (by, e.g., HCN) (Scheme 1).[6c] The activation mode is consistent with the observation that electron-poor aryl ureas readily form cocrystals with a variety of proton acceptors that involve two-hydrogen-bond interactions.[7] Moreover, the high enantioselectivity arises from the significant steric effect of the amide portion of the catalyst. This important mechanistic insight renders this class of compounds as general acid catalysts for catalyzing a wide range of asymmetric organic transformations of imines with a variety of nucleophiles. These ureas and thioureas, by optimizing their structures, have been discovered to promote highly enantioselective Mannich,[8] hydrophosphonylation,[9] Henry,[10] cyanosilylation,[11] acyl-Pictect–Spenger (Scheme 1, reaction b),[12] aza-Baylis–Hillman,[13] and acyl-Mannich reactions.[14]

Recently, List and co-workers used thiourea catalyst **2c** for enantioselective hydrogenation of nitroolefins with Hantzsch ester as the reducing reagent (Scheme 2).[15]

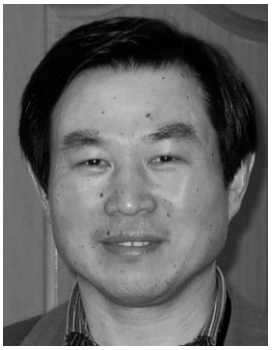
Nagasawa and co-workers prepared C_2-symmetric chiral 1,2-diaminocyclohexane-derived bisthiourea **3** (Scheme 3).[16] It was proposed that the two thiourea moieties in **3** simultaneously activate both cyclohexanone and aldehydes for the Morita–Baylis–Hillman (MBH) reaction. As demonstrated,



Scheme 2. Thiourea-promoted asymmetric hydrogenation.

Abstract in Chinese:

基于氢键的有机小分子不对称催化作为有机小分子催化的一个热门领域,近年来引起了化学家的高度兴趣,并取得了很好的结果。借助于有机小分子催化剂与反应底物之间的氢键作用,通过高立体选择诱导有效地活化亲电的醛羰基、酮羰基、Schiff 碱、硝基和环氧丙基等官能团,从而高选择性地合成多种重要的药物、天然产物、生物活性化合物及手性砌块。反应条件温和、产率优良、对映选择性及非对映选择性高,具有广阔的应用前景。限于篇幅,本文将重点综述手性脲和硫脲、手性 1,2-二醇和手性磷酸二酯等有机小分子催化剂在基于氢键作用的不对称催化反应中的应用方面的最新进展。



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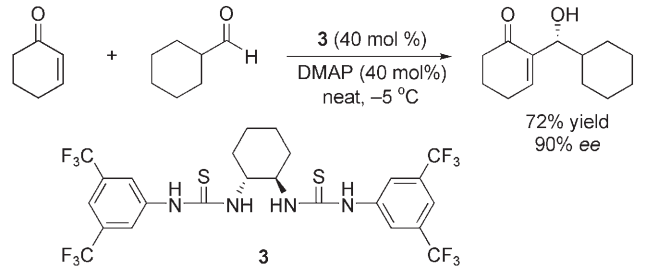
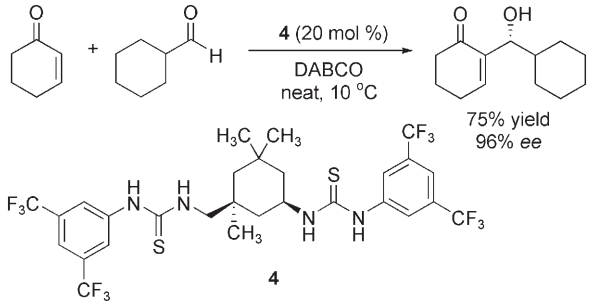


Scheme 3. Asymmetric Morita–Baylis–Hillman reaction promoted by C_2-symmetric bisthiourea **3**. DMAP = 4-dimethylaminopyridine.

catalyst **3** enabled the MBH reaction with low to excellent levels of enantioselectivity (19–99% *ee*) in the presence of the Lewis base DMAP as an external nucleophile.

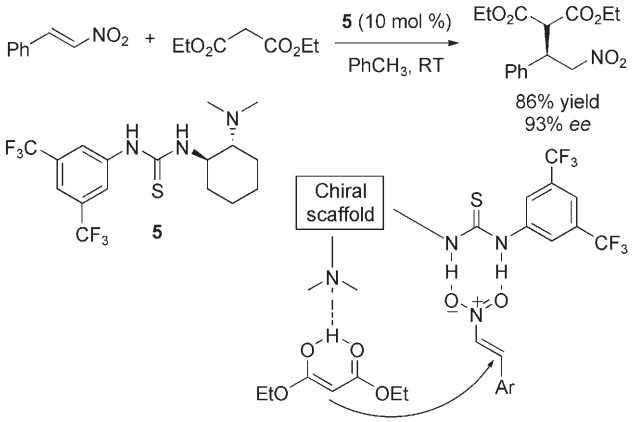
Berkessel et al. developed chiral isophoronediamine-derived bisthiourea **4** for a similar purpose (Scheme 4).[17] Under optimized reaction conditions, enantioenriched allylic alcohols with good to excellent enantioselectivities (up to 96% *ee*) were obtained from the reaction of cyclohexanone with aliphatic aldehdyes in the presence of 20 mol% of **4** and DABCO under neat conditions.



Scheme 4. Asymmetric Morita–Baylis–Hillman reaction catalyzed by chiral bisthiourea **4**. DABCO = 1,4-diazabicyclo[2.2.2]octane.

2.2. Chiral Cyclohexane Diamine Based Bifunctional Thiourea Catalysts

The Jacobsen ureas and thioureas are monofunctional catalysts that work through the sole activation of electrophiles. Inspired by efficient and specific enzyme-mediated catalysis, which relies on the synergistic cooperation of a number of functional groups, synthetic organic chemists have developed bifunctional organocatalysts. The combination of H-bond donors and Brønsted or Lewis base functionalities in a chiral scaffold has recently emerged as a viable strategy for the design of bifunctional organocatalysts. These catalysts share common structural features. Two functional acid/base groups are positioned in a chiral scaffold. An H-bond donor (Brønsted acid) is used for activation of the electrophile, whereas a Lewis base is used for activation of the nucleophile. Notably, Takemoto and co-workers designed novel bifunctional amine thiourea **5** (Scheme 5).[18] The catalyst was assembled on the basis of the same chiral framework of a



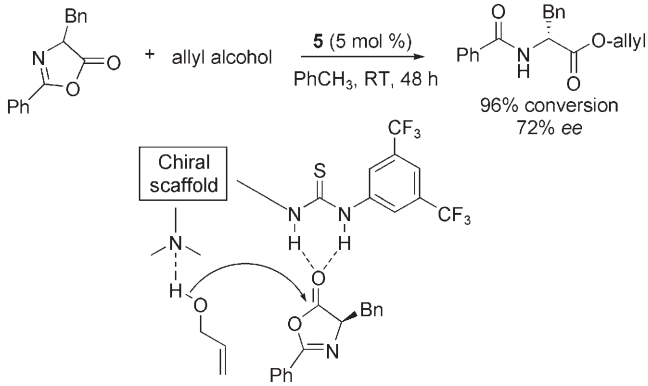
Scheme 5. Michael reaction catalyzed by the Takemoto bifunctional amine thiourea.

1,2-*trans* diamine that Jacobsen used. The chiral thiourea with a neighboring tertiary amine group serves as a bifunctional organocatalyst to activate the Michael acceptor through interaction with the nitro group and nucleophilic enol species simultaneously. It was successfully demonstrated that this catalyst effectively promoted the highly enantioselective conjugate addition of malonates to nitroolefins.

More significantly, the bifunctional organocatalyst has been exploited for a diverse array of asymmetric conjugate-addition processes of stable nucleophilic enols and thiols with enones[19a] and α,β-unsaturated imides,[19b] along with nitroolefins[19c] as well as in the aza-Henry process[19d] and Mannich reaction.[19e]

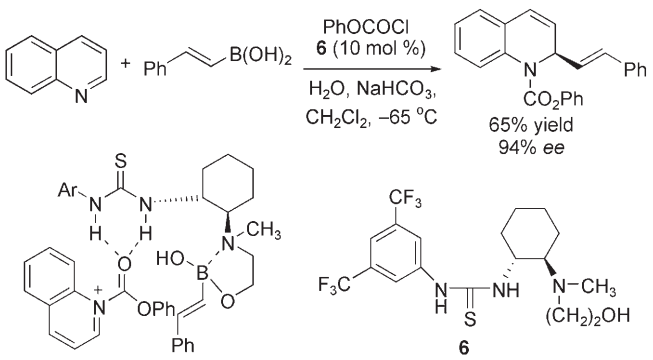
Berkessel et al. reported the use of catalyst **5** for highly efficient dynamic kinetic resolution of azalactones to give biologically important α-amino acids (Scheme 6).[20a] A similar activation mode involving both tertiary amine and thiourea as catalyst with respective OH and CO groups in the substrates was proposed. They also successfully extended the strategy for kinetic resolution of oxazinones for the preparation of chiral β-amino acids.[20b]

More recently, Takemoto and co-workers extended the domain of the bifunctional organocatalyst and developed new bifunctional aminol thiourea **6** for the highly enantiose-



Scheme 6. Asymmetric ring opening of azalactones with allyl alcohol catalyzed by chiral amine thiourea **5**.

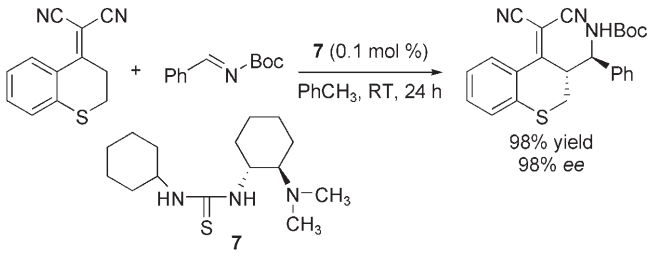
lective Petasis-type reaction of phenyl chloroformate activated quinolines with vinyl boronic acids (Scheme 7).[21] This process affords synthetically useful 1,2-dihydroquinoline adducts with high levels of enantioselectivity. The 1,2-amino



Scheme 7. Asymmetric Petasis-type reaction catalyzed by aminol thiourea **6**.

alcohol moiety in **6** plays a critical role in achieving the high enantioselectivity of the process. It was proposed that the functionality effectively activates vinylboronic acid with formation of a five-membered ring. In contrast, the lack of the OH group or the use of a 1,3-aminol or 1,2-diamine led to poor stereocontrol.

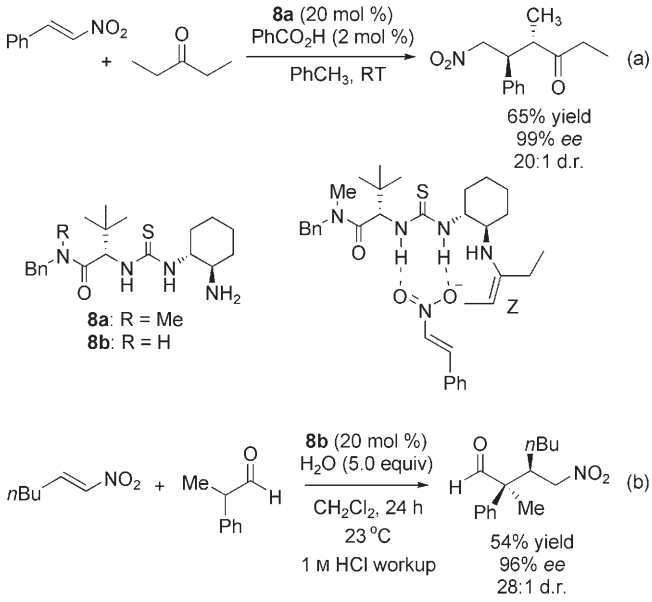
Chen and co-workers demonstrated that the simple amine thiourea **7** catalyzed the direct vinylogous Mannich reaction between dicyanoolefins and *N*-Boc benzaldimines with high *ee* values (Scheme 8).[22] The employment of 0.1 mol% of the catalyst was found to be sufficient for the process.



Scheme 8. Direct asymmetric vinylogous Mannich reaction catalyzed by chiral amine thiourea **7**. Boc = *tert*-butoxycarbonyl.

Chiral pyrrolidine-derived organocatalysts are effective for the highly enantioselective Michael addition of cyclohexanone and its analogues to nitroolefins.[4k,l] However, poorer catalytic activity and enantioselectivity were generally observed for acyclic ketones. Huang and Jacobsen reported primary amine thiourea **8a** as an efficient catalyst for the conjugate addition of acyclic ketones to nitroalkenes with high enantioselectivity (Scheme 9, reaction a).[23a] The bifunctional catalyst activates both substrates simultaneously through respective H-bond and *Z*-enamine interactions.

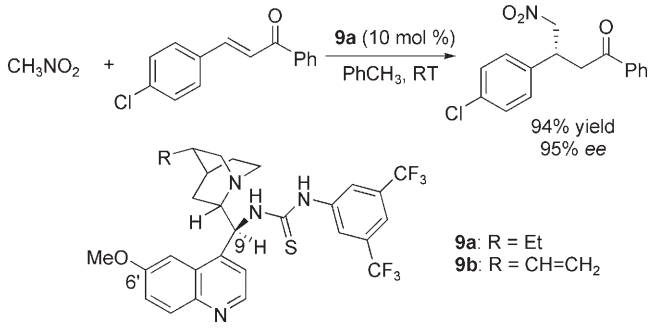
The analogue **8b** was found to be an effective promoter for the highly enantio- and diastereoselective conjugate addition of α,α-disubstituted aldehydes to aliphatic nitroolefins, which are also difficult substrates for chiral pyrrolidine organic catalysts (Scheme 9, reaction b).[23b] Tsogoeva et al. also reported chiral bifunctional primary amine and amidine thioureas for similar purposes.[24a–c]



Scheme 9. Direct Michael addition of acyclic ketones and α,α-disubstituted aldehydes to nitroalkenes catalyzed by primary amine thioureas **8**.

2.3. Cinchona Alkaloid Derived Bifunctional Thiourea Catalysts

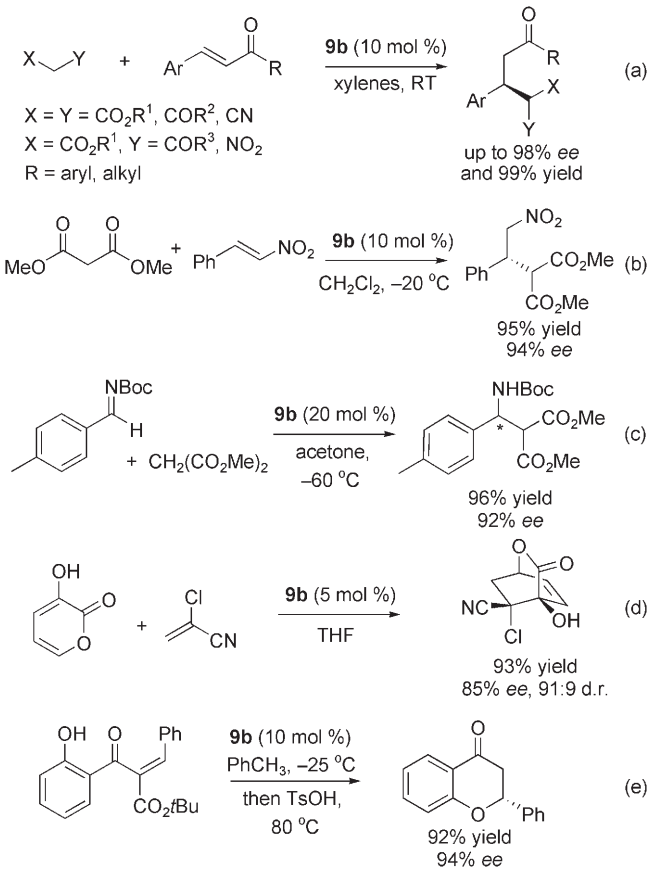
The natural products cinchona alkaloids and their modified forms are important chiral ligands widely used in asymmetric organometallic catalysis.[25] In the recent past, they have also been explored for organocatalytic enantioselective transformations with a great success. Naturally, the "privileged" chiral skeletons can serve as a platform for the creation of a new class of bifunctional organocatalysts by incorporation of thiourea moieties. To this end, Soós and coworkers designed the new cinchona alkaloid derived thiourea **9a** (Scheme 10).[26] It was employed as a catalyst for



Scheme 10. Michael addition of nitromethane to chalcones catalyzed by cinchona alkaloid derived bifunctional thioureas **9a**.

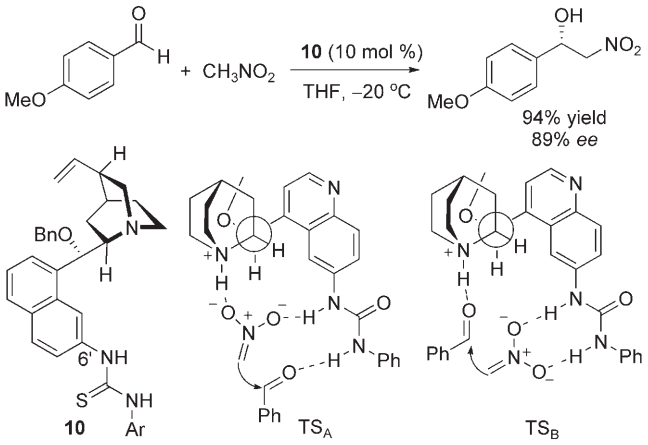
the Michael addition of nitromethane to chalcones to afford highly enantioenriched adducts.

Since the pioneering work of Soós and co-workers, cinchona alkaloid derived bifunctional thioureas **9** have been intensively explored for asymmetric organic processes and demonstrated to be one of the most useful organocatalysts. Notable examples include conjugate addition of a wide range of nucleophilic enol species to enones (Scheme 11, reactions a and b)[27a–c] as well as the Mannich (Scheme 11, reaction c),[27d] Diels–Alder (Scheme 11, reaction d),[27e] and intramolecular oxa-Michael reactions (Scheme 11, reaction e).[27f]



Scheme 11. Asymmetric reactions catalyzed by cinchona alkaloid derived bifunctional thiourea **9b**. Ts = *p*-toluenesulfonyl.

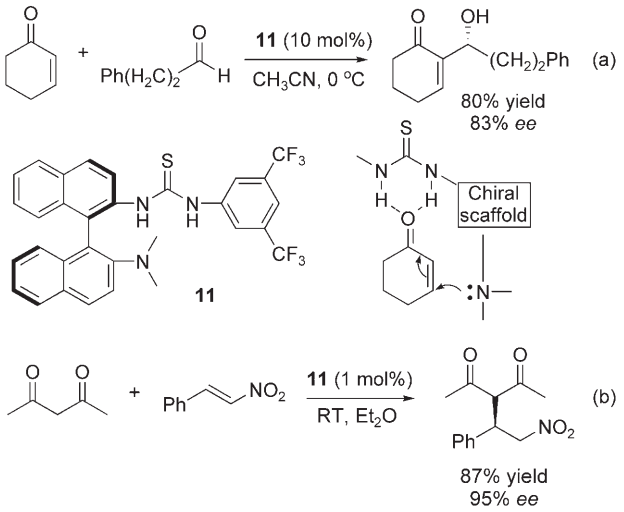
Inspired by their early work in the use of cinchona alkaloid derivatives as catalysts for the asymmetric Henry reaction between active electron-deficient aromatic aldehydes and nitromethane, Hiemstra and co-workers designed the more active cinchona alkaloid based bifunctional thiourea **10**, in which the thiourea moiety is incorporated at the 6′-position (Scheme 12).[28a] As shown, the catalyst displayed higher catalytic activity and worked well for less reactive aromatic aldehydes that contain electron-donating groups. It is believed that the synergistic dual activation of both substrates and the stronger two-H-bonding interactions are critical for enhanced activity and stereoselectivity. A mechanistic investigation was conducted by using density functional theory (DFT) calculations.[28b] The rate-determining step is the nucleophilic attack of the nitromethide anion on the activated aldehyde for the formation of the C–C bond. Two activation modes of substrates were proposed. In transition state A (TS_A), the nucleophilic nitromethide anion forms a H-bond network between the positively charged trialkylammonium ion and one H-bond donor from the thiourea moiety, while the aldehyde complexes with the other H-bond donor of the thiourea. In the second binding mode (TS_B), the opposite coordination pattern was proposed. DFT calculations indicated that the activation barriers for the formation of the two transition states were similar. Therefore, either pathway could be possible for forming the C–C bond.



Scheme 12. Asymmetric Henry reaction catalyzed by cinchona alkaloid derived bifunctional thiourea **10**.

2.4. Chiral Naphthyl-Derived Bifunctional Thiourea Catalysts

Chiral axial binaphthyl is another important class of "privileged" scaffold that has been widely used in organometallics as ligands.[25] The incorporation of a thiourea moiety into the chiral framework can create a novel class of organocatalysts. Along these lines, Wang and co-workers designed new bifunctional binaphthyl-derived amine thioureas (Scheme 13).[29a] After a variety of organocatalysts were screened, catalyst **11** was identified as the optimal promoter for the highly enantioselective Morita–Baylis–Hillman reaction of cyclohexenone with a wide range of aldehydes without the need for external additives (Scheme 13, reaction a).[29a] Notably, although the aromatic amine in **11** is a much weaker nucleophile than aliphatic amines and phosphines, it still serves as an effective donor for the initial Michael addition reaction as a result of the significant thiourea activation of the carbonyl group. The study also revealed that the 3D orientation of the two functionalities is critical for catalyst activity and stereocontrol. In contrast, as shown above, the Takemoto catalyst **5** afforded poorer results, al-

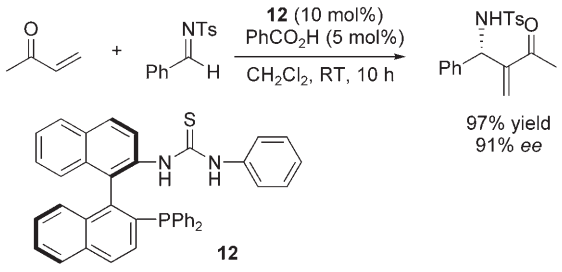


Scheme 13. Asymmetric Morita–Baylis–Hillman and Michael addition reactions catalyzed by chiral binaphthyl-derived bifunctional amine thiourea **11**.

though it contains a stronger nucleophilic aliphatic tertiary amine.

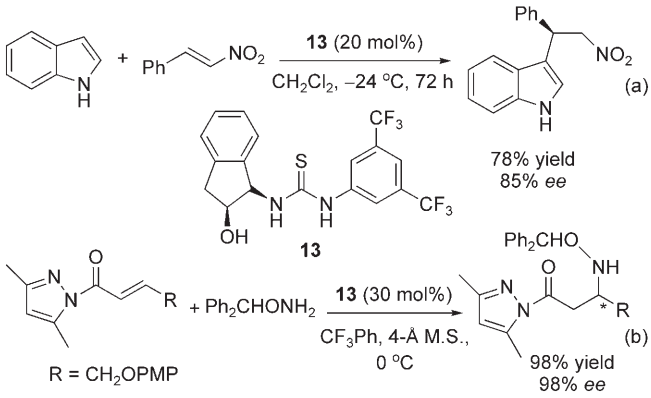
Organocatalyst **11** was also demonstrated to catalyze efficiently the highly enantioselective Michael reaction of a 1,3-diketone as donor with β-nitrostyrenes (Scheme 13, reaction b).[29b] Because of its high catalytic activity, utilization of catalyst **11** in amounts as low as 1 mol% was sufficient for the process. Moreover, the Michael addition products could be readily converted into valuable α-substituted β-amino acid building blocks.

In a related study, replacement of the weakly nucleophilic tertiary aromatic amine in **11** by a stronger phosphine nucleophile resulted in bifunctional catalyst **12** (Scheme 14).[30] The catalyst was found to promote efficiently the aza-Morita–Baylis–Hillman reaction in high yields and with good to high levels of enantioselectivity.



Scheme 14. Asymmetric aza-Morita–Baylis–Hillman reaction catalyzed by chiral binaphthyl-derived bifunctional phosphine thiourea **12**.

Connon and co-workers designed and evaluated a series of C_2-symmetric binaphthyl-derived thioureas for the asymmetric Friedel–Crafts reaction of indoles with nitroolefins and found that catalyst **13** afforded the desired products in good yields but low with enantioselectivity (12–50% *ee*).[31a] A more efficient process was developed by Ricci and co-workers (Scheme 15, reaction a).[31b] Catalyst **13** was identified from a series of organocatalysts, including C_2-symmetric chiral bisthioureas and hydroxy thioureas, for the reaction. Much-improved enantioselectivity (71–89% *ee*) was observed with the catalyst.

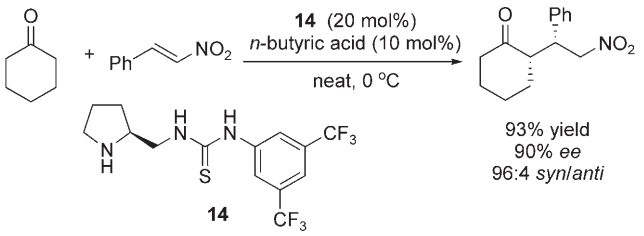


Scheme 15. Asymmetric Friedel–Crafts alkylation and Michael addition reactions catalyzed by chiral hydroxythiourea **13**. M.S. = molecular sieves, PMP = *p*-methoxyphenyl.

Sibi and Itoh discovered the same catalyst **13** for the Michael addition of hydroxylamines to α,β-unsaturated pyrazole amides (Scheme 15, reaction b).[31c] In general, good to high enantioselectivity (67–95% *ee*) was achieved despite high catalyst loading (30–100 mol%).

2.5. Other Chiral Bifunctional Thiourea Catalysts

Combining pyrrolidine and thiourea functionalities, Tang and co-workers created the new bifunctional chiral pyrrolidine thiourea catalyst **14** (Scheme 16).[32] The catalyst efficiently catalyzed the direct Michael addition of cyclohexane to nitroalkenes with high enantio- and diastereoselectivity.



Scheme 16. Asymmetric Michael reaction of cyclohexanone with nitroalkenes promoted by chiral pyrrolidine thiourea **14**.

Recently, Ellman and co-workers developed a novel class of chiral urea catalysts that incorporates a chiral *N*-sulfinylurea moiety (Scheme 17).[33] The function of the *N*-sulfinylurea group is twofold: it serves as a Brønsted acid for activation of electrophiles and a chirality-control element. After a variety of this class of catalysts were screened, catalyst **15** was identified to be an efficient promoter for the highly

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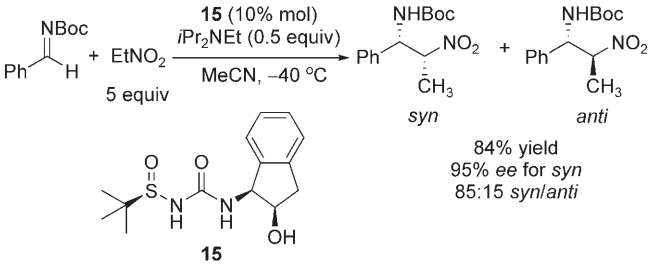


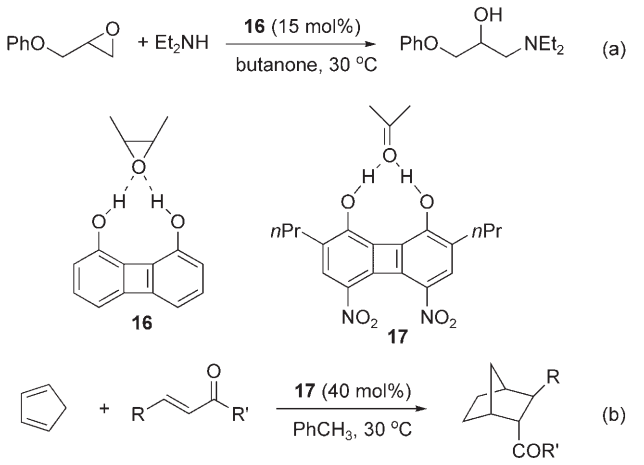
Scheme 17. Asymmetric aza-Henry reaction promoted by chiral *N*-sulfinyl urea **15**.

enantioselective aza-Henry reaction of both aromatic and aliphatic imines with nitroalkanes.

3. Enantioselective Reactions Promoted by Chiral Diol-Based Catalysts

3.1. Enantioselective Reactions Catalyzed by Chiral Monofunctional Diol-Based Catalysts

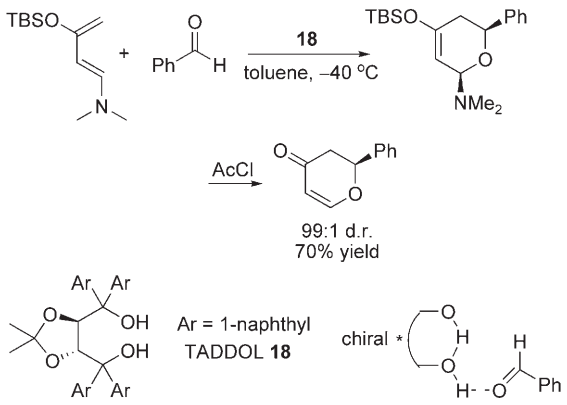
In a similar manner to ureas and thioureas, diols can also provide two-hydrogen-bond donors.[34] The seminal work by Hine et al. demonstrated that 1,8-biphenylene diol **16** is a general acid catalyst used to activate epoxides efficiently towards nucleophilic attack (Scheme 18, reaction a).[35a] The



Scheme 18. Diol-catalyzed reactions.

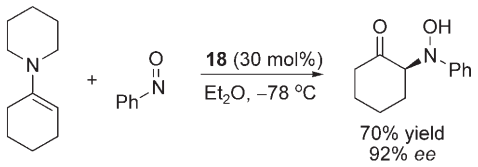
reaction of phenylglycidyl ether with diethylamine catalyzed by the diol was about 13 times faster than that catalyzed by phenol, which indicates that double hydrogen bonding is more effective than single. In 1990, Kelly et al. extended this concept to carbonyl compounds, devised a number of novel biphenylene diol catalysts, and identified **17** for the Diels–Alder reaction (Scheme 18, reaction b).[35b]

However, the use of chiral diols for asymmetric catalysis did not emerge until 2003. Inspired by the work of Toda in the utilization of TADDOLs for molecular recognition,[36] Rawal and co-workers neatly demonstrated that chiral hydrogen-bond catalyst **18** could deliver high levels of enantioselectivity for hetero-Diels–Alder reactions of aldehydes with highly electron-rich aminodienes (Scheme 19).[37a,b] X-ray crystal-structure analysis showed the formation of a hydrogen-bond network between the diol moiety and the substrate benzaldehyde.[37c] Interestingly, the network features an intramolecular hydrogen bond between the two hydroxy motifs and an intermolecular hydrogen bond with the carbonyl oxygen atom of benzaldehyde. This observation suggests that single-hydrogen-bond activation is involved in the diol catalysis. This catalytic tactic was further extended to hetero-Diels–Alder reactions of the Brassard diene with aldehydes as well as Diels–Alder reactions of aminodienes[37c,d] and Mukaiyama aldol reactions.[37e,f]



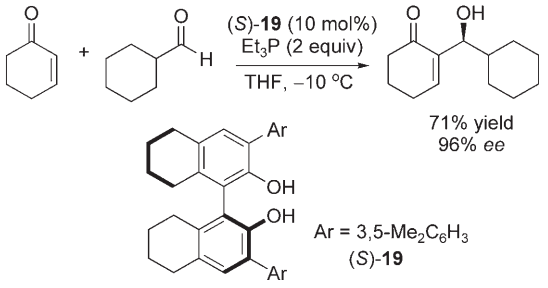
Scheme 19. Diels–Alder reaction catalyzed by chiral diol TADDOL **18**. TBS = *tert*-butyldimethylsilyl.

Chiral diol **18** can go beyond the activation of carbonyl compounds. Momiyama and Yamamoto recently showed that this mode of catalysis can be applied to the activation of nitroso compounds in an asymmetric α-amination process (Scheme 20).[38] The process is highly regioselective for the formation of C–N bonds, which is in contrast to the chiral-secondary-amine-catalyzed asymmetric α-aminoxylation of aldehydes and ketones with nitroso compounds to generate C–O bonds.[39]



Scheme 20. α-Amination reaction catalyzed by chiral diol TADDOL **18**.

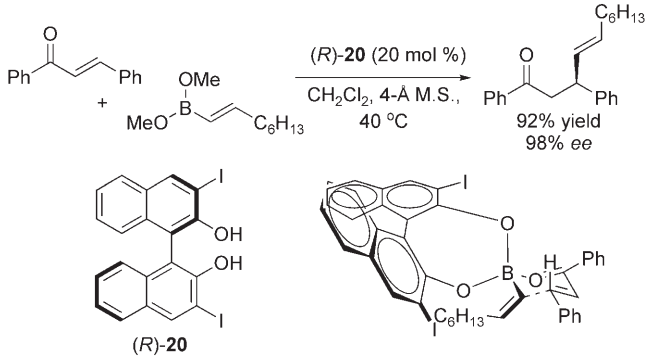
On the basis of preceding work by Yamada and Ikegami, who used phenol, BINOL, and triphenylphosphine to cocatalyze the Morita–Baylis–Hillman reaction of cyclic enones with aldehydes,[40] McDougal and Schaus developed an asymmetric version of the process in the presence of chiral BINOL (*S*)-**19** (Scheme 21).[41] Besides the base additive, the steric demands at the 3,3′-positions and the two hydroxy



Scheme 21. Asymmetric Morita–Baylis–Hillman reaction catalyzed by chiral BINOL **19**.

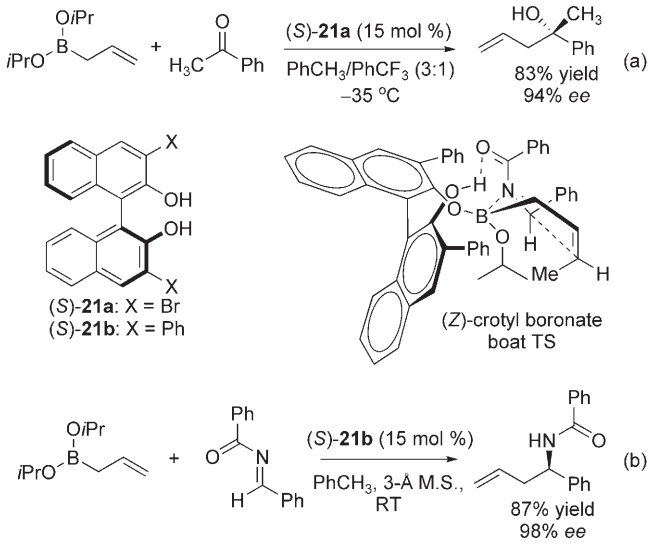
groups play key roles in governing the enantioselectivity of the process.

Wu and Chong described (*R*)-BINOL **20**, which catalyzed the highly enantioselective conjugate alkenylation reaction of enones with borates (Scheme 22).[42] It was postulated that the chiral promoter **20** is involved in the activation of borate through formation of a strained chiral borate complex for nucleophilic attack of the enone. A proposed six-membered chairlike transition state may account for the observed stereochemical outcome.



Scheme 22. Asymmetric conjugate-alkenylation reaction catalyzed by chiral BINOL **20**.

Schaus and co-workers reported an asymmetric allylboration reaction of ketones (Scheme 23, reaction a).[43a] Screening of a variety of BINOLs resulted in catalyst (*S*)-**21a**, which served as an efficient promoter for the process under optimized reaction conditions (15 mol% **21a**, $PhCH_3/PhCF_3$ (3:1) at −35 °C) to afford homoallylic alcohols in high yields (76–93%) and with high *ee* values (90–98%). A similar transition-state model to that of Chong was proposed for the asymmetric transformation. Recently, the strategy was extended to the highly enantioselective allylboration process with acyl imines as the electrophile (Scheme 23, reaction b).[43b] Notably, in the mechanistic studies, the boronates were found to be activated by one of the OH groups of the chiral diols, whereas the second OH moiety interacted with the acyl imine (Scheme 23, reaction b). The model is different from that proposed earlier for ketone substrates, which

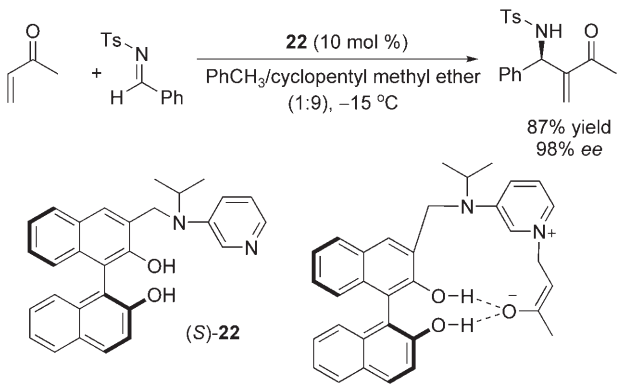


Scheme 23. Asymmetric allylboration reactions catalyzed by chiral BINOLs **21**.

involved dual-hydrogen-bond activation. Furthermore, a more active boat transition state was hypothesized for the observed stereochemistry.

3.2. Enantioselective Reactions Promoted by Chiral Bifunctional Diol-Based Catalysts

Inspired by the seminal work of Shibasaki and co-workers, in which Lewis acids equipped with additional Brønsted or Lewis bases were employed in catalyst design,[44] Sasai and co-workers developed the novel bifunctional amine diol catalyst **22** for the highly enantioselective aza-Morita–Baylis–Hillman reaction in high yields (Scheme 24).[45a] Importantly, they demonstrated that both functionalities are essential for the activity and enantioselectivity of the process. This investigation indicates that bifunctional organocatalyts are more effiective than monofunctional ones as a result of their synergistic cooperative activation of substrates and the formation of a more rigid transition state. Furthermore, unlike



Scheme 24. Asymmetric aza-Morita–Baylis–Hillman reaction catalyzed by chiral bifunctional amine BINOL **22**.

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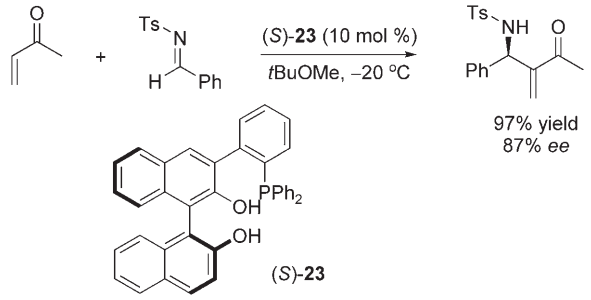
monofunctional organocatalysts, the bifucntional promoters that catalyzed Morita–Baylis–Hillman reactions did not require additional acid or base additives.

Using a similar strategy, Sasai and co-workers developed another bifunctional BINOL organocatalyst **23** by replacing the amine with a phosphine (Scheme 25).[45b] Catalyst **23** efficiently catalyzed the aza-Morita–Baylis–Hillman reaction in high yields and with good enantioselectivity.



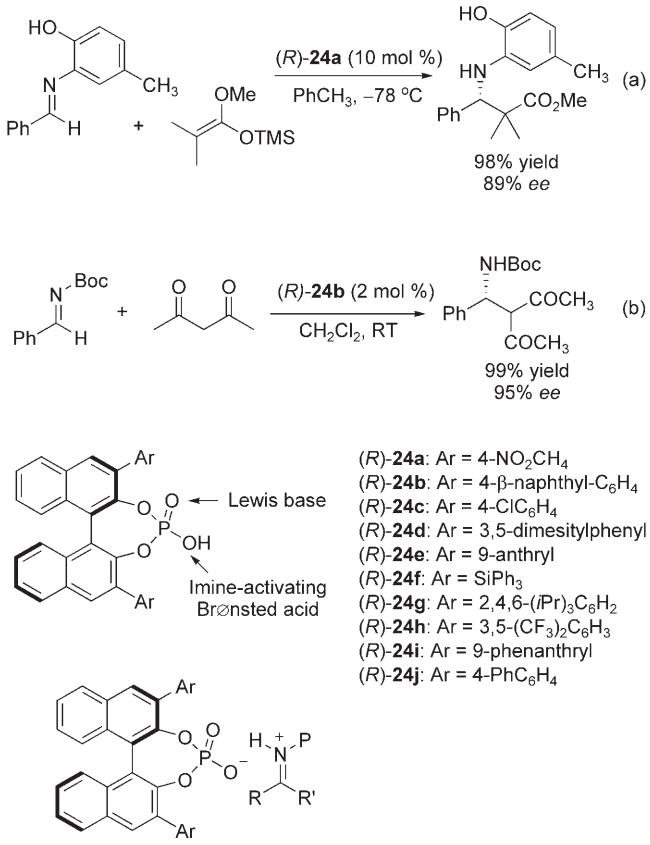
Scheme 25. Asymmetric aza-Morita–Baylis–Hillman reaction catalyzed by chiral bifunctional phosphine BINOL **23**.

4. Asymmetric Reactions Catalyzed by Chiral Phosphoric Acids

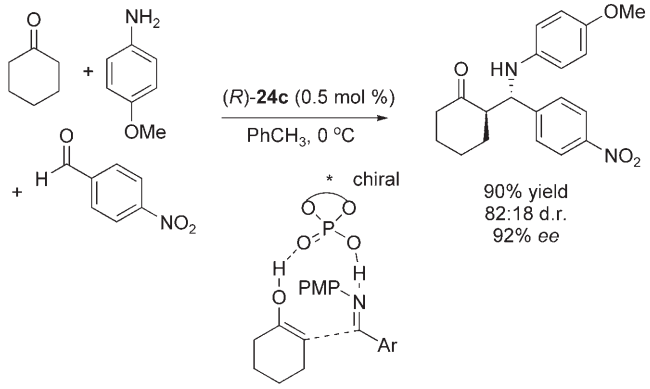
4.1. Asymmetric Mannich Reactions Catalyzed by Chiral Phosphoric Acids

The pioneering works by Akiyama et al.[46a] and Uraguchi and Terada,[46b] in which axially chiral phosphoric acids derived from binaphthols were used for enantioselective Mannich reactions with enols as the nucleophile, have stimulated considerable synthetic interest in the last three years (Scheme 26).[47] Because of their capacity to activate imines through efficient Brønsted acid/base ion-pair interaction, a wide range of nucleophiles have been demonstrated to participate in asymmetric nucleophilic-addition processes. Notably, these chiral phosphoric acids can be considered to be bifunctional organocatalysts as, besides the acidic OH group, the C=O group can serve as a Lewis base. As demonstrated, in some cases, both functionalities play roles in asymmetric catalysis.

A more atom-economical direct three-component asymmetric Mannich reaction catalyzed by chiral phosphoric acid (*R*)-**24c** was disclosed (Scheme 27).[48] The reaction of cyclohexanone and its analogues, *p*-methoxyphenylamine, and aromatic aldehydes in toluene in the presence of only 0.5 mol% of **24c** gave rise to highly enantioenriched β-amino carbonyls (up to 98% *ee*) with respectable d.r. The process also worked for acyclic ketones but with lower *ee* values (70–86%). It was believed that the bifunctional feature of the phosphoric acid plays a key role in its high catalytic activity and the stereoselectivity of the direct Mannich reaction. The basic P=O and acidic OH motifs facilitate the formation of enol from ketone.



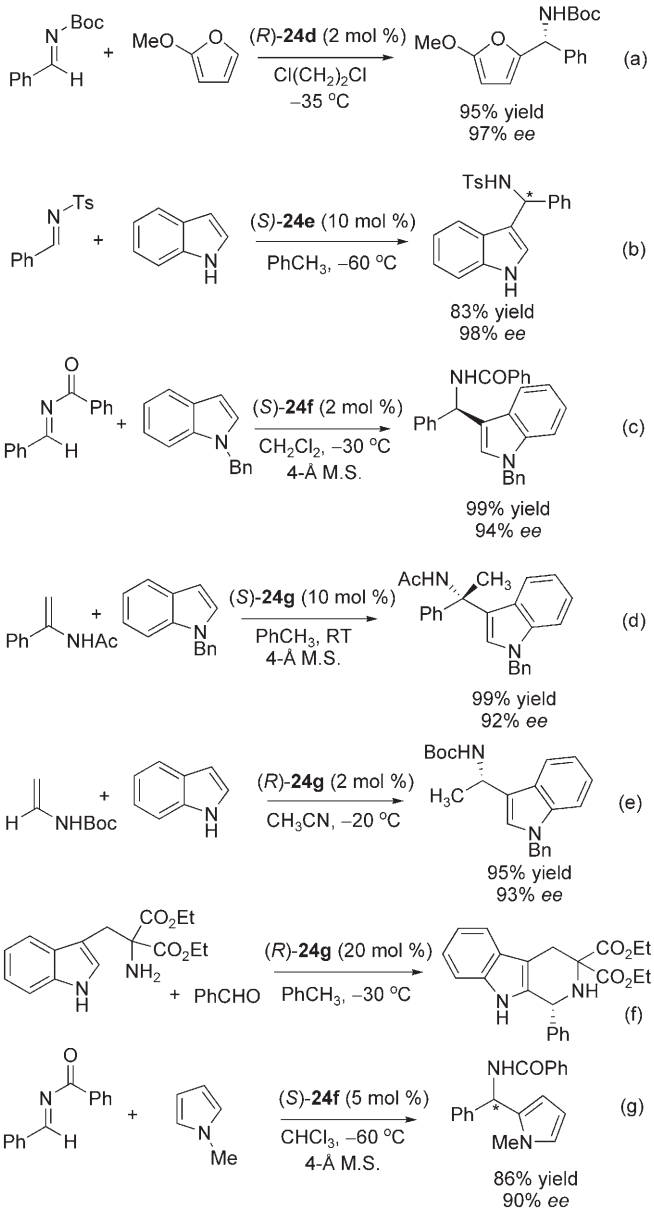
Scheme 26. Asymmetric Mannich reactions catalyzed by chiral phosphoric acids **24a** and **24b**.



Scheme 27. Asymmetric three-component Mannich reaction catalyzed by chiral phosphoric acid (*R*)-**24c**.

4.2. Asymmetric aza-Friedel–Crafts Reactions Catalyzed by Chiral Phosphoric Acids

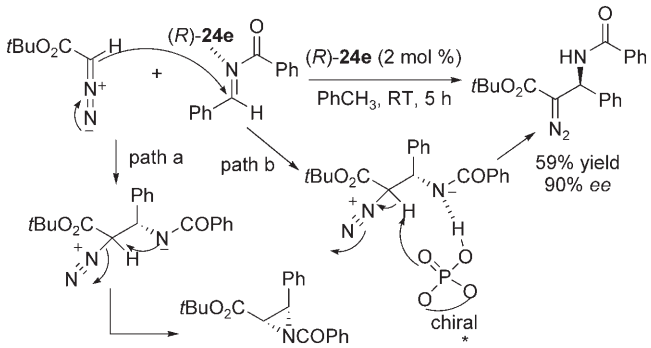
Electron-rich aromatic compounds readily participate in Friedel–Crafts reactions. As demonstrated, various such substances are able to participate in aza-Friedel–Crafts processes with different forms of imines catalyzed by chiral phosphoric acids (Scheme 28). The reactions afford a wide range of functionalized, synthetically useful, and enantiomerically active amine building blocks. These electron-rich aromatic



Scheme 28. Asymmetric aza-Friedel–Crafts reactions catalyzed by chiral phosphoric acids.

systems include furans (Scheme 28, reaction a),[49a] indoles (Scheme 28, reactions b–f),[49b–f] and pyrroles (Scheme 28, reaction g).[49g] The driving force for the highly efficient aza-Friedel–Crafts reactions arises from the strong activation of the imines by chiral phosphoric acids, as with Lewis acids.

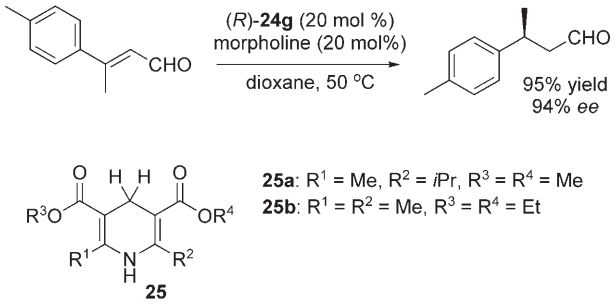
In conjunction with their recent discovery of a chiral phosphoric acid catalyzed aza-Friedel–Crafts reaction (Scheme 28, reaction a),[49a] Terada and co-workers proposed to use diazoacetate as the nucleophile for an aza-Darzens-type reaction with an imine (Scheme 29, path a),[50] which would produce a chrial aziridine. However, the direct alkylation product, the α-diazo-β-amino ester, was obtained instead. It was postulated that the product was formed by a Friedel–Crafts-type reaction (Scheme 29, path b). Deprotonation of a C–H bond, assisted by the basic O=P moiety of the catalyst, proceeded rather than an aza-Darzen process after nucleophilic attack of the imine. Under the optimized reaction conditions, the α-diazo-β-amino esters were furnished in good yields (57–89%) and with high levels of enantioselectivity (86–97% *ee*) in the presence of (*R*)-**24e**.



Scheme 29. Asymmetric direct alkylation of α-diazoester catalyzed by chiral phosphoric acid (*R*)-**24e**.

4.3. Asymmetric Hydrogenations Catalyzed by Chiral Phosphoric Acids

The employment of Hantzsch esters as the nucleophile for asymmetric hydrogenation, which originates from biological systems, was first developed independently by the groups of List[51a] and MacMillan[51b] in the highly enantioselective hydrogenation of the C=C bond of enals (Scheme 30).



Scheme 30. Asymmetric hydrogenation catalyzed by chiral phosphoric acid (*R*)-**24g**.

The strategy of using Hantzsch esters as hydride sources for the asymmetric reduction of imines by chiral phosphoric acids as a chiral inducer proved to be a fruitful approach to the preparation of chiral amines (Scheme 31).[52] It was shown that a variety of imines can participate in the processes to produce a diverse array of synthetically and biologically important chiral amines. Rueping et al. first realized the use of chiral phosphoric acid (*R*)-**24h** as a catalyst for the asymmetric hydrogenation of ketimines with Hantzsch ester **25b** in good yields (46–91%) and with good *ee* values (70–84%) (Scheme 31, reaction a).[53a] They also successfully applied the strategy to the asymmetric reduction of quinolines

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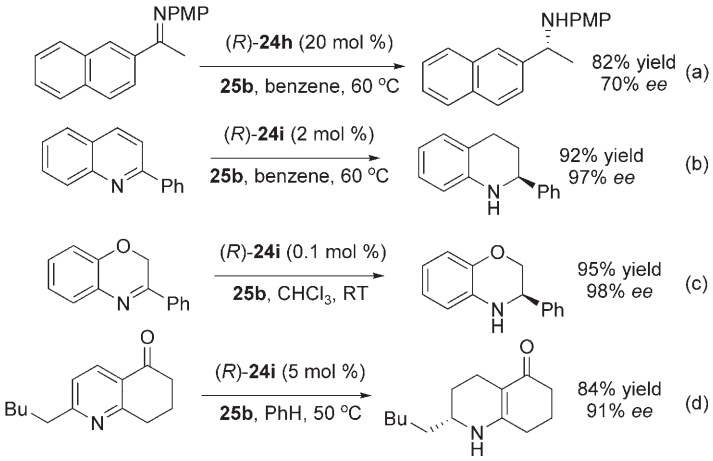
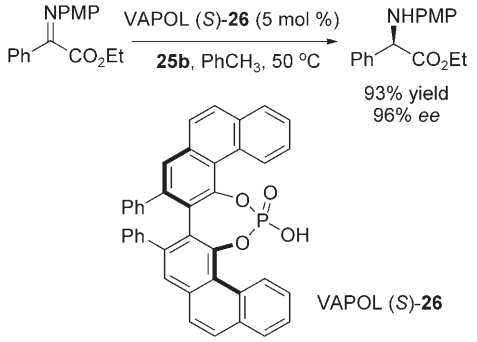


Scheme 31. Asymmetric hydrogenations catalyzed by chiral phosphoric acids.

(Scheme 31, reaction b),[53b] benzoxazines, benzothiazines, and benzoxazinones (Scheme 31, reaction c),[53c] as well as pyridines (Scheme 31, reaction d).[53d] Almost simultaneously, the groups of List[54a] and MacMillan[54b] reported the use of the more bulky chiral phosphoric acids (*S*)-**24g** and (*R*)-**24f** for the reduction of ketimines with Hantzsch esters with improved enantioselectivity.

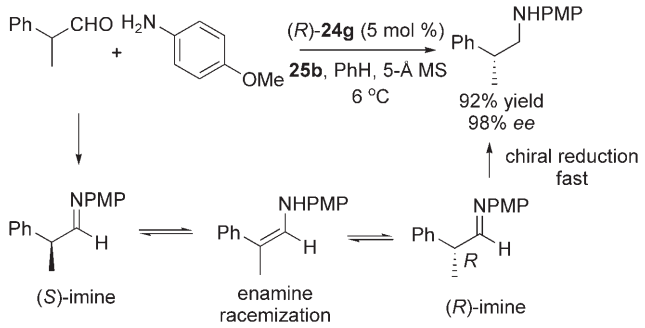
Recently, the groups of Antilla[55a] and You[55b] independently described the chiral phosphoric acid catalyzed enantioselective hydrogenation of α-iminoesters (Scheme 32). The process afforded an alternative organocatalytic approach for



Scheme 32. Asymmetric hydrogenation for the synthesis of α-amino acids catalyzed by chiral VAPOL-derived phosphoric acid (*S*)-**26**.

the preparation of α-amino acids. In the Antilla approach, chiral vaulted VAPOL-derived phosphoric acid (*S*)-**26** was used as promoter,[55a] whereas binaphthyl-derived phosphoric acid (*S*)-**24e** was employed by You and co-workders.[55b] In both cases, high levels of enantioselectivity (up to 99%) were achieved.

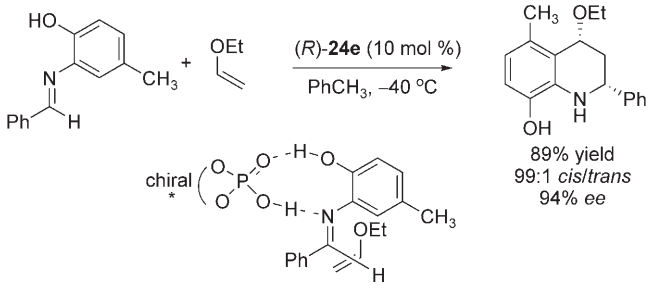
Combining the enamine and reductive-amination approaches, List and co-workers developed a novel process for the generation of enantioenriched amines from α,α-disubstituted aldehydes and anisidines (Scheme 33).[56] A dynamic kinetic resolution involving an imine/enamine transformation was proposed. In the presence of (*R*)-**24g** and Hantzsch ester **25b**, the reduction of the *R* imine was faster than that of the *S* enantiomer.



Scheme 33. Asymmetric reduction by dynamic kinetic resolution catalyzed by chiral phosphoric acid (*R*)-**24g**.

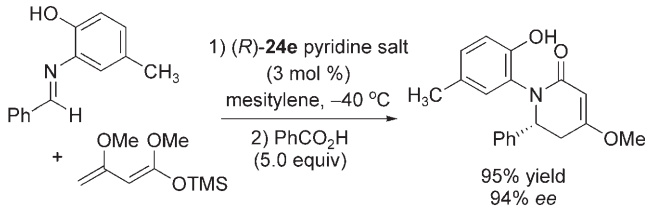
4.4. Asymmetric Diels–Alder Reactions Catalyzed by Chiral Phosphoric Acids

With the realization of the strong activation capacity of Brønsted acids with imines, the resulting imines can naturally participate in aza-Diels–Alder reactions with electron-rich dienes or inverse-electron-demand aza-Diels–Alder reactions. Along these lines, Akiyama et al. developed the chiral phosphoric acid (*R*)-**24e** as a catalyst for the asymmetric inverse-electron-demand aza-Diels–Alder reaction of aldimines with vinyl ethers (Scheme 34).[57a] The process afforded synthetically useful chiral tetrahydroquinones with high efficiency. The OH motif of the *N*-aryl aldimines were found to be critical for attaining high enantioselectivity and reaction yields. In contrast, the absence of the OH group resulted in no reaction. Accordingly, it was surmised that two hydrogen bonds were involved in a nine-membered cyclic transition state.



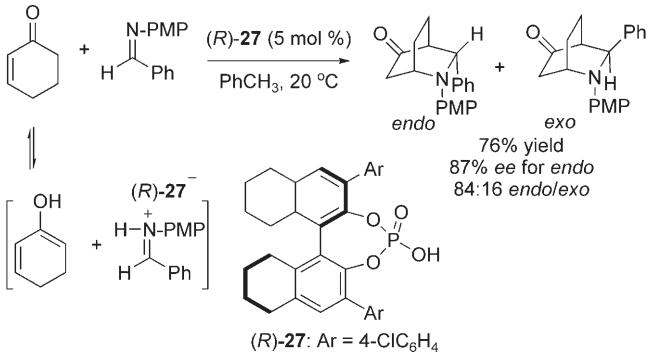
Scheme 34. Asymmetric inverse-electron-demand aza-Diels–Alder reaction catalyzed by chiral phosphoric acid (*R*)-**24e**.

Akiyama and co-workders also successfully exploited the activation mode for a normal asymmetric aza-Diels–Alder reaction between aldimines and Brassard dienes (Scheme 35).[57b] It was found that the (*R*)-**24e** pyridine salt rather than its acid form led to improved reaction yields in spite of comparable enantioselectivity.



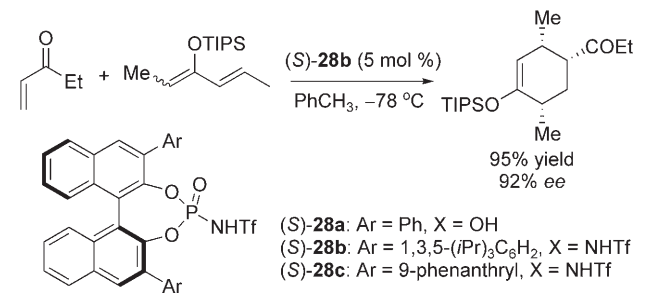
Scheme 35. Asymmetric aza-Diels–Alder reaction of aldimines with Brassard dienes catalyzed by chiral phosphoric acid (*R*)-**24e**.

Analogously, Gong and co-workers[57c] and Rueping and Azap[57d] independently employed the enantioselective aza-Diels–Alder reaction between cyclohexenone and aldimines (Scheme 36). Under acidic conditions, cyclohexenone underwent enolization to generate a reactive diene in situ for the enantioselective aza-Diels–Alder reaction with imines activated by chiral phosphoric acid (*R*)-**27**.



Scheme 36. Asymmetric aza-Diels–Alder reaction of aldimines with cyclohexenone catalyzed by chiral phosphoric acid (*R*)-**27**.

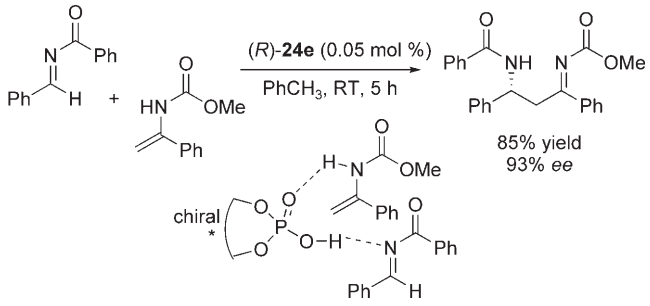
The use of chiral phosphoric acids for catalyzing aza-Diels–Alder reactions has been a great success (Schemes 34–36). However, attempts to apply the catalytic system for the Diels–Alder reaction of enones with dienes has proved to be difficult, as demonstrated by Nakashima and Yamamoto (Scheme 37).[58] No reaction occurred even with highly reactive silyloxydienes when chiral phosphoric acid (*S*)-**28a** was used, presumably due to the low acidity of the phosphoric acid. Accordingly, the more acidic NHTf group was introduced into the system, and a new class of chiral *N*-Tf phosphoramides were designed and synthesized. This type of catalyst exhibited high catalytic activity, and their screening resulted in the best promoter **28b** for achieving the Diels–Alder reaction in good yields and with high enantioselectivity.



Scheme 37. Asymmetric Diels–Alder reaction of enones with silyloxydienes catalyzed by chiral *N*-Tf phosphoramide (*S*)-**28b**. Tf = trifluoromethanesulfonyl, TIPS = triisopropylsilyl.

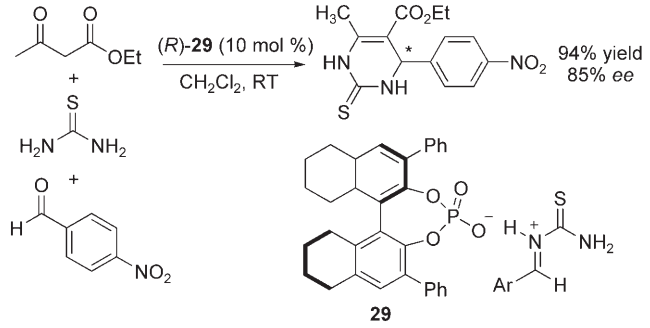
4.5. Other Asymmetric Reactions Catalyzed by Chiral Phosphoric Acids

The power of chiral phosphoric acids has been demonstrated for promoting other types of asymmetric organic transformations. Terada et al. neatly demonstrated an enantioselective azaene-type reaction between *N*-acylimines and enamides or enecarbamates catalyzed by Brønsted acid (*R*)-**24e** to afford β-aminoimine adducts, which were subsequently hydrolyzed to give β-amino ketones in high yields and with high *ee* values (92–98%) (Scheme 38).[59] The reaction could be carried out at extremely low catalyst loading (0.05–0.1 mol%). Its high catalytic activity and enantioselectivity may be attributed to the cooperative activation of substrates.



Scheme 38. Asymmetric aza-ene-type reaction catalyzed by chiral phosphoric acid (*R*)-**24e**.

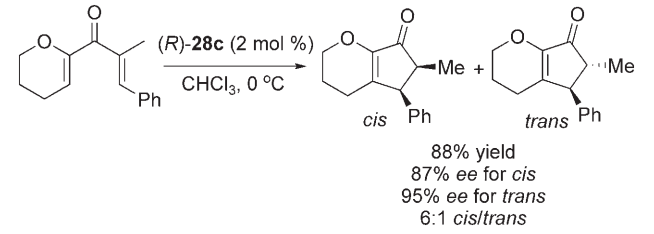
Gong and co-workers reported the efficient three-component Biginelli reaction of ketoesters, (thio)ureas, and aromatic aldehydes catalyzed by chiral phosphoric acid (*R*)-**29** to give highly enantioenriched and biologically interesting 3,4-dihydropyrimidin-2-(1*H*)-ones (Scheme 39).[60] The high



Scheme 39. Asymmetric three-component Biginelli reaction catalyzed by chiral phosphoric acid (*R*)-**29**.

enantioselectivity arises from the strong interaction (activation) of the catalyst with the *N*-acyliminium ion formed, which is derived from an aldehyde and a (thio)urea.

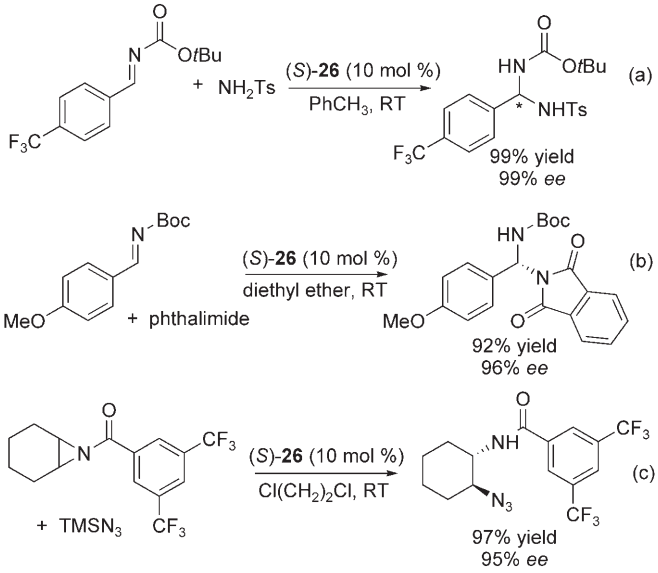
So far, chiral phosphoric acid catalyzed reactions have only been involved in the activation of aldimines or ketoimines owing to the ready formation of an intermediary chiral ion pair. However, examples of the use of chiral Brønsted acids for activation of electrophilic carbonyls for nucleophic attack are very rare.[58] Recently, Rueping et al. developed the first organocatalytic enantioselective Nazarov cyclization reaction, which serves as a versatile approach to the synthesis of functionalized five-membered-ring systems (Scheme 40).[61] After various chiral phosphoric acids and *N*-



Scheme 40. Asymmetric Nazarov reaction catalyzed by chiral phosphoric acid (*R*)-**28c**.

Tf phosphoramides were screened, catalyst (*R*)-**28c** was identified as the best promoter for the process. Notably, only a handful of examples of asymmetric versions of the process have been described, of which most require the employment of large amounts of chiral metal complexes.

Antilla and co-workers first used chiral VAPOLs as catalysts for promoting a variety of reactions. Besides the asymmetric hydrogenation in 2005 discussed above (Scheme 32),[55a] they described a novel, highly enantioselective amidation reaction of imines with amides (Scheme 41,



Scheme 41. Asymmetric amidation and desymmetrization reactions catalyzed by chiral VAPOL-derived phosphoric acid (*S*)-**26**.

reaction a).[62a] Recently, they successfully exploited the catalytic system for the highly enantioselective addition of imides to imines (Scheme 41, reaction b).[62b] Furthermore, an elegant desymmetrization of *meso*-aziridines has been described by the same group (Scheme 41, reaction c).[62c]

5. Hydrogen-Bond-Mediated Asymmetric Cascade Reactions

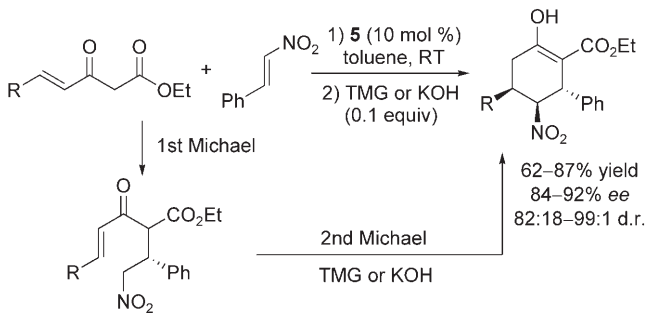
The scope of organocatalyzed asymmetric reactions has been significantly expanded by their ability to promote cascade processes. In the last few years, a number of elegant cascade reactions have been reported.[63] These daunting synthetic technologies serve as powerful tools for the efficient assembly of complex molecular architectures. Moreover, in these cascade processes, only a single reaction solvent, workup procedure, and purification step is required to produce a product that would otherwise be derived from a several-step sequence. Therefore, cascade reactions with the significant improvement of synthetic efficiency, the avoidance of toxic agents, and the decrease in waste and hazardous by-products fall under the banner of "green chemistry".

The predominant strategy is the use of covalent-bond-driven chiral-amine-catalyzed cascade reactions.[63] In contrast, the utilization of the noncovalent hydrogen bond as the activation force for such processes is much less explored, and only a handful of examples can be identified.[64]

5.1. Asymmetric Cascade Reactions Catalyzed by Chiral Bifunctional Amine Thioureas

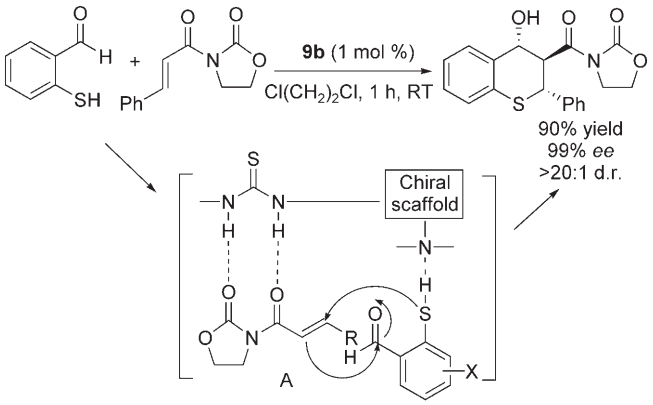
Takemoto and co-workers reported the cascade Michael–Michael reaction of γ,δ-unsaturated β-ketoesters with *trans*-β-nitrostyrene catalyzed by amine thiourea **5** (Scheme 42).[65] The process gave products in high yields (62–87%) and with high enantio- (84–92% *ee*) and diastereoselectivities (d.r. 82:18–>99:1). Although the reaction is considered to be a cascade process, the addition of a base (TMG or KOH) was essential for the second Michael reaction to occur.

Wang and co-workers recently reported a powerful **9b**-catalyzed cascade Michael–aldol process for the preparation



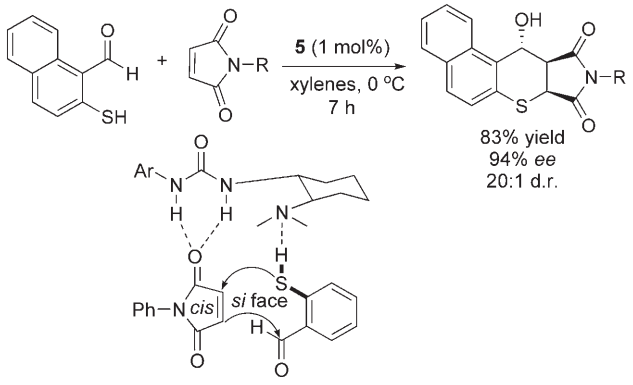
Scheme 42. Asymmetric Michael–Michael reactions catalyzed by chiral amine thiourea **5**. TMG = 1,1,3,3-tetramethylguanidine.

of synthetically useful and medicinally important chiral thiochromanes (Scheme 43).[66a] This new process, which started with simple substances, was promoted by using as little as 1 mol% of **9b** and resulted in the formation of three stereogenic centers in a one-pot synthesis from simple achiral compounds. The activity of the catalyst derives from noncovalent hydrogen-bonding interactions in the bifunctional amine thiourea unit in **9b**, which synergistically activates both the Michael donor and acceptor.



Scheme 43. Asymmetric cascade Michael–aldol reactions catalyzed by cinchona alkaloid derived bifunctional thiourea **9b**.

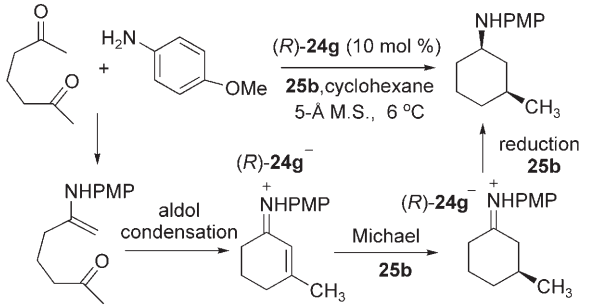
With a similar strategy, the process was successfully extended to the use of maleimides as the Michael acceptor for a new version of a cascade Michael–aldol reaction (Scheme 44).[66b] The "one-pot" process gives biologically interesting succinimide-containing benzothiopyrans with good to high *ee* and d.r. values. Again, significantly, the powerful process catalyzed by **5** with as little as 1 mol% catalyst loading afforded products with the generation of three stereogenic centers in a single operation.



Scheme 44. Asymmetric cascade Michael–aldol reaction catalyzed by chiral amine thiourea **5**.

5.2. Asymmetric Cascade Reactions Catalyzed by Chiral Phosphoric Acids

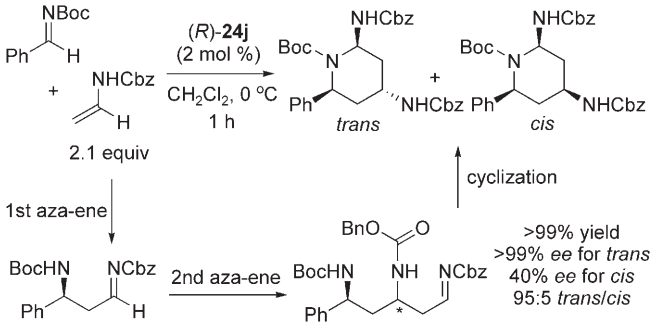
On the basis of their early work on chiral phosphoric acid mediated dynamic kinetic resolution with enamine/imine chemistry, Zhou and List further elaborated the concept for an elegant cascade intramolecular aldol-condensation/Michael/reductive-amination process to afford chiral substituted cyclohexylamines (Scheme 45).[67]



Scheme 45. Asymmetric cascade processes through imine/enamine and reductive amination catalyzed by chiral phosphoric acid (*R*)-**24g**.

Furthermore, Rueping et al. described a chiral phosphoric acid promoted cascade hydrogenation reaction of quinolines (Scheme 31, reaction b).[53b]

On the basis of their early experience on chiral phosphoric acid catalyzed azaene-type reactions,[59] Terada et al. developed a cascade aza-ene-type/cyclization process promoted by chiral phosphoric acid (*R*)-**24j** for the preparation of chiral piperidines (Scheme 46).[68] They found that the enamide participated in the second aza-ene-type reaction when 2.1 equivalents were used. Critically, less-hindered enamides were essential for the cascade process.



Scheme 46. Asymmetric cascade aza-ene-type/cyclization reaction catalyzed by chiral phosphoric acid (*R*)-**24j**. Cbz = benzyloxycarbonyl.

6. Conclusions and Perspectives

Interest in organocatalysis has increased spectacularly in the last few years as a result of both the novelty of the concept and, more significantly, the fact that the operational simplicity, decreased toxicity, efficiency, and selectivity renders

many organocatalyzed reactions complementary and/or superior to those performed with more-conventional methods. As discussed in this Focus Review, the examples given neatly demonstrate that chiral ureas and thioureas, diols, and phosphoric acids with the capacity of affording efficient H-bond activation of electrophiles display effective and unique modes of catalysis and, thus, have established their status as "privileged" functional groups in the design of organocatalysts. Undoubtedly, the future direction is to continue to expand the scope of organocatalysis through identification of new modes of reactivity and the design of novel catalyst structures. Therefore, the formidable challenge is to devise organocatalysts with unique structural features that have the capacity of activating new substrate functionalities, thereby creating new organic transformations, including powerful cascade reactions.

Acknowledgements

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