Small-Molecule H-Bond Donors in Asymmetric Catalysis

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1. Introduction

Enantioselective synthesis with small-molecule chiral hydrogen-bond donors has emerged as a frontier of research in the field of asymmetric catalysis. Organic chemists have discovered that low molecular weight synthetic molecules possessing distinct hydrogen-bond donor motifs associated with complementary functional and/or structural frameworks catalyze an array of C−C and C−heteroatom bond-forming reactions with high enantioselectivity and broad substrate scope.[1] Although the vast majority of developments in hydrogen bonding in asymmetric catalysis have materialized only within the last 5 years, the foundations of this subfield of organocatalysis were laid by research in various disciplines over the past several decades.

Detailed investigations into the mechanism of action of various enzymes identified a key role for hydrogen bonding (abbreviated H-bond) in electrophile activation.[2] Independently, and more or less simultaneously, well-defined achiral H-bond donors were discovered to catalyze organic transformations. In pioneering studies, Hine and co-workers identified meta- and para-substituted phenols and biphenylenediols as catalysts for addition of diethylamine to phenyl glycidyl ether (Scheme 1).[3] Hine and co-workers proposed that the enhanced activity of the biphenylenediol in solution relative to phenol resulted from simultaneous donation of two H-bonds to the electrophile, a model that was given strong support from a solid-state 1:1 structure of the catalyst and substrate.[4]

Other investigations of solid-state and solution-state structures by researchers in the field of molecular recognition made clear that dual hydrogen-bond donors could be used to direct the assembly of molecules with almost as much control as covalent bonds.[5] In a series of seminal hydrogen-bond-directed cocrystallization studies, Etter and co-workers recognized the ability of electron-deficient diaryl ureas to form cocrystals with Lewis bases such as nitroaromatic compounds, ethers, ketones, and sulfoxides.[6] These studies provided the basis for the development of achiral (thio)urea-based H-bond donor catalysts. In 1994, Curran and Kuo demonstrated for the first time that urea derivatives are competent organic catalysts in the context of the allylation of cyclic sulfinyl radicals with allyltributylstannane and the Claisen rearrangement of allyl vinyl ethers (Scheme 2).[7]

Many of the early studies of asymmetric catalysis by chiral organic small molecules implicated H-bonding between the

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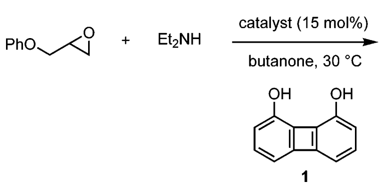
Abigail Doyle was born in Princeton, NJ, in 1980. She received her A.B. and A.M. degrees in Chemistry from Harvard University in 2002. In 2003, she began her graduate studies at Harvard University under the supervision of Professor Eric Jacobsen. Her research includes the discovery of a transition-metal-catalyzed enantioselective alkylation of tributyltin enolates with alkyl halides and development of a thiourea catalyst for enantioselective nucleophilic additions to prochiral oxocarbenium ions.

Eric Jacobsen was born and raised in New York City. He earned his B.S. degree from New York University (1982), where he was introduced to research in organic chemistry by Yorke Rhodes. He earned his Ph.D. degree from UC Berkeley in 1986 with Robert Bergman and carried out postdoctoral studies at MIT with Barry Sharpless. He began his independent career at the University of Illinois at Urbana—Champaign in 1988, moving to Harvard University in 1993. He is currently the Sheldon Emory Professor of Organic Chemistry. His research interests lie in the discovery, mechanistic elucidation, and application of new catalytic reactions.

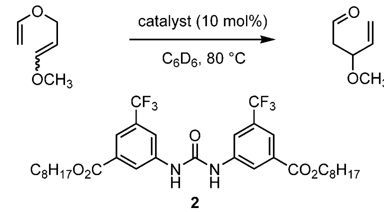
Scheme 1. Biphenylenediol-Promoted Epoxide-Opening Reaction



catalyst	k_{rel}
phenol	1.0
1	12.5

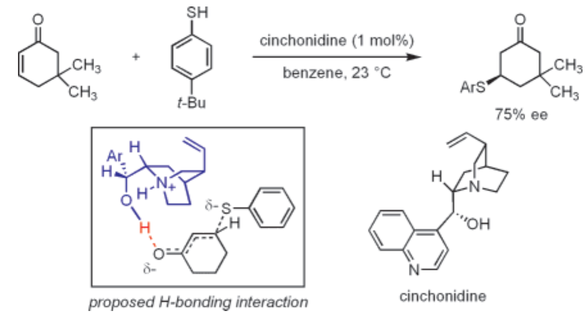
catalyst and electrophile as a mechanism for electrophile activation as well as transition-state organization. These include the following: Wynberg's 1981 report that the cinchona alkaloids quinine, quinidine, cinchonine, and cinchonidine, each of which bear free OH groups in proximity to the basic quinuclidine nitrogen, catalyze enantioselective conjugate addition reactions to carbonyl compounds (Scheme 3);[8] Inoue's discovery the same year of diketopiperazine cyclo(L-phenylalanine-L-histidine) as a competent catalyst for

Scheme 2. Claisen Rearrangement Catalyzed by an Achiral Urea

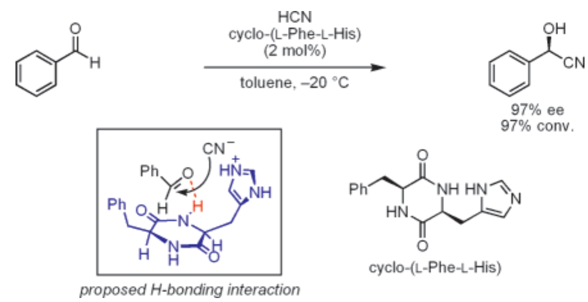


catalyst	k_{rel}
none	1.0
2	2.7

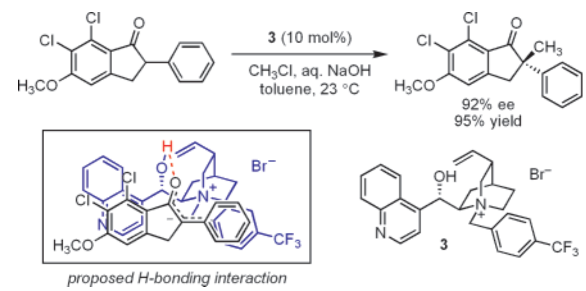
Scheme 3. Cinchonidine-Catalyzed Thiol Conjugate Addition



Scheme 4. Asymmetric Cyanation of Aldehydes by a Cyclic Dipeptide Catalyst



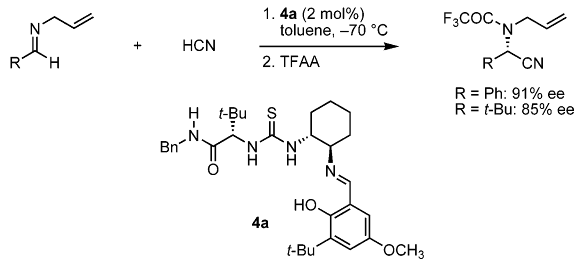
Scheme 5. Asymmetric Phase-Transfer-Catalyzed Enolate Alkylation



the hydrocyanation of benzaldehydes (Scheme 4);[9] and ground-breaking studies by scientists at Merck, reported in 1984, on *N*-alkyl cinchona alkaloid derivatives as highly efficient and enantioselective phase-transfer catalysts for the alkylation and Michael addition of indanone nucleophiles (Scheme 5).[10]

While each of these discoveries was widely appreciated in the field for its fundamental and practical significance, researchers in asymmetric catalysis failed to seize the potential of H-bonding until much later. Awareness of H-bonding as a key activation mechanism and design principle for small-molecule chiral catalysts grew in this decade and may be attributed to experimental and theoretical studies of catalytic reactions that had been discovered years earlier: the urea-

Scheme 6. Thiourea-Catalyzed Asymmetric Strecker Reaction (First-Generation Catalyst)



and thiourea-catalyzed asymmetric Strecker reaction and the proline-catalyzed enantioselective aldol reaction.

In 1998, Sigman and Jacobsen reported that urea and thiourea derivatives catalyze enantioselective hydrocyanation reactions of imines derived from both aromatic and aliphatic aldehydes (Scheme 6).[11] In 2002, a mechanistic analysis based on NMR, kinetic, structure−activity, and theoretical studies revealed that the thiourea functionality was responsible for catalytic activity and that the imine substrate interacts with the catalyst via a dual H-bond interaction to the urea protons (Figure 1).[12] By contrast, calculations

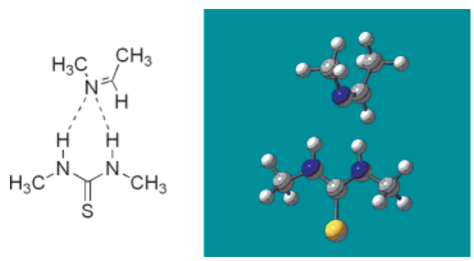
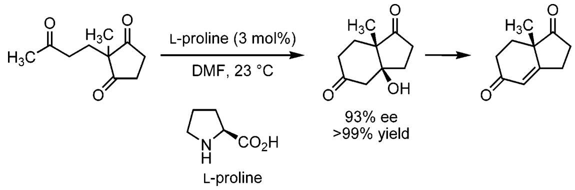


Figure 1. Dual H-bond interaction in thiourea-catalyzed enantioselective Strecker reaction.

predicted that the catalyst−aminonitrile product complex features a weaker and singly hydrogen-bonded interaction, providing a compelling explanation for the basis of catalyst turnover. This study led to identification of catalysts of broad scope (see section 6.3) and, more significant, helped to establish that simple H-bond donors could serve as useful asymmetric catalysts.

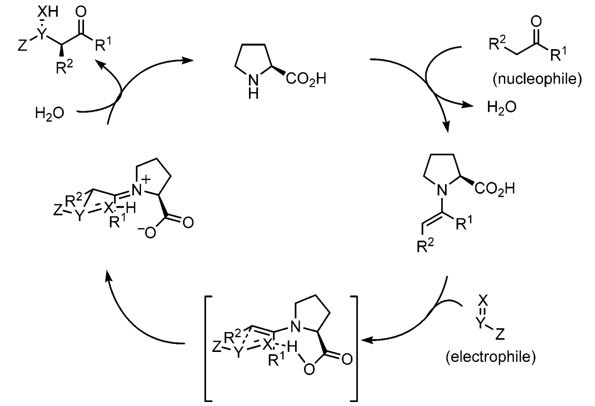
The renaissance in this decade of proline as a chiral catalyst also served to illuminate the importance of H-bonding in asymmetric catalysis. In the early 1970s, proline was identified by Hajos and Parrish at Hoffman-La-Roche and Eder, Sauer, and Wiechert at Schering AG as a highly enantioselective catalyst for aldol cyclizations of triketones (Scheme 7).[13]

Scheme 7. Proline-Catalyzed Aldol Cyclization



The mechanism of this reaction remained a topic of considerable debate in the ensuing years, but recent theoretical and experimental investigations have provided compelling evidence that proline acts as a multifunctional catalyst.[14] The secondary amine of proline undergoes condensation with one of the carbonyls of the substrate to generate a nucleophilic

Scheme 8. Proposed Mechanism for Proline-Catalyzed Transformations



enamine, and the carboxylic acid group serves to orient and activate the electrophile in a highly ordered transition state (Scheme 8). The role of the H-bond donor was shown to be of critical importance: it governs the facial selectivity of C−C bond formation by orienting the electrophile relative to the pyrrolidine ring and lowers the activation barrier to C−C bond formation by stabilizing charge buildup in the transition state.[14h] On the basis of these investigations, substantial research has been devoted more recently toward devising proline analogs bearing H-bond donors of varying acidity and structure. More important, this understanding of the mechanism of proline-catalyzed reactions has inspired the development of entirely new classes of bifunctional catalysts bearing H-bond donor components. The discussion of proline-catalyzed reactions in this review will be confined to a discussion of those derivatives designed to modulate the H-bond donating ability of the catalysts (see section 2.1). A separate review within this organocatalysis issue provides a comprehensive discussion of proline-catalyzed reactions.

At least partly as a direct result of these insights into the mechanism of catalysis by thiourea and amino acid derivatives there has been a veritable explosion of research activity relating to the design and development of chiral hydrogen-bond donor catalysts in the past 5 years. The H-bond donor catalysts identified to date possess a wide range of structural and functional frameworks (Figure 2) and differ widely in the identity of the H-bond donor motif with acidities spanning over 20 pK_a units (Figure 3). Mechanisms for electrophile activation and catalysis by these compounds certainly vary greatly. However, in spite of the obvious differences, the catalysts can be seen to share a common fundamental design feature: a single or dual H-bond donor site flanked by sites for secondary interaction with substrates, such as aromatic, weakly basic or acidic, or strongly basic functionality.

Catalysts have been identified for enantioselective addition reactions to carbonyl, nitroalkene, α,β-unsaturated carbonyl, imine, and iminium ion electrophiles. Recent progress in the field has also revealed that H-bond donors are remarkably general and enantioselective catalysts for mechanistically distinct reaction pathways, from 1,2- and 1,4-addition reactions to concerted cycloadditions and acyl transfer reactions. This review aims to provide a comprehensive examination, through December 2006, of asymmetric catalysis by chiral H-bond donors, organized by electrophile and reaction classes. Organized in this way, it becomes clear that chiral small-molecule H-bond donors already represent an important and broadly applicable class of catalysts for enantioselective synthesis in spite of the youth of the field. More

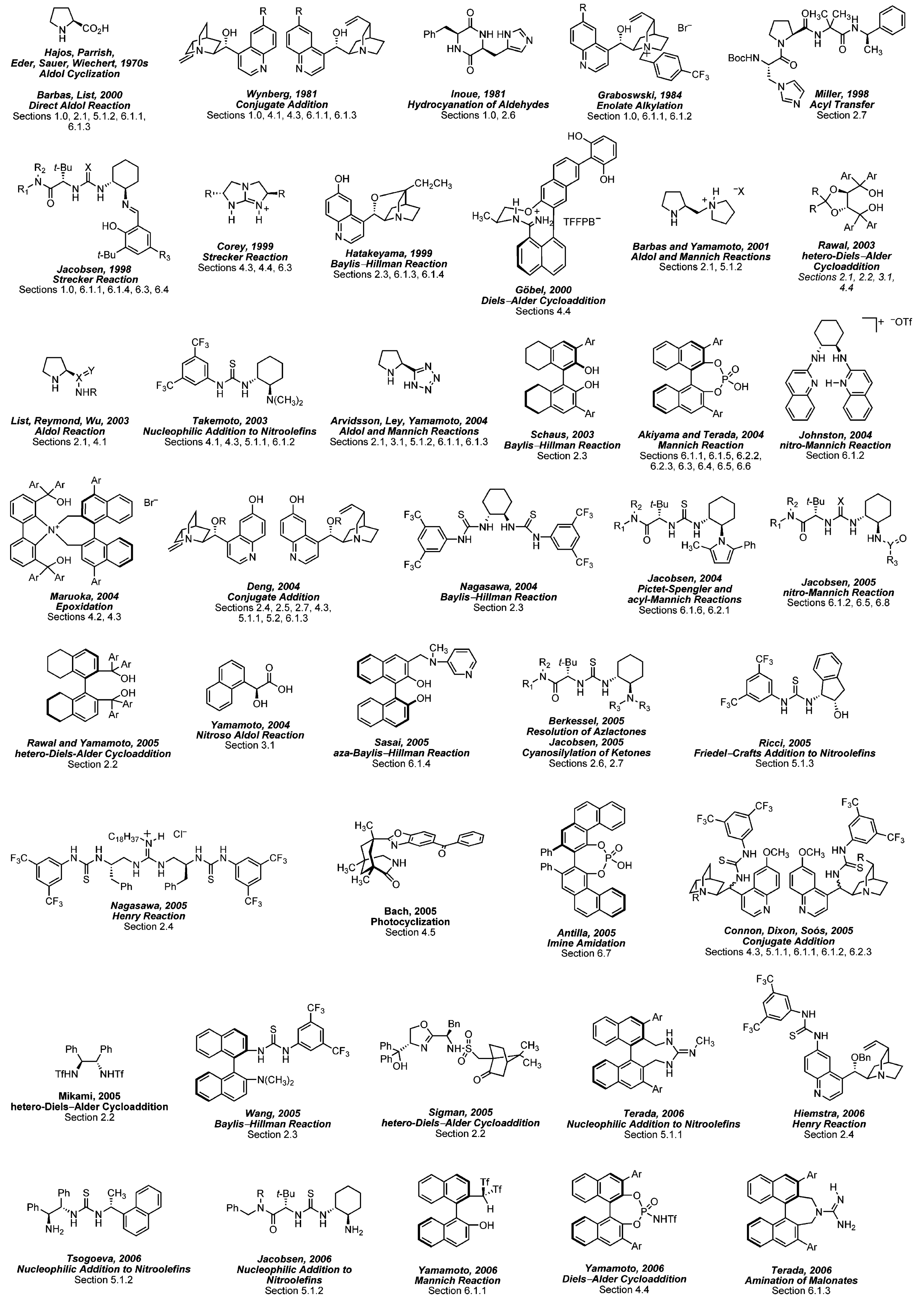


Figure 2. Representative H-bond donor asymmetric catalysts.

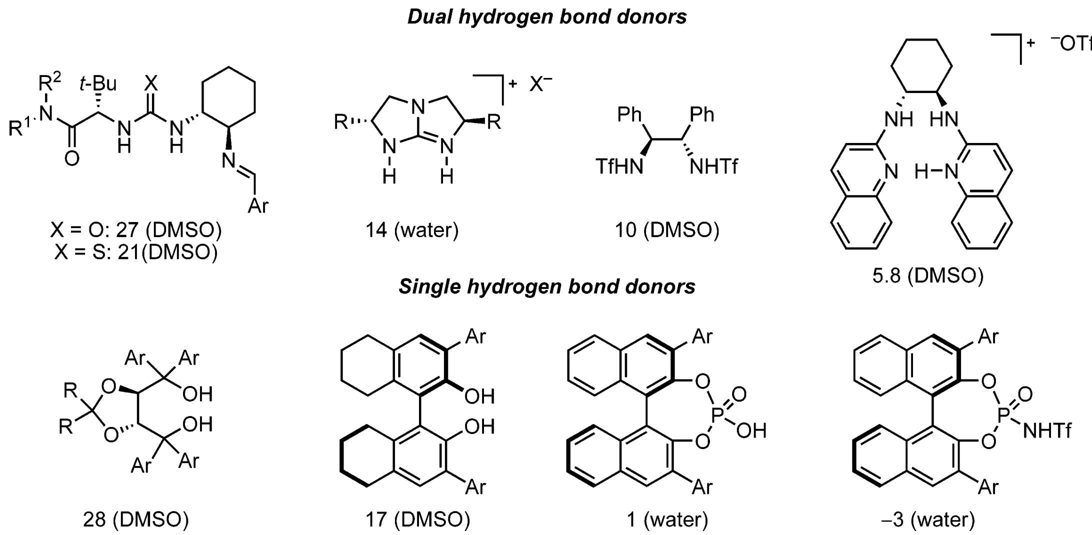
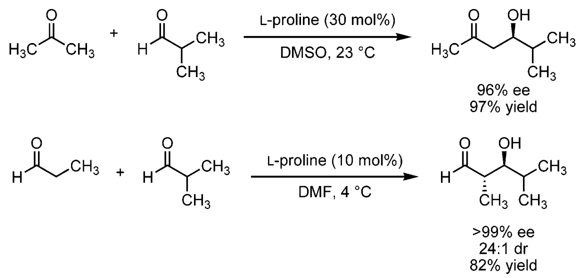


Figure 3. Approximate pK_as of H-bond donor motifs in small-molecule catalysis.[15]

Scheme 9. Proline-Catalyzed Direct Crossed Aldol Reactions



focused and detailed discussions, including proposed models of activation and enantioinduction, of certain types of these catalysts can be found within separate reviews within this special issue on organocatalysis.

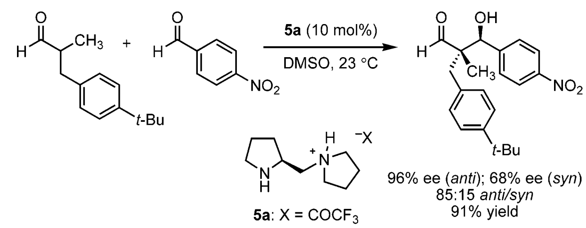
2. Carbonyl Electrophiles

2.1. Aldol Reaction[16]

The discovery of the proline-catalyzed enantioselective aldol cyclization of triketones[13] enabled enantioselective syntheses of complex natural products such as steroids and terpenoids by offering a practical and enantioselective route to the Wieland−Miescher ketone.[17] The broader implications of the method for asymmetric catalysis, however, were not appreciated until decades later. In 2000, List, Lerner, and Barbas reported the discovery of proline-catalyzed direct aldol reactions of acetone and aldehydes (Scheme 9),[18] and subsequently, a number of research groups have reported enantio- and diastereoselective variants of the proline-catalyzed aldol reaction that provide operationally simple routes to a range of aldolate structural motifs.[19] β-Hydroxy aldehydes, important building blocks for polypropionate and polyacetate natural products, for example, can be prepared in high enantio- and *anti*-diastereoselectivity by proline-catalyzed direct aldol reactions between nonequivalent aldehyde donors and acceptors.[20] This reaction highlights the impressive chemo- and stereocontrol available to proline catalysis.

While proline is an attractive catalyst in terms of its simplicity, ease of use, and accessibility,[21] drawbacks of this amino acid as an organic catalyst include its low reactivity

Scheme 10. Ammonium Catalyst for Intermolecular Aldol Reactions



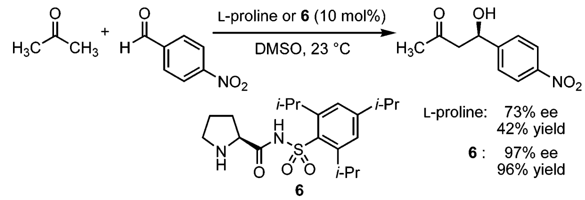
and low solubility in common organic solvents. As a means to developing proline catalysts with increased reactivity, substrate scope, and selectivity, researchers have focused particular attention on modifying the H-bond-donating component of the molecule.

Ammonium catalysts **5**, 1:1 salts of a proline-derived diamine and acid, have been shown to display improved reactivity to proline in aldol reactions.[22] The ammonium functional group of **5a** likely assumes the role of the carboxylic acid as the H-bond donor, where the greater acidity of the ammonium ion (pK_a = 10 in DMSO) to that of a carboxylic acid (pK_a = 12 DMSO) has been suggested to explain the enhanced reactivity of **5**. Aldol reactions catalyzed by the ammonium catalyst **5a** also exhibit improved reaction scope, allowing for the enantioselective synthesis of quaternary stereocenters in the reactions of α,α-disubstituted aldehydes as aldol donors and aromatic aldehydes as aldol acceptors (Scheme 10).[23]

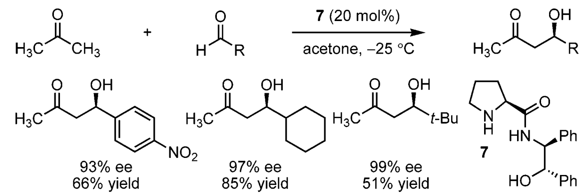
Proline analogues bearing secondary amides, thioamides, and acylsulfonamides as H-bond donors have also been investigated as catalysts for aldol reactions.[24] These modified catalysts display significant improvements in catalyst reactivity and enantioselectivity relative to proline (Scheme 11). Wu and co-workers examined replacing the carboxylic acid functional group of proline for a dual H-bond donor. The secondary amide catalyst **7** displays greater generality with respect to the structure of the aldol acceptor: high enantioselectivity is observed for the aldol addition of acetone to aromatic and aliphatic aldehydes (Scheme 12).[25]

Tetrazoles are commonly used as pharmacophores for carboxylic acids, with some of the principal differences being that the tetrazole group imparts increased solubility in organic solvents and the pK_a of tetrazole in DMSO is 8.2, 4 pK_a

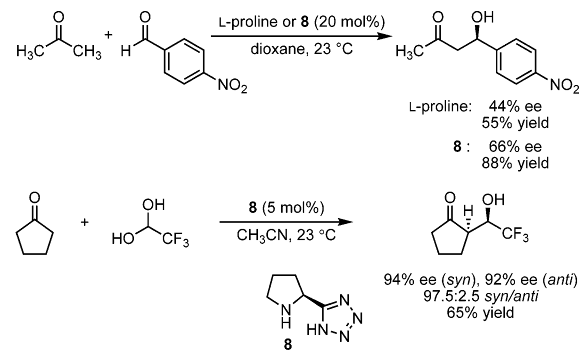
Scheme 11. Aldol Reaction Catalyzed by an Acylsulfonamide Proline Derivative



Scheme 12. Modified Proline Derivative for Aldol Addition Reactions



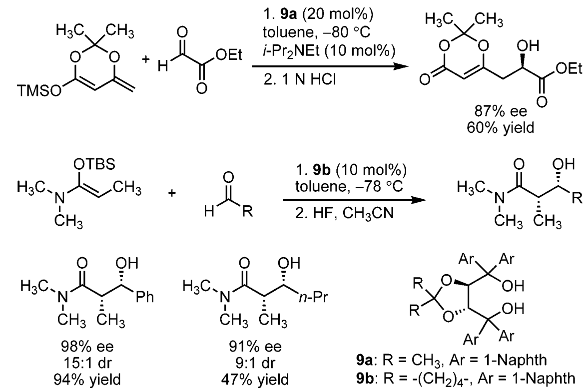
Scheme 13. Tetrazole Proline Analogue for Aldol Reactions



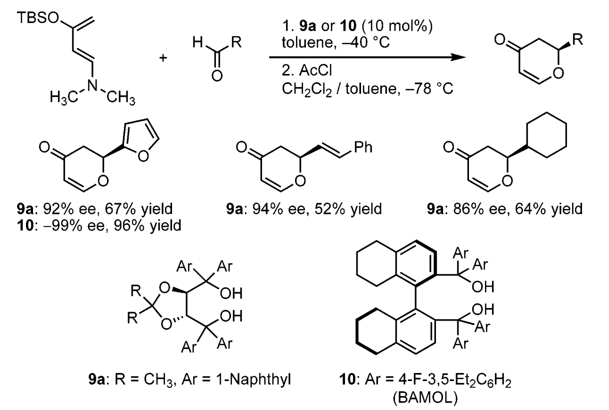
units lower than that of acetic acid in DMSO.[26] In 2004, the groups of Yamamoto, Ley, and Arvidsson each reported the application of tetrazole proline analogue **8** to proline-catalyzed reactions.[24e,27] Consistently better enantioselectivity and yields of β-hydroxy ketones are observed with tetrazole catalyst **8** than with proline in direct aldol reactions across a wide range of organic solvents (Scheme 13).[27d,28] Moreover, catalyst **8** outperforms proline with respect to yield, enantioselectivity, reaction time, substrate scope, and catalyst loading for aldol reactions with highly reactive aldehydes as the aldol acceptor.[27a,29] On the basis of these results it seems likely that the design of other new proline analogues with different H-bond donor components will lead to the identification of even more efficient and general catalysts for direct aldol reactions.

TADDOL derivatives and chiral biphenols have emerged recently as H-bond donor catalysts for enantioselective reactions and proven remarkably effective for the activation of aldehyde and ketone electrophiles toward nucleophilic attack.[30] For example, enantioselective aldol reactions with preformed enolates have been successfully realized with chiral diol catalysts. Rawal and co-workers reported that TADDOL **9a** catalyzes the vinylogous Mukaiyama aldol reaction of dienol ethers with highly reactive aldehydes, including ethyl glyoxylate and electron-deficient benzaldehydes.[31] The range of aldehydes that undergo TADDOL **9b**-catalyzed Mukaiyama aldol reaction with electron-rich *O*-silyl-*N*,*O*-acetals is considerably greater than that for the vinylogous Mukaiyama aldol reaction (Scheme 14).[32] Electron-rich and -poor aromatic aldehydes undergo reactions in high syn diastereoselectivity and excellent enantioselectivity. Furthermore, reaction with an aliphatic aldehyde, *n*-butyraldehyde, was shown to proceed in 9:1 dr and 91% ee. Rawal and co-workers demonstrated that the β-hydroxy amide products that result can be transformed into β-hydroxy aldehydes with little or no epimerization using Schwartz's reagent.

Scheme 14. Enantioselective Mukaiyama Aldol Reactions Catalyzed by TADDOL Derivatives



Scheme 15. TADDOL-Catalyzed Enantioselective Hetero-Diels−Alder Reactions



2.2. Hetero-Diels−Alder Cycloaddition[33]

The hetero-Diels-Alder cycloaddition of electron-rich dienes and aldehydes provides access to useful structural motifs for synthesis, including dihydropyrones and γ-lactones. TADDOL derivatives were first introduced as chiral H-bond donor catalysts in the context of the enantioselective hetero-Diels−Alder reaction of aminosiloxydienes.[34] Rawal and co-workers observed that protic solvents such as 2-butanol accelerated the hetero-Diels−Alder reaction of unactivated aldehydes and ketones.[35] The researchers subsequently explored the use of chiral alcohols as catalysts for the enantioselective transformation. In the presence of 20 mol % TADDOL **9a**, 1-amino-3-siloxybutadiene reacts with a variety of aromatic, aliphatic, and α,β-unsaturated aldehydes to afford, after treatment with acetyl chloride, dihydropyrones in good yield and excellent enantioselectivity (Scheme 15).[34,36] Cycloadditions with BAMOL **10**, a related diol catalyst with an axially chiral 1,1′-biaryl-2,2′-dimethanol scaffold, proceed in comparable yield and enantioselectivity to reactions catalyzed by **9a**.[37] An X-ray structure of a BAMOL (**10**)-benzaldehyde complex illustrates that the diol and dienophile associate, at least in the solid-state structure, via a single H-bond and that an intramolecular H-bond exists between the two hydroxy groups of the chiral diol (Figure 4). Cycloadditions of benzaldehydes with 1,3-dimethoxy-1-

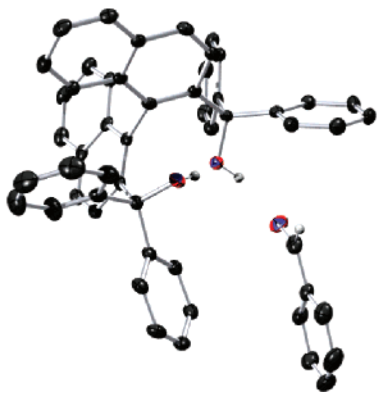
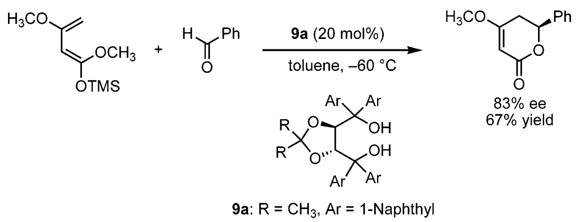
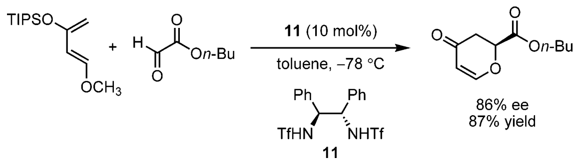


Figure 4. Crystal structure of a BAMOL−benzaldehyde complex.

Scheme 16. Synthesis of Enantioenriched γ-Lactones



Scheme 17. Sulfonamide-Catalyzed Diels−Alder Reaction of Glyoxylates

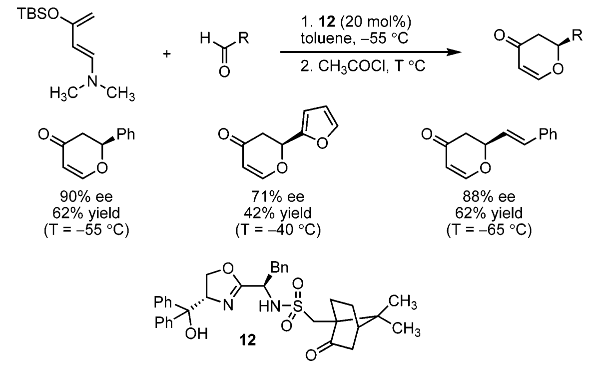


(trimethylsilyloxy)butadiene (Brassard's diene) are also catalyzed by TADDOL **9a** and provide direct access to enantioenriched γ-lactone derivatives (Scheme 16).[38]

Subsequent to Rawal's report on TADDOL-catalyzed hetero-Diels−Alder reactions, a variety of other quite different chiral frameworks and H-bond donors have been identified as catalysts for similar transformations. Mikami and Tonoi reported that addition of water to a lanthanide bis-trifluoromethanesulfonylamide (bis-triflylamide)-catalyzed hetero-Diels−Alder (HDA) reaction led to increases in chemical yield and enantioselectivity of the cycloaddition products.[39] On the basis of this observation, Mikami hypothesized and subsequently verified that bis-trifylamide (**11**) alone is an active catalyst for the HDA reaction; compound **11** was shown to promote the HDA reaction of TIPS-substituted Danishefsky's diene with glyoxylates and phenylglyoxals to afford dihydropyrones in 77−87% ee and good yield (Scheme 17).[40] On the basis of ^{1}H NMR titration experiments, Mikami proposed that the bis-triflylamide catalyst acts as a dual H-bond donor catalyst. The limitation of this methodology to glyoxylate reaction partners suggests that two-point binding to the catalyst may be necessary in order to activate and orient the dienophiles toward nucleophilic attack.[15c,41]

Sigman and Rajaram have shown that simple aromatic aldehydes can be activated as dienophiles for hetero-Diels−Alder reactions using the sulfonylamide-containing catalyst **12** (Scheme 18).[42] Catalyst **12** was designed to present two H-bond donating groups, a sulfonamide and a tertiary alcohol, across a rigid oxazoline scaffold. In the presence of this dual H-bond donor, electron-rich and electron-poor aryl aldehydes undergo cyclization to yield dihydropyrones in 71−91% ee.

Scheme 18. Sulfonamide-Catalyzed Diels−Alder Reaction of Aldehydes



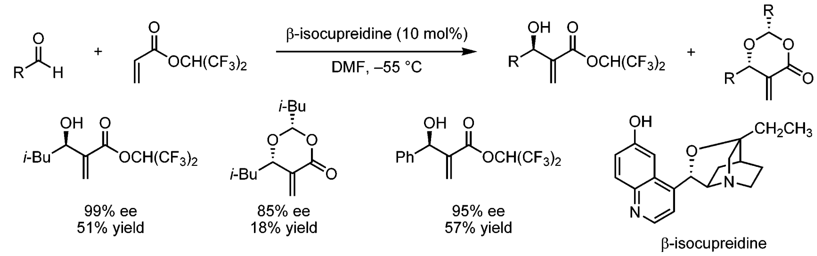
2.3. Baylis–Hillman Reaction[43]

The Baylis−Hillman reaction, the nucleophilic amine- or phosphine-catalyzed addition of electron-deficient alkenes to aldehydes, generates densely functionalized allylic alcohols of considerable value for the synthesis of complex natural products.[44] Since the Baylis−Hillman reaction is notorious for slow reaction rates, significant effort has centered on improving its reaction efficiency. In 1988, Roos and coworkers reported that alcohol additives, including phenols and BINOL, provide significant rate accelerations for the reaction.[45] This laid the foundation for the recent discovery of a remarkable variety of chiral H-bond donor catalysts for the transformation.

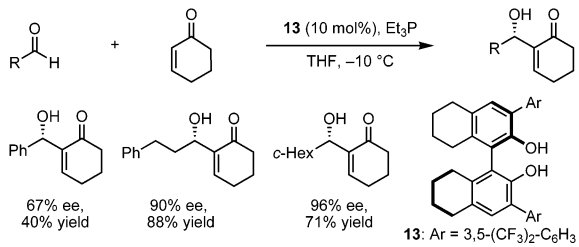
Cinchona alkaloids and their derivatives have been used broadly in the field of enantioselective synthesis as chiral resolving agents, ligands for transition-metal catalysts, and organocatalysts.[46] Each of these applications relies on the exceptional nucleophilicity and Lewis basicity of the quinuclidine nitrogen of cinchona alkaloids. However, in certain cases, H-bond donor groups ancillary to the basic nitrogen have proven important for catalysis. Hatakeyama and coworkers examined hydroxy-containing cinchona alkaloids as catalysts for the Baylis−Hillman reaction of hexafluoroisopropyl acrylate and aldehydes (Scheme 19).[47] They found that β-isocupreidine (abbreviated β-ICD), which is readily prepared from quinidine, promotes the reaction in high enantioselectivity with aliphatic and aromatic aldehydes. The hydroxy group of β-isocupreidine was shown to be crucial for reactivity and enantioselectivity, suggesting a role for H-bonding in the rate- and enantioselectivity-determining transition states of the transformations. Unfortunately, the enantiomer or pseudoenantiomer of β-isocupreidine is not readily accessible, preventing access to the enantiomeric series of Baylis−Hillman products.[11]

The axially chiral backbone of BINOL constitutes a privileged scaffold for chiral ligands in asymmetric catalysis and has recently been identified as an important framework for H-bond donor catalysts.[48] Schaus and McDougal demonstrated that octahydro-BINOL derivatives such as **13** catalyze the asymmetric Morita−Baylis−Hillman reaction of cyclohexenone with aldehydes promoted by triethylphosphine as the stoichiometric nucleophile (Scheme 20).[49] Aliphatic aldehydes undergo reaction in 82−96% ee, whereas aromatic and α,β-unsaturated aldehydes products are obtained in diminished enantioselectivities and yields.[50]

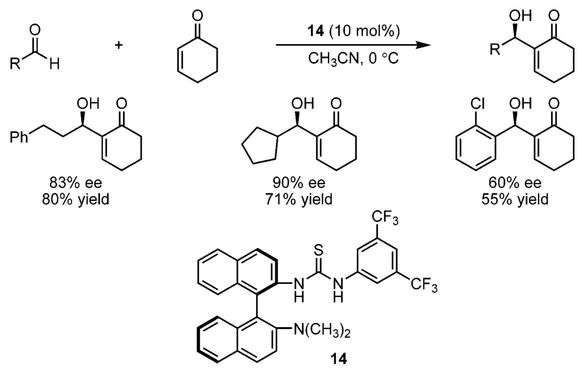
Scheme 19. Baylis−Hillman Reaction Catalyzed by β-Isocupreidine



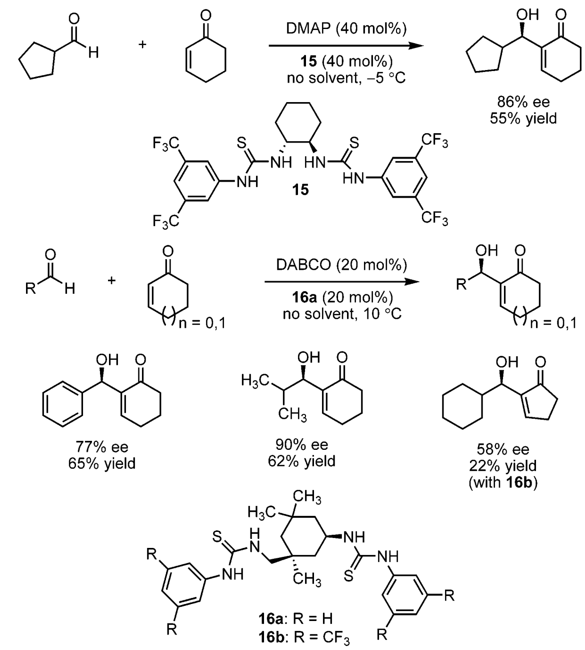
Scheme 20. BINOL Catalyst for Enantioselective Baylis−Hillman Reactions of Cyclohexenone



Scheme 21. Thiourea Tertiary Amine Catalyst for Enantioselective Baylis−Hillman Reactions



Scheme 22. Bis-thiourea Catalysts for Enantioselective Baylis−Hillman Reactions



Aliphatic aldehydes are also the best substrates for binapthylamine catalyst **14** in Baylis−Hillman reactions of cyclohexenone. Reactions with 10 mol % **14** proceed in good yields and 60−94% ee (Scheme 21). The active dipolar nucleophilic intermediate is proposed to arise from addition of the tertiary amine of catalyst **14** into cyclohexenone, which is activated by a dual H-bond to the catalyst.[51]

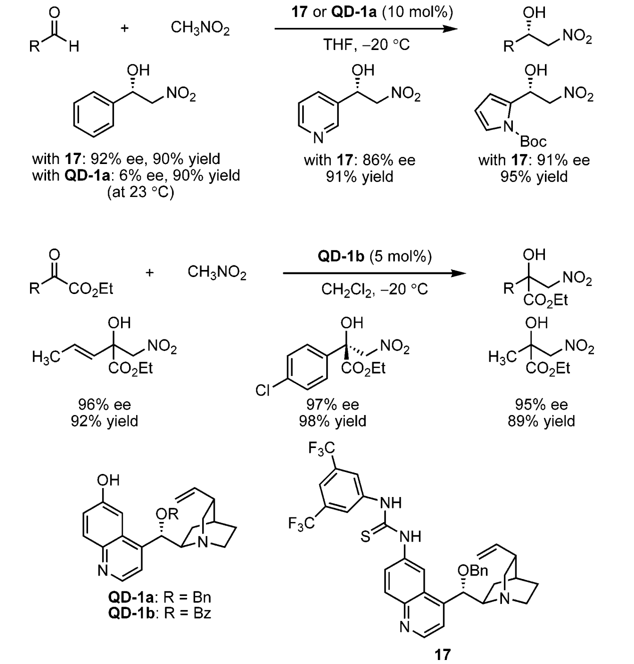
In contrast, Nagasawa and co-workers developed bis-thiourea catalyst **15** to accelerate the DMAP-catalyzed reaction of cyclohexenones and aldehydes by simultaneous activation of both electrophile components through H-bond donation (Scheme 22).[52] The authors achieved the highest asymmetric induction with cyclic aliphatic aldehydes and 40 mol % of the bis-thiourea catalyst under solvent-free conditions. More recently, Berkessel and co-workers reported an improved bis-thiourea catalyst **16**, derived from the 1,4-diamine IPDA (3-(aminomethyl)-3,5,5-trimethyl-cyclohexylamine), for Baylis−Hillman reactions of aromatic and aliphatic aldehydes.[53] Cyclohexenone and cyclopentenone were shown to be capable Michael acceptors for the enantioselective Baylis−Hillman reaction in the presence of **16** and DABCO as the nucleophilic promoter.

2.4. Henry Reaction[54]

Hiemstra and co-workers reported that 6′-thiourea-substituted cinchona alkaloid derivative **17** serves as an effective enantioselective catalyst for addition of nitromethane to carbonyl compounds (the Henry or nitroaldol reaction, Scheme 23).[55] The researchers previously found that 6′-OH catalyst **QD-1a**, designed by Deng and co-workers as a bifunctional organic catalyst that contains both a phenol and a quinuclidine moiety for dual activation, promoted the reaction with 4-NO_2-benzaldehyde in low enantiomeric excess.[56] Replacing the phenolic functional group with a thiourea led to a substantially improved catalyst for the Henry reaction. High asymmetric induction was observed for benzaldehyde and heteroaromatic aldehyde derivatives with 10 mol % **17**. Deng and co-workers subsequently showed that the 6′-OH cinchona alkaloid **QD-1b** is an excellent catalyst for the reaction of α-ketoesters with nitromethane.[57] The highly enantioenriched products from the Henry reaction can be elaborated to aziridines, *β*-lactams, and α-alkylcysteines.

The bisthiourea-guanidinium ion **18** has been identified by Nagasawa and co-workers as an enantio- and diastereoselective catalyst for Henry reactions of achiral or chiral α-branched aliphatic aldehydes (Scheme 24).[58] In addition to enantioselective nitromethane additions, catalyst **18** promotes highly syn-selective additions of nitroalkanes to functionalized aliphatic aldehydes.[59] Nagasawa and co-workers successfully utilized this reaction in an enantioselective synthesis of (4*S*,5*R*)-*epi*-cytoxazone, a type-2 cytokine selec-

Scheme 23. Cinchona Alkaloid Derivatives for Enantioselective Henry Reactions



tive inhibitor. A likely role of the thiourea is as activator of the aldehyde by dual H-bond donation while the guanidinium ion ion pairs with the nitronate nucleophile. In the presence of 10 mol % (*R*,*R*)-guanidinium thiourea **18**, optically active (*S*)-α-amino and α-alkoxy aldehydes react with nitromethane in high anti-diastereoselectivity, enhancing the otherwise moderate facial selectivity of the substrates.

2.5. Friedel–Crafts Addition[60]

Enantioselective elaboration of indoles is of considerable interest in the synthesis of natural products and bioactive compounds. Deng's **Q-1** and **QD-1** catalysts, bearing free hydroxyquinoline moieties, have been shown to promote the enantioselective addition of indoles to α-ketoesters and electron-deficient benzaldehydes (Scheme 25).[61] Previously, Török and co-workers demonstrated that a free C-9 hydroxyl was required for high enantioselectivity in cinchona-alkaloid-catalyzed additions of indole to ethyl trifluoropyruvate (Scheme 26), thereby establishing the importance of H-bond donor groups in these enantioselective Friedel−Crafts additions.[62]

2.6. Cyanation of Carbonyl Derivatives[63]

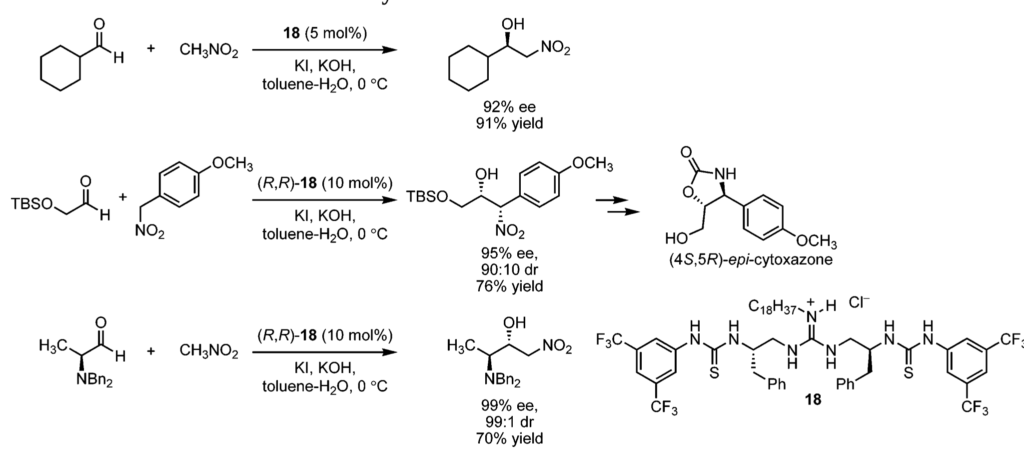
The success of proline as an enantioselective catalyst for aldol reactions, as discussed in section 2.1, demonstrates that only a single amino acid is necessary to mimic an enzyme and mediate an efficient and selective transformation. Small peptides have also found application as organocatalysts for enantioselective transformations.[64] One of the first demonstrations of a small peptide-catalyzed enantioselective transformation was reported by Inoue and co-workers in 1981.[9a,b,65] Diketopiperazine cyclo(L-phenylalanine-L-histidine) was identified as a competent catalyst for the hydrocyanation of benzaldehydes (Scheme 27). This catalyst was found to be highly enantioselective for electron-rich aromatic aldehydes. Despite the relative simplicity of the catalyst, its mechanism of action remains poorly understood.[66] A number of factors have complicated mechanistic studies, including the fact that the method of preparation of the catalyst is crucial to its activity and that the hydrocyanation reaction displays autoinduction.[67] Nonetheless, it has been ascertained that the reactions are second order in catalyst and that the catalyst likely activates the aldehyde electrophile via H-bond donation.[67b,68]

More recently, a thiourea-tertiary amine catalyst **19** was discovered by Fuerst and Jacobsen for the asymmetric cyanosilylation of carbonyl compounds (Scheme 28).[69] This represents one of the most effective and selective general cyanation catalysts for aromatic aldehydes and ketones. At this stage, this system is one of only a few examples of enantioselective thiourea catalysis in 1,2-carbonyl addition chemistry. DFT calculations of the catalytic system support a mechanism wherein the tertiary amine of **19** activates HNC, the active nucleophile generated upon tautomerization of HCN, toward 1,2-addition to a thiourea-bound ketone or aldehyde.[70] Calculated transition-state energies correlate well with the experimentally observed sense and degree of enantioinduction for a variety of ketone electrophiles. Insights from these studies have led to the design and evaluation of improved dipeptide catalyst **20** for substrates such as dialkyl ketones that underwent trimethylsilylcyanation with low ee's with **19**. The enantioenriched cyanohydrin products resulting from these reactions are extremely useful as precursors to α-hydroxy acids, *β*-amino alcohols, and other chiral building blocks.[66]

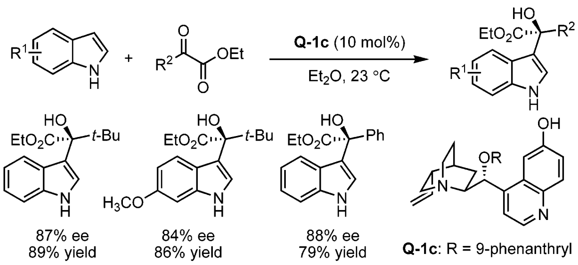
2.7. Resolution and Desymmetrization[71]

Advances in understanding and predicting the secondary structure of peptides have allowed for the design of chiral

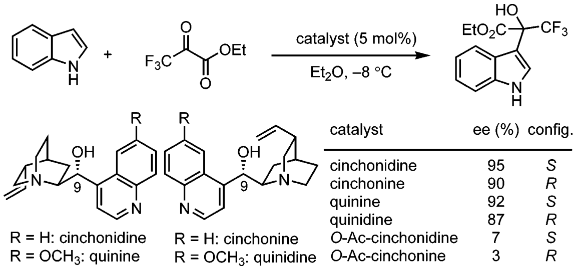
Scheme 24. H-Bond-Assisted Phase-Transfer Catalysis



Scheme 25. Enantioselective Friedel−Crafts Reactions with α-Ketoesters

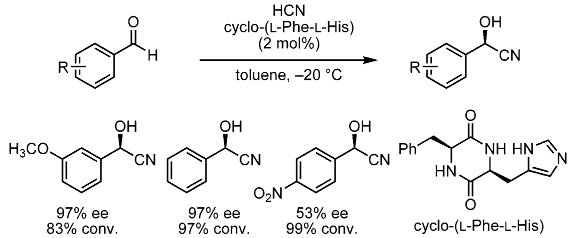


Scheme 26. Enantioselective Friedel−Crafts Reactions of Indole with Ethyl-3,3,3-trifluoropyruvate

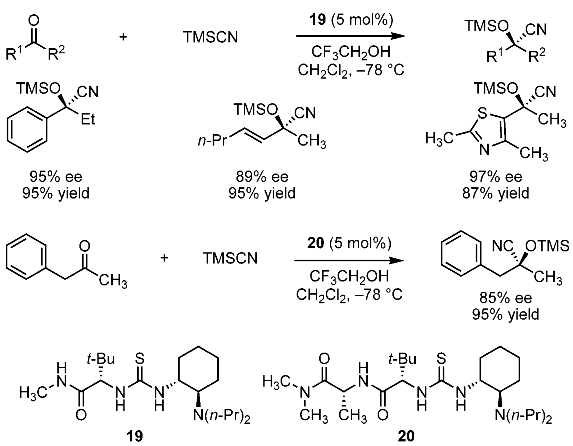


catalyst	ee (%)	config.
cinchonidine	95	*S*
cinchonine	90	*R*
quinine	92	*S*
quinidine	87	*R*
O-Ac-cinchonidine	7	*S*
O-Ac-cinchonine	3	*R*

Scheme 27. Cyclic Peptide-Catalyzed Hydrocyanation of Benzaldehydes

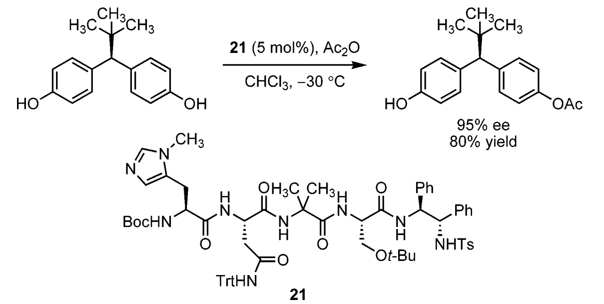


Scheme 28. Silylcyanation of Ketones Catalyzed by Tertiary Amine Thioureas

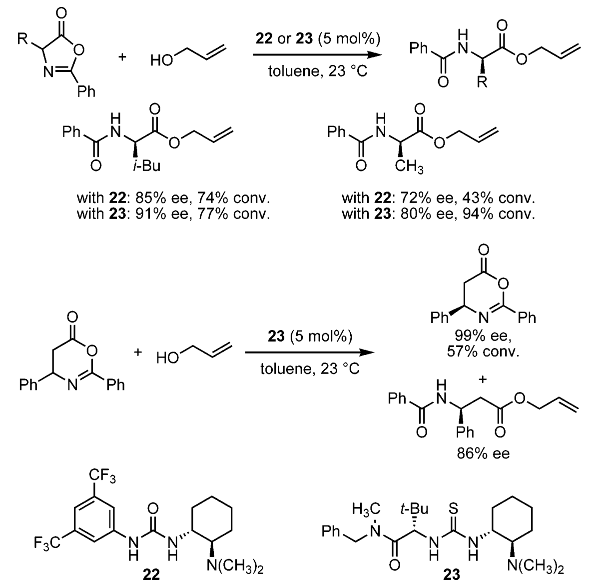


peptide scaffolds with predictably placed catalytic functional groups. Capitalizing on methods for automated synthesis and evaluation of peptide-based catalyst libraries, Miller and co-workers investigated the use of small-molecule peptide organocatalysts for enantioselective acyl, phosphoryl, and sulfinyl transfer reactions.[72] The Miller group's catalyst design involves incorporation of a nucleophilic *N*-alkyl imidazole moiety onto a rigid scaffold that presents possible H-bonding interactions for asymmetric induction. The research group identified catalysts for kinetic resolutions that display very high selectivity factors for a broad range of secondary and tertiary alcohols.

Scheme 29. Peptide-Catalyzed Remote Desymmetrization of a Meso Diol



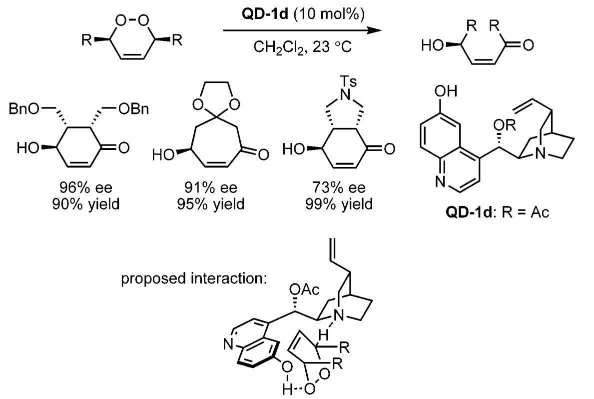
Scheme 30. Resolutions of Azlactones and Oxazinones



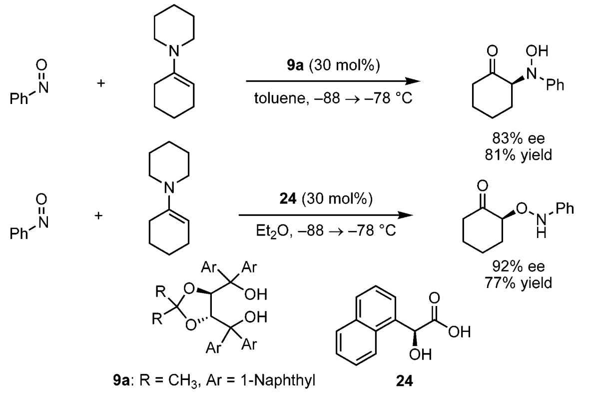
A particularly striking application of these catalysts has been to the remote desymmetrization of meso compounds by group transfer catalysis, where the site of chemical catalysis is far removed from the prochiral stereogenic center (Scheme 29).[73] Enzymes are generally considered to be uniquely proficient at the task of very long-range stereoinduction. However, a collaborative effort between scientists at Merck and the Miller lab led to the discovery that a pentapeptide **21** catalyzes the acylation of a diphenol in 95% ee and 80% isolated yield. Remarkably, the phenol functionality on the substrate is >5.7 Å from the stereogenic center. The Miller group also investigated these catalysts for chemoselective transformations on multifunctional compounds such as the natural product erythromycin.[74]

Chiral ureas and thioureas have also been investigated as small-molecule catalysts for acyl transfer reactions. In the presence of urea **22**, racemic azlactones were found to undergo dynamic kinetic resolution by nucleophilic addition of allyl alcohol to generate protected natural and unnatural α-amino acids in high enantiomeric excess (Scheme 30).[75] A second-generation catalyst, **23**, closely related to the tertiary amine catalyst **19** developed for ketone cyanosilylation, was subsequently discovered to be more enantioselective for the dynamic kinetic resolution.[76] The researchers proposed that the thiourea catalyst mimics the mechanism of a serine protease, activating the azlactone via dual H-bond donation and activating allyl alcohol by general base catalysis. This catalyst can also be applied to the preparation of *β*-amino acids by a related kinetic resolution of oxazinones with allyl alcohol.[77]

Scheme 31. Enantioselective Kornblum DeLaMare Rearrangement



Scheme 32. Enantio- and Regioselective Nitroso Aldol Reactions



Toste and co-workers have shown that Deng's bifunctional cinchona alkaloid catalyst **QD-1d** is highly enantioselective for the desymmetrization of bicyclic endoperoxides to γ-hydroxyenones (Scheme 31).[78] The proposed model for catalysis features the tertiary amine positioned for E2 elimination of the alkoxy leaving group and the 6′-hydroxy group H-bonded to that leaving group. Taken together, these studies serve to illustrate the high stereocontrol for remarkably distinct reaction pathways that is possible through cooperative action of a nucleophilic amine and H-bond donor in small-molecule catalysis.

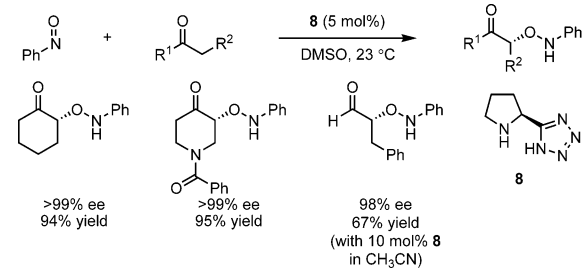
3. Nitrosobenzene Electrophiles

3.1. Nitroso Aldol Reaction[79]

Nitrosobenzene is a versatile electrophile that can undergo addition either at oxygen or at nitrogen in reactions with enolate derivatives. Yamamoto and Momiyama demonstrated that the proper choice of H-bond donor catalyst can lead to complete control of regioselectivity in enamine addition to nitrosobenzene.[80] With piperidine cyclohexene enamine as a nucleophile, the *N*-nitroso adduct is obtained in 83% ee with 30 mol % of TADDOL **9a** as catalyst, while the *O*-nitroso adduct is obtained with the same nucleophile in 92% ee with 30 mol % 1-naphthyl glycolic acid **24** as catalyst (Scheme 32). Similar to TADDOL, glycolic acid **24** can adopt a structure with an intramolecular H-bond between the hydroxy and carboxylic acid functional groups. Yamamoto and co-workers attribute the activity of catalyst **24** to such an interaction, but the mechanistic basis for the control of regioselectivity with the two catalysts awaits elucidation.

Direct *O*-nitroso aldol-type reactions have been realized using pyrrolidine-tetrazole catalyst **8**.[27b] Excellent enantioselectivities were observed for a variety of aldehyde and ketone nucleophiles (Scheme 33). Yamamoto and co-workers also investigated tandem *O*-nitroso aldol/Michael reactions of cyclic enones to generate nitroso Diels–Alder adducts in high enantioselectivity.[81]

Scheme 33. Direct *O*-Nitroso Aldol Reaction



4. α,β-Unsaturated Carbonyl Electrophiles

4.1. Conjugate Addition of Thiols[82]

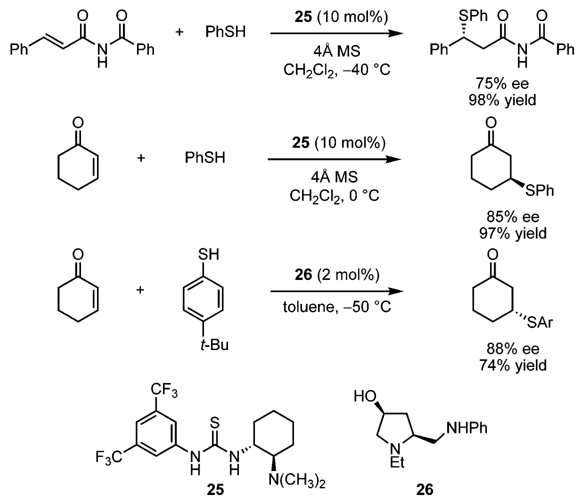
As noted in the introduction to this review, Wynberg and co-workers performed pioneering studies with cinchona alkaloids as chiral nucleophilic catalysts for enantioselective 1,2- and 1,4-additions to carbonyl compounds. In 1981, they reported that natural products quinine, quinidine, cinchonine, and cinchonidine promote the addition of aromatic thiols to cycloalkenones in higher rates and enantioselectivities than derivatives acetylated at the C9-OH position (Scheme 3).[8] This observation led to the proposal that cinchona alkaloids operate by bifunctional mechanisms, participating in simultaneous activation of the cyclic enone and the thiol by the hydroxy and quinuclidine groups, respectively. It must be noted, however, that the presence of an H-bond donor OH group is not a requirement for enantioselective catalysis with cinchona alkaloid derivatives in this reaction. Deng and co-workers reported recently that $(DHQD)_2PYR$, a dimeric quinidine derivative in which the alcohol is derivatized as an aryl ether, catalyzes highly enantioselective 1,4-additions of aromatic thiols to cyclic enones.[83] However, these reactions proceed with the opposite sense of asymmetric induction with respect to the absolute configuration of the C-8 and C-9 cinchona alkaloid skeleton, suggesting that the two reactions are characterized by distinct mechanisms.

Chen and co-workers reported that tertiary amine-thiourea derivative **25**, discovered originally by Takemoto and co-workers as a catalyst for enantioselective additions of malonate esters to β-nitrostyrenes (section 5.1.1),[84] promotes the addition of thiophenol to α,β-unsaturated imides and ketones in up to 85% ee (Scheme 34).[85] Catalysis of the enantioselective addition of thiols to enones has also been reported with hydroxyproline derivative **26**, which was suggested to activate the enone toward nucleophilic attack by H-bonding from the secondary alcohol.[86]

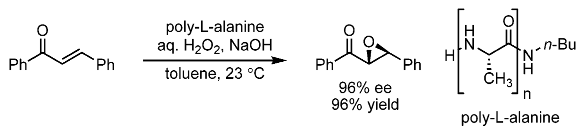
4.2. Nucleophilic Epoxidation[87]

In 1980, Juliá reported the epoxidation of chalcones catalyzed by poly-L-alanine of an average length of 30 amino acids (Scheme 35).[88] The Juliá reaction conditions are triphasic, consisting of the insoluble polyamino acid catalyst, an aqueous solution of NaOH and H_2O_2, and a solution of the chalcone in an organic solvent. Epoxidation reactions performed in protic organic solvents lead to lower enantioselectivity and yield, a fact that may be attributed to inhibition of H-bonding between the catalyst and the ketone

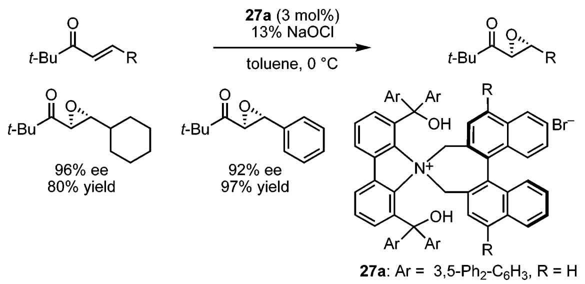
Scheme 34. Enantioselective Thiol Conjugate Addition Reactions



Scheme 35. Juliá−Colonna Epoxidation of Chalcones



Scheme 36. Ammonium-Catalyzed Nucleophilic Epoxidation



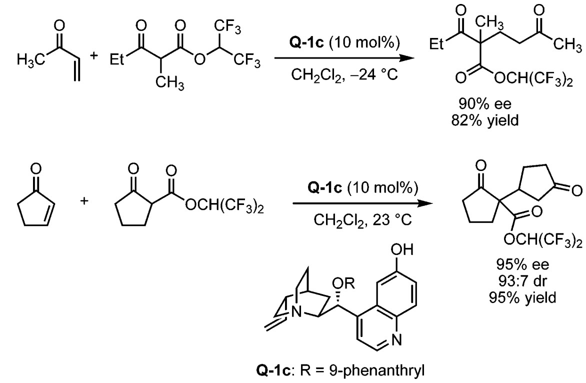
electrophile. Since the original report, numerous modifications to the reaction procedure have been described leading to improvements in the reaction scope, efficiency, and enantioselectivity.[87b,89]

Maruoka and co-workers designed synthetic ammonium salts that incorporate H-bond donor moieties for enantioselective phase-transfer reactions of prochiral electrophiles.[90] One of these catalysts, **27a**, has been shown to promote the epoxidation of α,*β*-unsaturated ketones with sodium hypochlorite in high enantioselectivity and yield (Scheme 36). Enantiofacial discrimination of the prochiral faces of the enone is thought to arise through transition-state organization due to H-bond donation from the diarylmethanol moiety of **27a** to the electrophile. Secondary H-bond interactions also play a crucial role in phase-transfer catalysis of transformations of prochiral nucleophiles, such as enolates in alkylation reactions.[10,91]

4.3. Conjugate Addition of C-Centered Nucleophiles[92]

The first documented example of a catalytic enantioselective conjugate addition was the cinchona alkaloid-catalyzed addition of cyclic *β*-ketoesters to methyl vinyl ketone reported by Wynberg in 1975.[93] Recent research efforts directed at modifying the H-bond donor of naturally occurring cinchona alkaloids have led to the identification of more enantioselective and general catalysts for this type of transformation. Deng discovered that cinchona alkaloid derivatives bearing a free hydroxy group at the 6-position of the quinoline are especially effective.[94] In particular, catalyst **Q-1c** was shown to promote the highly enantioselective conjugate addition of α-substituted-*β*-ketoesters to enones in a powerful method for the construction of quaternary stereocenters (Scheme 37). Furthermore, *β*-substituted enones can be used as Michael acceptors for the direct generation of products bearing contiguous tertiary and quaternary stereocenters in high diastereoselectivity and enantioselectivity. The scope of this catalytic method is remarkably broad with α,*β*-unsaturated aldehydes also serving as competent Michael acceptors (Scheme 38).[95] Deng and co-workers demonstrated the utility of the enantioenriched aldehyde products in the application of the method to a concise enantioselective synthesis of (+)-tanikolide.[95]

Scheme 37. Conjugate Additions to Enones

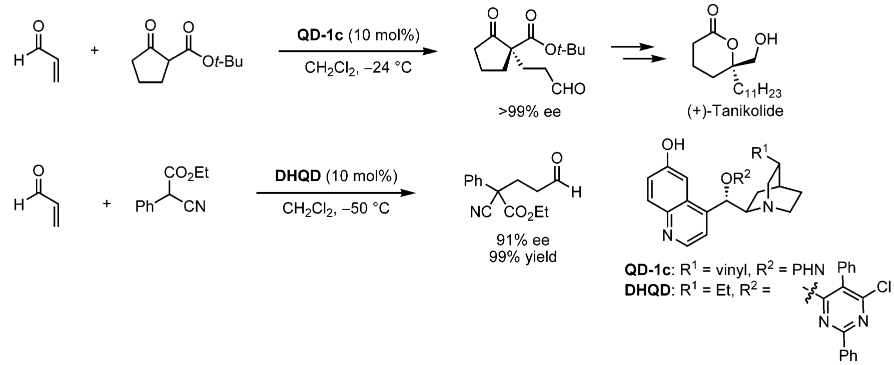


The groups of Soós, Connon, and Dixon independently developed H-bond donor catalysts by derivatizing the C-9 hydroxy group of cinchona alkaloids with a thiourea moiety (section 5.1.1). This modification follows from Wynberg's original proposal that the C-9 hydroxy group of cinchonine and cinchonidine catalysts can participate in electrophile activation by H-bond donation.[8a] The cinchona alkaloid-derived thiourea catalyst **28a** has found application in enantioselective 1,4-additions to enones. A variety of 1,3-dicarbonyl compounds are competent nucleophiles for **28a**-catalyzed enantioselective additions to chalcones.[96] Furthermore, Soós and co-workers found that catalyst **28a** promotes highly enantioselective Michael additions of nitroalkanes to chalcones, a reaction for which quinine itself is poorly reactive and only moderately enantioselective (Scheme 39).[97] This method offers an alternative to the direct conjugate addition of acetophenone to nitrostyrene derivatives (section 5.1.2) in the preparation of synthetically useful *γ*-nitroketones.

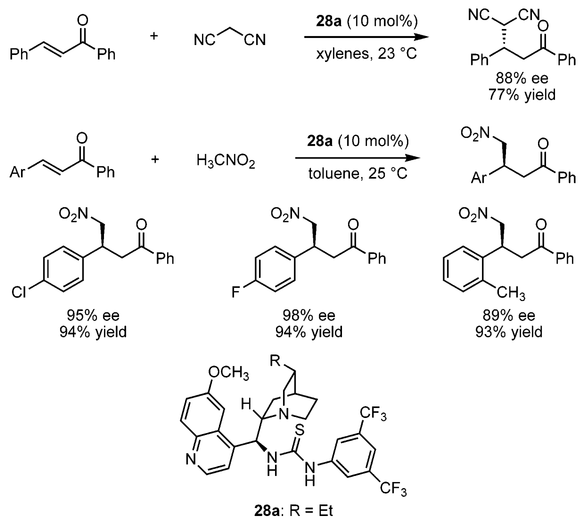
Many of the H-bond donors identified as catalysts for enantioselective conjugate addition of heteroatom-centered nucleophiles to α,*β*-unsaturated enones have also been applied to the 1,4-addition of carbon-centered nucleophiles. Maruoka and co-workers investigated a phase-transfer catalyst related to **27a** (Scheme 36) that promotes the enantioselective addition of diethyl malonate to chalcones.[98] Uniformly high enantioselectivities were reported for various chalcone derivatives (Scheme 40).

The Takemoto catalyst **25** was shown to be effective in the enantioselective conjugate addition of malononitrile, cyanoacetate, or nitroalkane nucleophiles to aliphatic and aromatic α,*β*-unsaturated imides (Scheme 41).[99] The impressively broad scope of the tertiary amine−thiourea motif for electrophile activation is evidenced by the ability of catalyst **25** to activate enone (section 4.1), α,*β*-unsaturated imide,

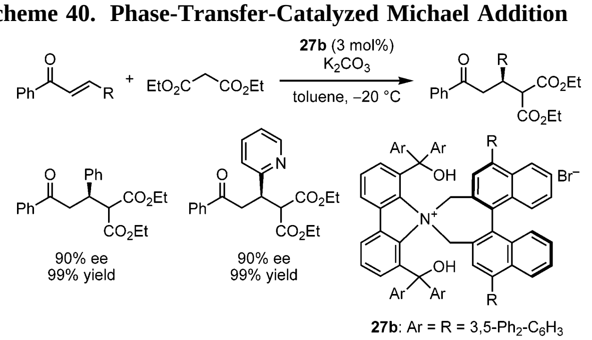
Scheme 38. Conjugate Addition to α,β-Unsaturated Aldehydes



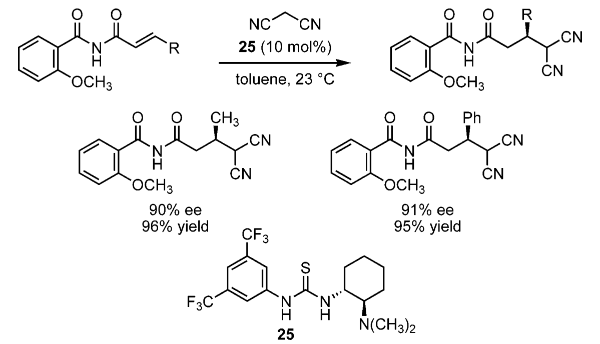
Scheme 39. Enantioselective Conjugate Additions to Chalcones



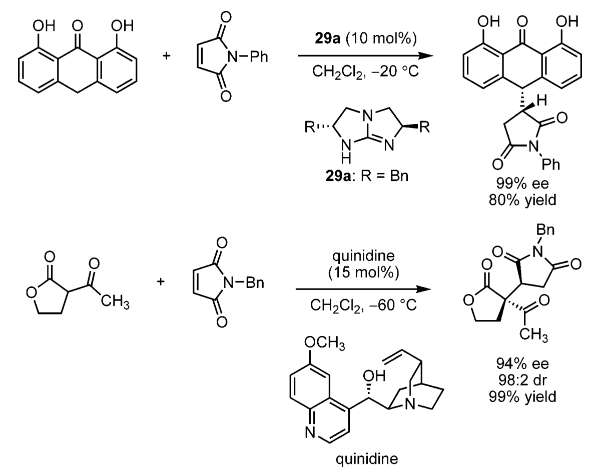
Scheme 40. Phase-Transfer-Catalyzed Michael Addition



Scheme 41. Enantioselective Additions to α,β-Unsaturated Imides



Scheme 42. Enantioselective Michael Additions to Maleimides



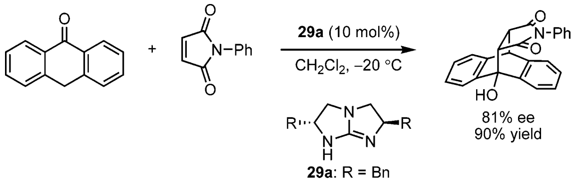
nitroolefin (section 5.1.1), and vinyl sulfone[100] electrophiles in highly enantioselective conjugate addition chemistry.

The Brønsted-basic bicyclic guanidine **29a** has been shown by Tan and co-workers to be an efficient catalyst for the enantioselective Michael reaction of 1,8-dihydroxy-9-anthrone (Scheme 42).[101] The guanidine catalyst was proposed to generate the active nucleophile in situ by deprotonation.[102] Although the role of the catalyst beyond its function as a Brønsted base has not been investigated, it is likely that H-bonding, ion-pairing, and π-interactions all contribute to the organization of a transition state that leads to high enantioinduction for reactions with maleimides and other electron-deficient Michael acceptors. High enantio- and diastereoselectivities can also be obtained in the quinidine-catalyzed conjugate addition of acyclic and cyclic β-keto esters and cyclic β-diketones to maleimides, providing access to chiral α-substituted succinimides.[103]

4.4. Diels–Alder Cycloaddition[104]

The Diels–Alder reaction is an indispensable reaction in synthetic organic chemistry, providing access to functionalized cyclohexenes with up to four new stereogenic centers.[105] As a result, extensive research effort has been dedicated to the development of chiral catalysts for highly stereo- and regioselective versions of the transformation.[104] The majority of successful examples of enantioselective catalytic Diels–Alder reactions has involved metal-centered Lewis-acid catalysts. However, more recent efforts have illustrated that small-molecule H-bond donors also hold promise as chiral catalysts for this class of reactions. In fact, small-molecule H-bond donors such as carboxylic acids and phenols were shown to catalyze the Diels–Alder reaction of cyclopentadiene and benzoquinone as early as 1942 by Wasserman and co-workers.[106]

Scheme 43. Bicyclic Guanidine Catalyst for Asymmetric Diels−Alder Reaction



Tan and co-workers reported that the guanidine catalyst **29a**, discussed in the previous section in the context of Michael reactions, also promotes the mechanistically related enantioselective Diels−Alder reaction of anthrones (Scheme 43).[101] Göbel and co-workers investigated the use of an axially chiral amidinium ion **30** in mediating enantioselective Diels−Alder reactions of vinyl dihydronapthalene derivatives with cyclopentene-1,2-dione derivatives.[107] Although modest enantioselectivities were obtained with the amidinium ion (up to 43% ee with a stoichiometric amount of catalyst), large rate accelerations were observed at substoichiometric catalyst loadings (Scheme 44). The researchers examined the catalytic activity of the amidinium 2-(benzylamino)-pyridinium ion for a related Diels−Alder reaction in the presence of noncoordinating counterions such as tetrakis(2,5-bis(trifluoromethyl)phenyl)borate (TFPB).[108]

Rawal and co-workers extended their investigations of chiral diol catalysts for hetero-Diels−Alder reactions (section 2.2) to carbo-Diels−Alder reactions between aminodienes and acroleins.[109] Catalyst **9a** was identified as optimal for reactions with 1-amino-3-siloxybutadiene (Scheme 45). Uniformly high yields and ee's were observed with alkyl α-substituted aldehydes to generate functionalized cyclohexenone products.

With a rich history as chiral ligands for transition metals and chiral shift reagents, chiral phosphoric acids have emerged more recently as an important class of H-bond donor catalysts. The majority of effective chiral phosphoric-acid catalysts possess the general structure shown in **31** (Scheme 46) and are derived from binapthol with varying aryl substitution at the 3 and 3′ positions.[1h,k] Application of chiral phosphoric-acid catalysis has been limited primarily to activation of relatively Brønsted-basic imine substrates (see section 6). However, Yamamoto and co-workers found that the more acidic *N*-triflyl phosphoramide variant **32** promotes cycloadditions with a limited set of 1-substituted 2-siloxydienes in high enantioselectivities under conditions where phosphoric acid **31** is inactive (Scheme 46).[15h] These promising results suggest that the phosphoramide class of catalysts might find considerable application in reactions of carbonyl electrophiles.

4.5. Photocyclization

The development of catalysts for highly enantioselective photochemical transformations constitutes a significant challenge.[110] Stoichiometric chirality transfer by hydrogen-bonded host−guest complexes, on the other hand, has been successfully applied to enantioselective and diastereoselective transformations of highly reactive intermediates.[111] For example, Bach and co-workers identified a chiral lactam **33a** derived from Kemp's triacid that mediates a variety of enantioselective reactions of prochiral secondary lactams (Scheme 47).[112] Although lactams are only weakly Brønsted acidic (pK_a of 24), alternating donor−acceptor functionality on the auxiliary and substrate produces a strong dual hydrogen-bond interaction, reminiscent of those interactions that govern DNA-base pairing.[113]

The challenge to achieving efficient enantioselective catalysis in any photochemical reaction is that the photoexcited intermediate must undergo reaction only while associated to the catalyst. Bach and co-workers were able to achieve a solution to this problem by incorporating a photoelectron acceptor into the chiral lactam framework of **33** such that excitation of the bound substrate is faster than excitation of untemplated substrate due to the distance dependence of electron transfer. In the presence of 30 mol % **33b**, (pyrrolidinylethyl)quinolone underwent cyclization to form a spiro lactam in 64% yield and 70% ee (Scheme 48).[114] Further work will be necessary to ascertain whether the efficiency and enantioselectivity in this type of photocyclization can be improved and whether the approach represents a general strategy for enantioselective catalysis of photochemical reactions.

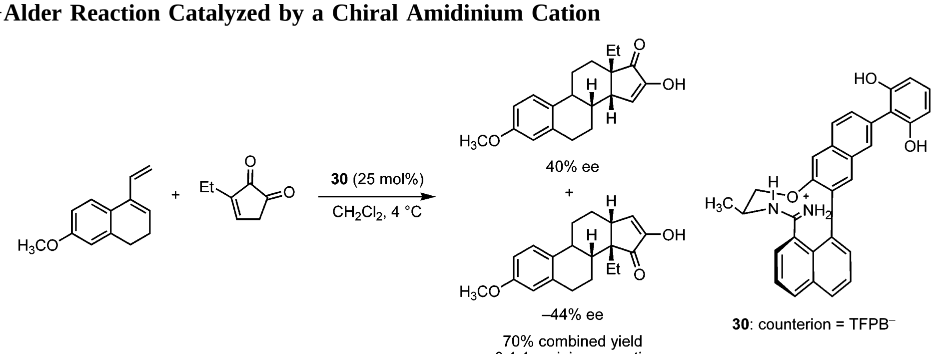
5. Other Michael Acceptors Including Nitroalkene Electrophiles[115]

5.1. Conjugate Addition of C-Centered Nucleophiles

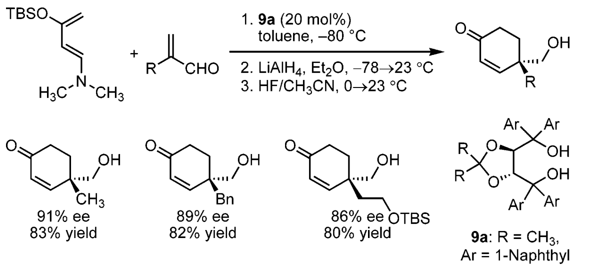
5.1.1. Malonate, Malononitrile, and β-Ketoester Nucleophiles

The versatility of the nitro group as a precursor to diverse functionality makes nitroalkenes attractive Michael acceptors for enantioselective 1,4-addition methodology.[116] The readily accessible cinchona alkaloid derivatives **Q-1** and **QD-1** have

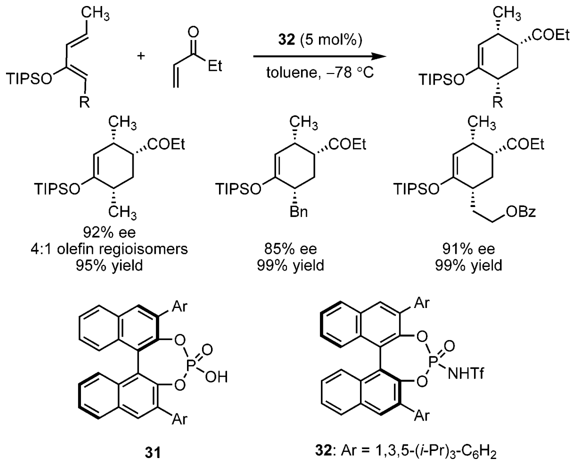
Scheme 44. Diels−Alder Reaction Catalyzed by a Chiral Amidinium Cation



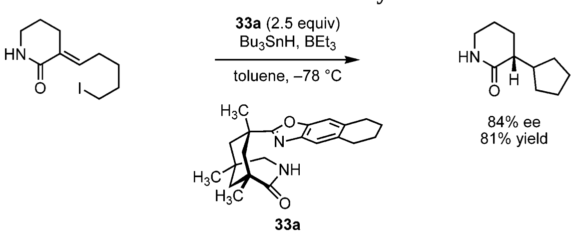
Scheme 45. TADDOL-Catalyzed Diels−Alder Cycloaddition



Scheme 46. Chiral Phosphoramide Catalyst



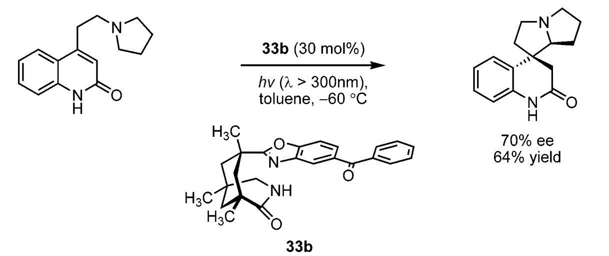
Scheme 47. Enantioselective Radical Cyclization



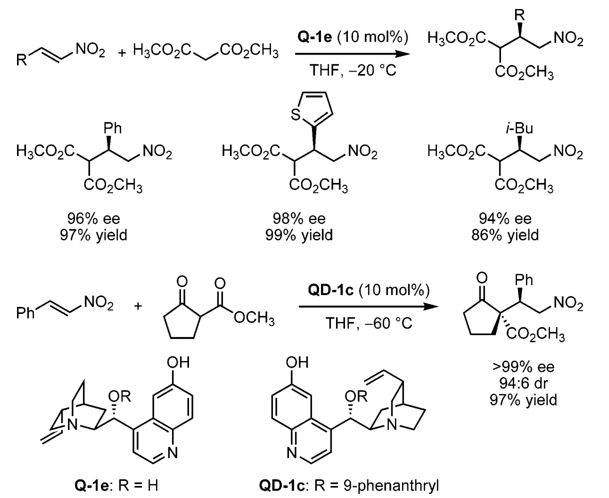
proven extremely versatile and effective for enantio- and diastereoselective conjugate addition reactions with structurally diverse nucleophile partners. The catalysts promote enantioselective conjugate additions of dimethyl malonate and ethyl acetoacetate to nitroalkenes bearing aryl, heteroaryl, and alkyl groups (Scheme 49).[117] Furthermore, efficient access to adjacent quaternary and tertiary stereocenters can be achieved through addition of substituted cyclic or acyclic β-ketoesters or α-cyanoacetate nucleophiles to aliphatic and aromatic nitroalkene partners in the presence of 10 mol % **QD-1c**.[118] Deng and co-workers also demonstrated that vinyl sulfones and α-chloroacrylonitrile are useful Michael acceptors with the same catalyst.[119] Reactions of trisubstituted nucleophiles with α-chloroacrylonitrile generate 1,3 tertiary−quaternary stereocenters with high catalyst control in both the conjugate addition and the protonation steps (Scheme 50). The utility of the method in the efficient generation of stereocomplex chiral building blocks was demonstrated in a concise formal total synthesis of the bromopyrrole alkaloid (−)-manzacidin A.[119b]

In 2003, Takemoto and co-workers reported the application of a tertiary amine−thiourea derivative **25** to the enantioselective addition of malonate esters to β-nitrostyrenes (Scheme

Scheme 48. Enantioselective Photocyclization Catalyzed by a Chiral Lactam



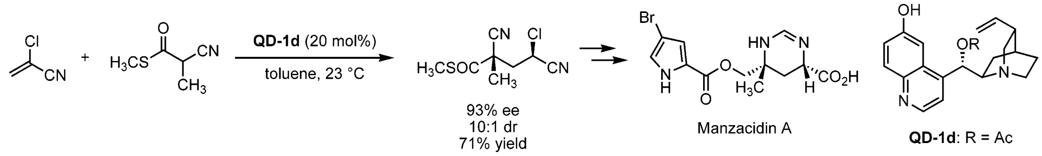
Scheme 49. Cinchona Alkaloid Derivatives as Catalysts for Enantioselective Nitroalkene Additions



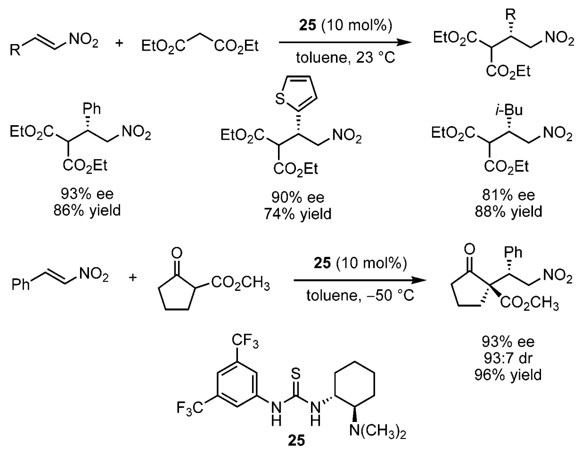
51).[84] In subsequent studies, a range of 1,3-dicarbonyl nucleophiles were shown to be compatible with the reaction conditions. Prochiral 1,3-dicarbonyl nucleophiles undergo C−C bond formation with the generation of adjacent tertiary and quaternary stereocenters in high enantio- and diastereoselectivity.[120] Additionally, γ,δ-unsaturated β-ketoesters undergo double Michael addition reactions, a transformation that was applied to the enantioselective synthesis of (−)-epibatidine (Scheme 52).[121] In these reactions, catalyst modification studies have revealed that both the thiourea and the tertiary amine moiety of the catalyst are necessary for reactivity and enantioselectivity.[122] Theoretical investigations conducted by Soós, Pápai, and co-workers support a dual activation mechanism of catalysis.[123] However, in contrast to qualitative models proposed by Takemoto and co-workers that involve electrophile activation through substrate binding to the thiourea,[84,120] the authors propose a reaction mechanism wherein the thiourea activates the deprotonated β-ketoester nucleophile and the protonated amino group of the catalyst activates the nitroalkene electrophile.

The presence of the thiourea moiety and its relative stereochemistry at C-8/C-9 were shown to be essential for the **28a**-catalyzed enantioselective conjugate addition of dimethyl and diethylmalonate to aryl, heteroaryl, and alkyl β-substituted nitroalkenes (Scheme 53).[124] Interestingly, the analogous C-9 quinine-derived catalyst proved to be substantially less enantioselective and reactive than **28a**. The catalyst is remarkably active and can be used in loadings as low as 0.5 mol % without compromising the efficiency or selectivity of the transformations. Connon and co-workers extended the methodology to a one-pot conjugate addition−cyclization reaction with dimethyl chloromalonate to generate enantioenriched nitrocyclopropanes as single diastereomers.[125]

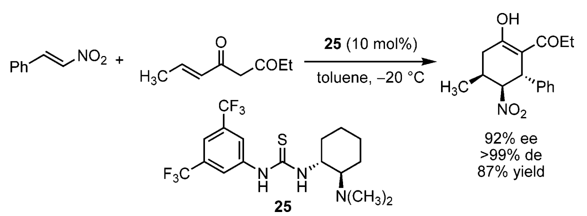
Scheme 50. Enantioselective Additions to α-Chloroacrylonitrile



Scheme 51. Enantioselective Conjugate Addition Reactions Catalyzed by a Tertiary Amine Thiourea



Scheme 52. Enantioselective Double Michael Addition



In comparison with chiral urea and thiourea derivatives, few examples have been identified thus far of chiral guanidinium ions participating successfully as dual H-bond donor chiral catalysts. Yet a number of features of guanidinium ions recommend their application as H-bond donor catalysts. In particular, in enzyme active sites the guanidinium moiety of arginine residues contributes to the stabilization of anionic reaction intermediates through electrostatic interactions and to substrate recognition through hydrogen bonding.[126] In host−guest chemistry, chiral guanidinium ions function as efficient anion receptors, including for enantioselective recognition of chiral guest molecules.[127] One challenge to the design of chiral guanidinium ion catalysts is that stereochemical elements can often only be introduced at sites remote from the planar active site. To address this challenge, Terada and co-workers prepared guanidine **34**, which contains an axially chiral binapthyl backbone that positions the 3 and 3′ aryl substituents in proximity to the catalyst active site. In 0.4−2 mol % loadings, guanidine **34** promotes addition of 1,3-dicarbonyl compounds, including α-substituted malonates, 1,3-diketones, and *β*-ketoesters, to conjugated aromatic and aliphatic nitroalkenes in high enantioselectivity (Scheme 54).[128] Catalyst **34** is proposed to both deprotonate the pronucleophile and activate the electrophile by dual H-bond donation. The guanidine catalyst can be recovered from the reaction mixture as its HCl salt, neutralized by basic resin, and reused without erosion in activity or enantioselectivity.

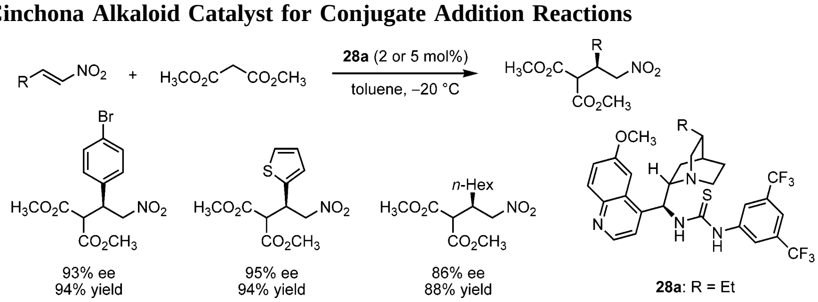
5.1.2. Aldehyde and Ketone Nucleophiles

The modified proline catalysts discussed in section 2.1 have also been applied to the direct addition of aldehydes and ketones to nitroalkenes. The proline-derived ammonium catalyst **5a** was shown by Barbas and co-workers to promote enantioselective additions of α,α-disubstituted aldehydes to *β*-nitrostyrene (Scheme 55).[129] Moderate syn diastereoselectivity was observed for the addition of racemic disubstituted aldehydes in the presence of 30 mol % **5**. Michael additions of ketones to *β*-nitrostyrenes with tetrazole catalyst **8** and its homoproline analogue **35** were found to be more enantioselective and display greater solvent scope relative to reactions catalyzed by proline itself.[24b,e,130]

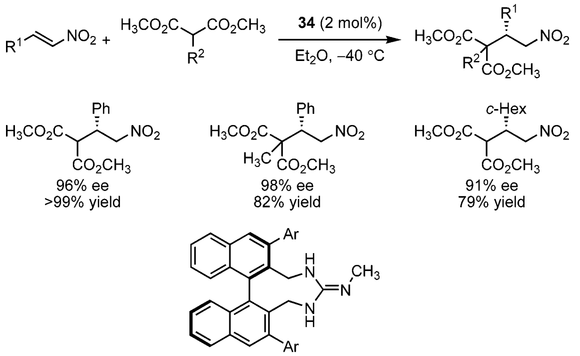
Primary amine-containing bifunctional thiourea catalysts have been identified recently for the direct addition of carbonyl nucleophiles to nitroalkenes. Primary amine catalysis is exploited in nature by enzymes such as type I aldolases that contain an active-site lysine residue.[131] Tsogoeva and Wei reported the primary amine−thiourea catalyst **36** for the addition of ketones to aromatic nitroalkenes (Scheme 56).[132] In the presence of **36**, addition of cycloalkanones to *β*-nitrosyrene generates syn adducts whereas addition of acyclic dialkylketones generates anti adducts, both in moderate diastereoselectivity and very high enantioselectivity. Computational studies support a mechanism involving nitroalkene activation by dual H-bond donation to a single oxygen atom of the nitro group in the transition state.[133]

In independent studies, Huang and Jacobsen discovered that primary amine **37a** catalyzes the addition of ketones to nitroalkenes. The catalyst displays a strong bias for activation of ethyl ketones, allowing highly regio- and anti-diastereoselective addition reactions of dialkyl ketones to *β*-alkyl and *β*-aryl nitroalkenes (Scheme 57).[134] Racemic α,α-disubstituted aldehydes also undergo conjugate addition to nitroalkenes in the presence of the closely related primary amine catalyst **37b**.[135] Nitroalkanes bearing adjacent quaternary and

Scheme 53. Thiourea−Cinchona Alkaloid Catalyst for Conjugate Addition Reactions

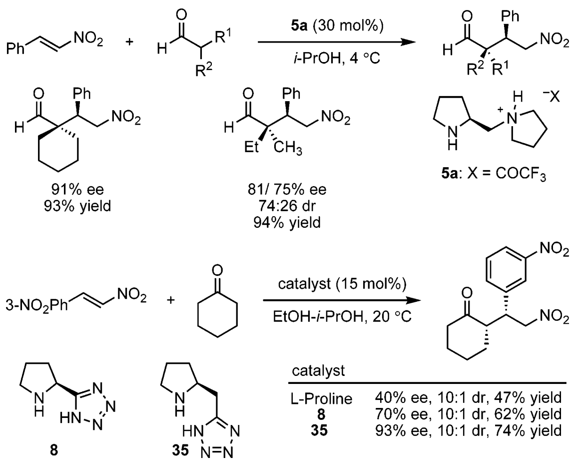


Scheme 54. Axially Chiral Guanidinium Catalysts for 1,3-Dicarbonyl Addition Reactions

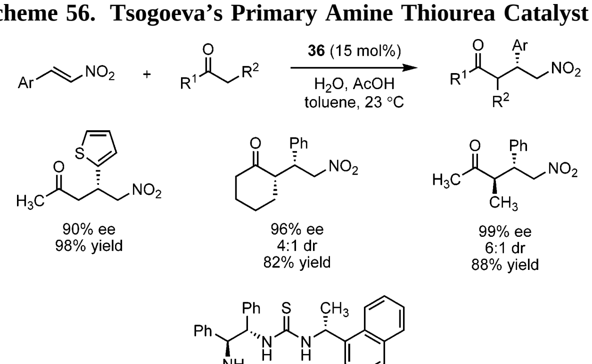


34: Ar = 3,4-bis(3,5-di-*tert*-butylphenyl)-phenyl

Scheme 55. Nitroalkene Additions Catalyzed by Proline Derivatives with Modified H-Bond Donors



Scheme 56. Tsogoeva's Primary Amine Thiourea Catalyst



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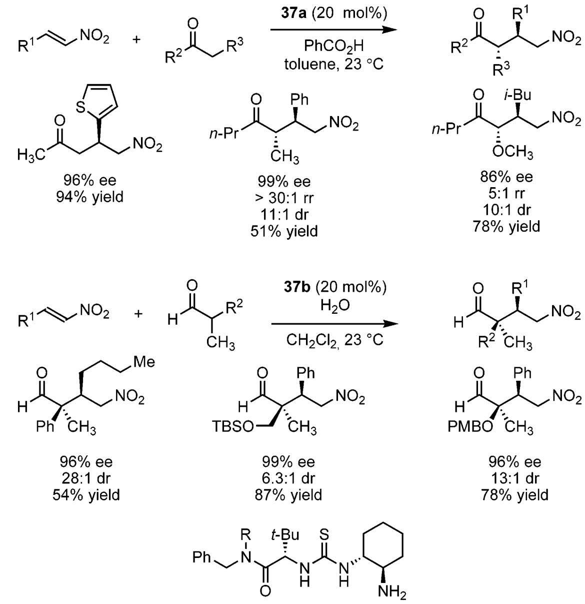
tertiary stereocenters can be prepared by this method in high enantioselectivity with excellent scope for both the nitroalkene and aldehyde partner. In all examples of primary amine-catalyzed conjugate addition reactions reported, added water or acid was observed to increase the rate of catalysis, likely serving to facilitate catalyst turnover by imine and enamine hydrolysis.

5.1.3. Indole

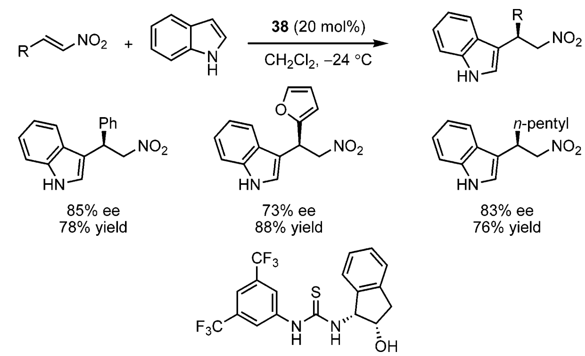
Bifunctional activation in the Friedel−Crafts addition of indoles to nitroalkenes has been examined by Ricci and coworkers with a catalyst **38** that contains both a thiourea and an adjacent hydroxy group (Scheme 58).[136] The optically active nitroalkane products were converted in a high-yielding reaction sequence to tryptamines and tetrahydro-β-carbolines without erosion in ee. Since only unprotected indoles

Scheme 57. Jacobsen's Thiourea Primary Amine Catalysts



37a: R = CH_3
37b: R = H

Scheme 58. Enantioselective Friedel−Crafts Addition of Indoles



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underwent reaction in good enantioselectivity, the authors proposed that the role of the hydroxy group may be to activate the nucleophile by accepting a H-bond from the indole N−H.

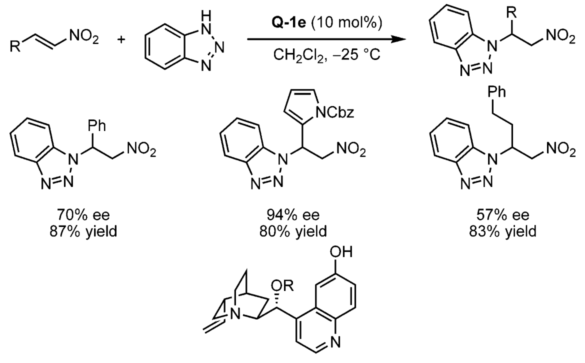
5.2. Conjugate Addition of *N*-Centered Nucleophiles

Wang and co-workers reported that weakly nucleophilic *N*-heterocycles, such as benzotriazole, triazole, and tetrazole, participate in catalytic conjugate addition reactions with nitroalkenes.[137] The reaction is catalyzed by cinchona alkaloid derivative **Q-1e** to give *N*-heterocyclic products in good enantioselectivities (Scheme 59).

6. Imine Electrophiles

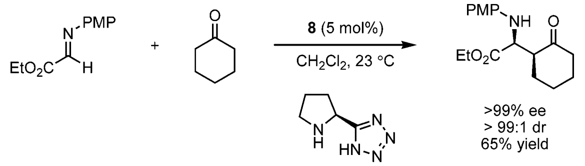
Compared to carbonyl compounds, imines are relatively strong and directional H-bond acceptors and therefore among the best potential substrates for enantioselective H-bond donor catalysis. It is therefore not surprising that the majority of applications of asymmetric H-bonding catalysis have been in the context of nucleophilic addition to imines. This work has led to an impressive variety of synthetically useful nucleophile−electrophile reactions.

Scheme 59. Enantioselective Addition of *N*-Heterocycles to Nitroalkenes



Q-1e: R= H

Scheme 60. Proline Tetrazole Catalyst for Enantioselective Mannich Reactions



8

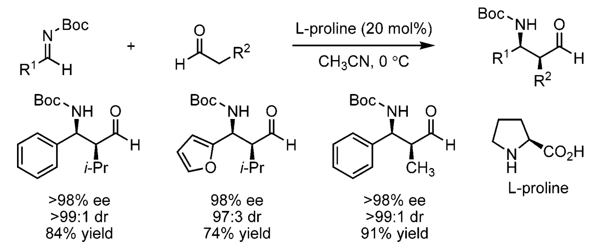
6.1. Additions of Enolates and Derivatives

6.1.1. Mannich Reaction[138]

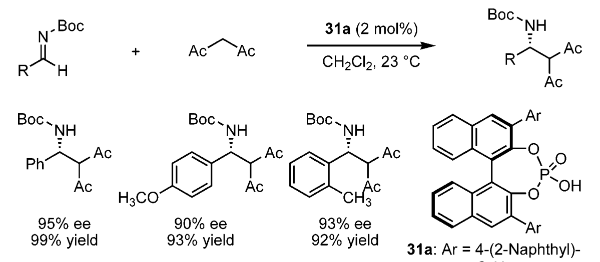
The Mannich reaction—addition of enolate equivalents to imines—represents one of the most powerful methods for accessing chiral β-amino carbonyl compounds. Shortly after their discovery that proline catalyzes direct aldol reactions of acetone and aldehydes, List and co-workers reported the application of proline catalysis to enantioselective Mannich reactions of *N*-aryl imines.[139] Proline catalysts with modified H-bond donating components have subsequently been investigated for the transformation. For example, the tetrazole-modified proline catalyst **8** has found application in the direct Mannich reaction of *N*-aryl imines in organic solvents wherein L-proline is insoluble and unreactive. Catalyst **8** promotes addition of cyclohexanone to *N*-PMP α-imino ethyl glyoxalate in dichloromethane in 65% yield and >99% ee (Scheme 60).[24e,27c] A practical limitation to methods with *N*-aryl imines is that strong oxidative or reductive conditions are often necessary for product amine deprotection. *N*-Carbamoyl imines, on the other hand, are particularly attractive reaction partners for the Mannich reaction because the addition products are obtained in a usefully protected form. Recently, List and Enders independently identified conditions wherein *N-tert*-butoxycarbonyl (*N*-Boc) imines undergo proline-catalyzed Mannich reactions in high diastereo- and enantioselectivity (Scheme 61).[140]

In 2004, the research groups of Akiyama and Terada independently reported the discovery and development of chiral phosphoric acids as chiral Brønsted acid catalysts in the context of the Mannich reaction of *N*-aryl and *N*-Boc imines. Terada and co-workers described that phosphoric acid **31a** catalyzes the direct Mannich reaction of para- and ortho-substituted aromatic *N*-Boc aldimines with acetyl acetone in 90−98% ee (Scheme 62).[141] Remarkable activity was observed with this class of H-bond donor catalyst: reactions run with 1 mol % **31a** are complete within 2 h, and the catalyst can be recovered in over 80% yield. A related catalyst **31b** was employed in loadings as low as 0.05 mol % in the highly enantioselective addition of enecarbamates to aromatic *N*-benzoyl imines in a formal aza−ene reaction (Scheme 63).[142] The β-amino-imine products can be readily transformed to *anti*-1,3-diamine derivatives by reduction with Red-Al.

Scheme 61. Proline-Catalyzed Mannich Reaction of *N*-Boc Imines

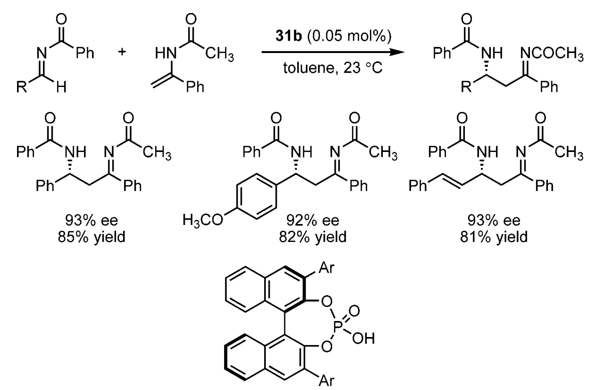


Scheme 62. Phosphoric-Acid-Catalyzed Direct Mannich Reaction



31a: Ar = 4-(2-Naphthyl)-C_6H_4

Scheme 63. Enantioselective Aza−Ene Reaction

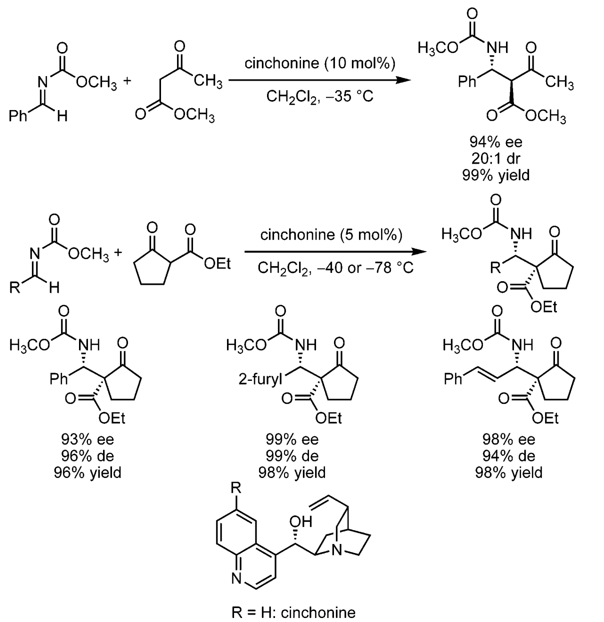


31b: Ar = 9-anthryl

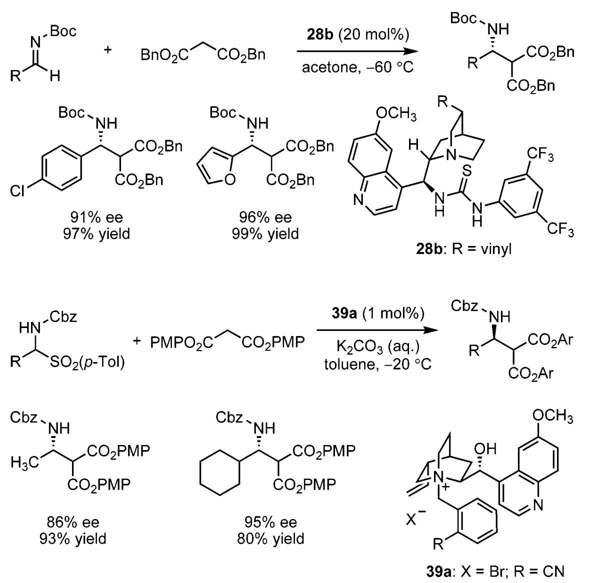
Malonates and β-ketoesters are attractive nucleophiles for direct Mannich reactions because the products that result can be readily transformed into enantioenriched β-amino acid derivatives. Schaus and co-workers reported highly enantioselective cinchonine and cinchonidine-catalyzed diastereoselective Mannich reactions of β-keto esters with aryl methyl carbamate imines.[143] The researchers subsequently expanded the scope of the reaction to include cyclic α-substituted β-keto esters as nucleophiles (Scheme 64).[144] The reaction provides a catalytic method for the construction of cyclic β-amino esters with α-quaternary stereogenic centers in high diastereo- and enantioselectivity.

Quinine-derived thiourea derivatives and quaternary ammonium salts derived from cinchona alkaloids have also been shown to catalyze direct Mannich reaction of β-dicarbonyl compounds. Deng and co-workers reported that high enantioselectivity was obtained for a variety of heteroaryl and aryl *N*-Boc imines of varying electronic properties with dibenzyl malonate (Scheme 65).[145] The method was applied successfully to alkyl *N*-Boc imines, albeit with stoichiometric

Scheme 64. Mannich Reactions Catalyzed by Cinchona Alkaloids



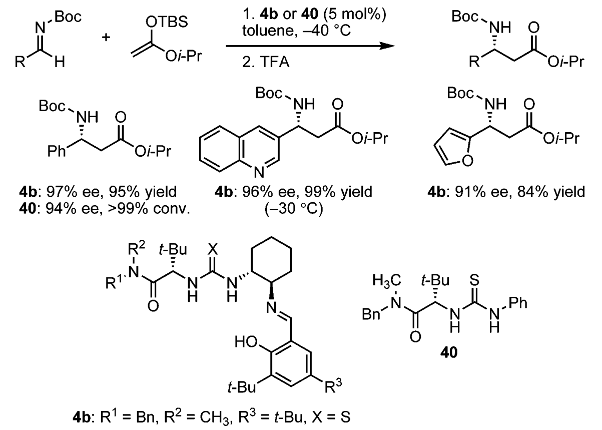
Scheme 65. Enantioselective Mannich Reaction Catalyzed by Cinchona-Derived Catalysts



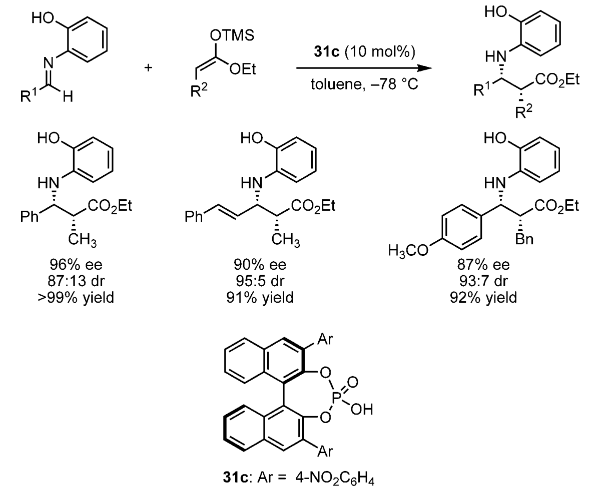
amounts of catalyst. Ricci and co-workers investigated α-amido sulfones derived from aliphatic aldehydes as precursors to aliphatic *N*-carbamoyl imines in phase-transfer-catalyzed direct Mannich reactions with malonate nucleophiles.[146]

In 2002, a thiourea catalyst **4b** was identified by Jacobsen and Wenzel for the Mannich reaction of silyl ketene acetals and *N*-Boc aldimines (Scheme 66).[147] This Mannich methodology allows ready access to Boc-protected β-amino acid derivatives from aromatic Boc aldimines. Ortho-, meta-, and para-substituted arylimines are excellent substrates for the reaction, and the catalyst is tolerant of Lewis-basic substrates such as thienyl and pyridyl imines, which are often poor substrates for metal-centered Lewis-acid catalysts. A systematic investigation of the catalyst structure−enantioselectivity profile in the Mannich reaction revealed that a significantly simplified thiourea **40** displays comparable reactivity and enantioselectivity to catalyst **4b**.[148]

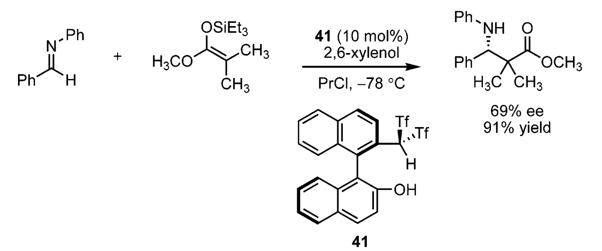
Scheme 66. Thiourea-Catalyzed Mannich Reaction of *N*-Boc Imines



Scheme 67. Phosphoric-Acid-Catalyzed Addition of Silyl Ketene Acetals to *N*-Aryl Imines



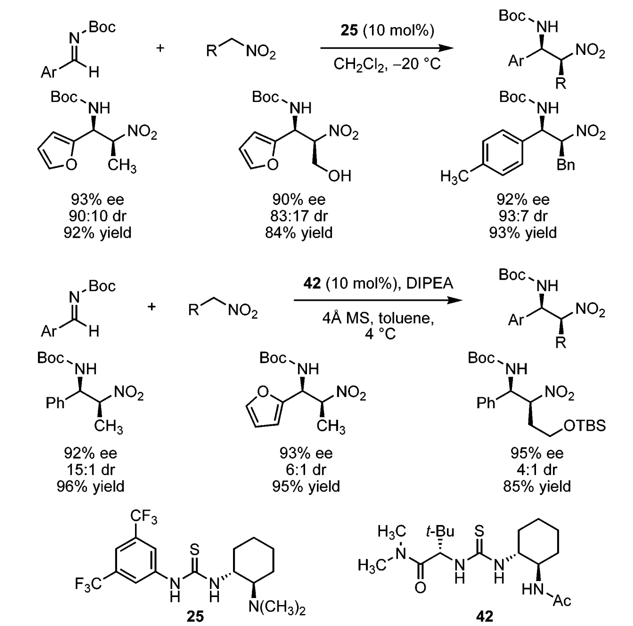
Scheme 68. BINOL Derivative as an Asymmetric Catalyst for the Mannich Reaction



The first report of chiral phosphoric-acid catalysis from Akiyama and co-workers identified phosphoric-acid **31c** as an enantioselective catalyst for the addition of silyl ketene acetals to aromatic and α,β-unsaturated *N*-aryl imines (Scheme 67).[149] The researchers subsequently discovered that a TADDOL-derived phosphoric acid also catalyzes the transformation.[150] The *ortho*-hydroxy group of the *N*-aryl aldimine substrates was found to be essential for enantioselectivity in these Mannich reactions, suggesting that the electrophile binds through simultaneous H-bond donor and acceptor interactions to the phosphoric-acid catalyst.

A novel H-bond donor catalyst **41** was identified by Yamamoto and co-workers for Mannich reactions of silyl ketene acetals with *N*-aryl and *N*-alkyl aldimine substrates (Scheme 68).[151] Like BINOL catalysts, **41** is characterized by a binapthol-derived chiral backbone and has the potential

Scheme 69. Enantioselective Nitro-Mannich Reactions



for intramolecular H-bonding to the phenol functional group. However, the researchers suggest that the greater acidity of the bis(trifluoromethanesulfonyl)methyl group of **41** relative to a BINOL might allow for catalysis of otherwise unexplored transformations.

6.1.2. Nitro Mannich Reaction[152]

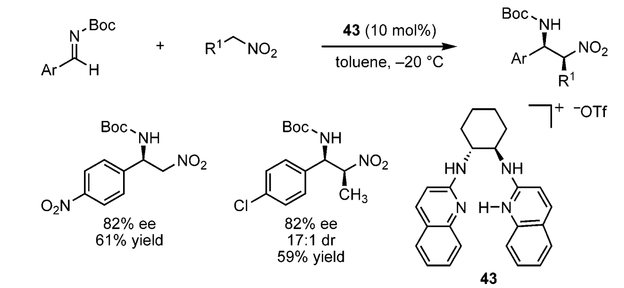
Addition of nitroalkanes to imines, known as the nitro-Mannich (or aza-Henry) reaction, allows access to vicinal diamines and α-amino carbonyl compounds by straightforward synthetic manipulations of the resulting products. Since 2004, several small-molecule H-bond donors have been identified for catalytic asymmetric versions of the transformation. Interestingly, most of these catalysts contain a thiourea dual H-bond donor and a tertiary amine Brønsted base. While it is likely that the tertiary amine serves to deprotonate the nitroalkane to generate the active nucleophile, the role of the thiourea is more uncertain since thioureas are known to bind to and modulate the reactivity of neutral carbonyl derivatives as well as nitronate anions.[5,6,7,153]

The Takemoto thiourea-tertiary amine catalyst **25** has been applied to the addition of nitroalkanes to aromatic *N*-phosphinoyl and *N*-Boc imines (Scheme 69).[154] Good diastereoselectivity in favor of the syn product is observed with nitroethane, and remarkable scope is observed with nitroalkanes bearing aryl, alcohol, ether, and ester functionality. Comparable enantioselectivities to those obtained with the Takemoto catalyst are observed with acetamide thiourea catalyst **42**, which promotes addition of nitroalkanes to aromatic *N*-Boc imines with high enantio- and diastereoselectivity for the syn adducts.[155] Good enantioselectivities are also observed with thiourea cinchona alkaloid catalyst **28b** for addition of nitromethane to aryl *N*-Boc imines.[156]

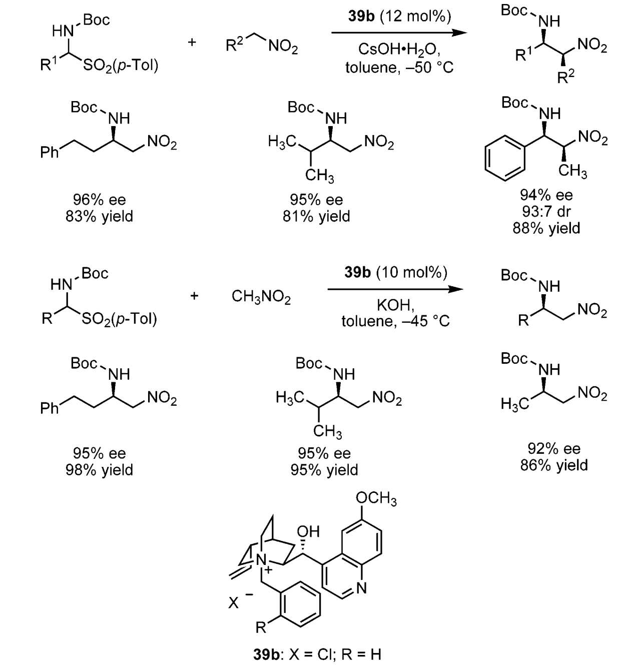
Johnston and co-workers applied the chiral bisamidine triflic acid salt **43** to the enantioselective addition of nitromethane to electron-deficient aromatic *N*-Boc imines (Scheme 70).[157] The catalyst was synthesized from *trans*-diaminocyclohexane and 2-chloroquinoline using palladium catalysis and determined to have a pK_a value of 5.78 in DMSO by Perrin's NMR titration procedure.[15d]

The aza-Henry reactions mentioned above are restricted to aromatic imines, a consequence at least in part of the instability of *N*-carbamoyl imines derived from enolizable aldehydes. α-Amido sulfones, on the other hand, can serve as bench-stable in situ precursors to aliphatic enolizable imines. In 2005, the groups of Palomo and Ricci independently reported that *N*-benzyl quininium chloride **39b** is a competent catalyst for the enantioselective addition of nitromethane to α-amido sulfones under phase-transfer conditions (Scheme 71).[158] High enantioselectivities and good yields can be obtained with linear and branched aliphatic electrophiles. Moreover, high syn-diastereoselectivities are observed for nitroethane addition. Palomo and co-workers found that catalysts with *O*-alkylated C-9 hydroxyl groups were significantly less reactive than those containing a free hydroxyl group, suggesting the possibility of H-bonding as a mechanism of activation.

Scheme 70. Amidinium-Catalyzed Enantioselective Nitro-Mannich Reaction



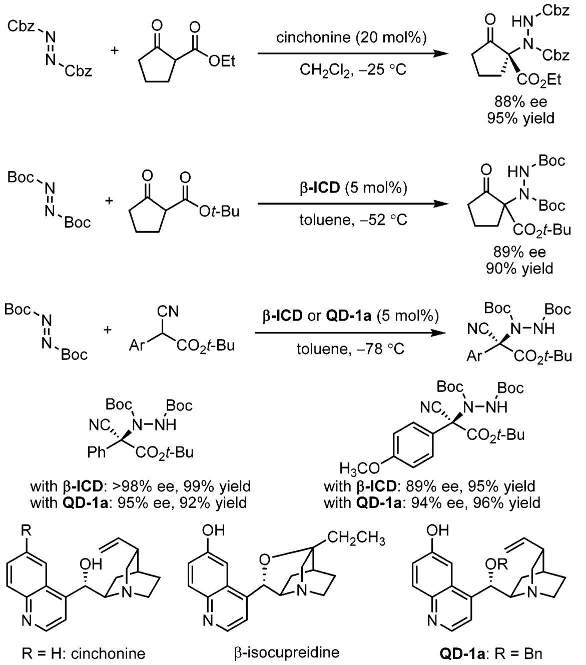
Scheme 71. Quininium-Catalyzed Aza-Henry Reactions of α-Amido Sulfones



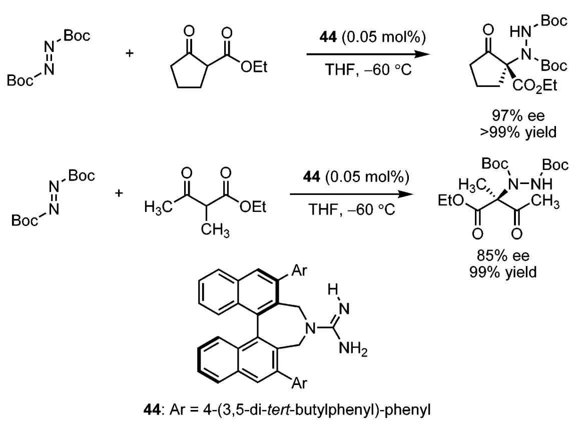
6.1.3. α-Hydrazination of Carbonyl Compounds

Electrophilic α-hydrazination of carbonyl compounds using azodicarboxylates is an efficient approach to the generation of nitrogen-bearing stereogenic centers from readily accessible racemic or prochiral precursors. Cinchonine, β-isocupreidine, as well as Deng's 6-OH modified cinchona alkaloid derivatives have been shown to promote direct α-hydrazinations of α-substituted-β-ketoesters and α-aryl-α-cyanoacetates (Scheme 72).[159] Reductive N−N bond cleavage of the hydrazine products provides access to tertiary

Scheme 72. Hydrazinations by Modified Cinchona Alkaloid Derivatives



Scheme 73. Axially Chiral Guanidine for α-Hydrazination of *β*-Ketoesters



α-amino carboxylic acid derivatives in highly enantioenriched form. Jørgensen and co-workers also reported atropselective hydrazination of activated 2-naphthols using dihydrocupreidine as a catalyst.[160]

Terada and co-workers developed the axially chiral guanidine **44** that, when protonated, generates a C_2-symmetric guanidinium ion. Guanidine **44** catalyzes enantioselective aminations of α-monosubstituted *β*-ketoesters and 1,3-diketones with di-*tert*-butyl azodicarboxylate with catalyst loadings as low as 0.05 mol % (Scheme 73).[161] Both acyclic and cyclic malonates undergo reaction with high enantioselectivity in the presence of **44**, albeit with opposite sense of stereoinduction. The authors attributed the change in stereochemical outcome to two different modes of dual hydrogen bonding of the malonate derivatives to the guanidinium ion.

L-Proline has been identified as a highly effective catalyst for enantioselective amination of linear aldehydes and α-aryl branched aldehydes, but reactions of α,α-dialkyl aldehydes proved less successful.[162] Barbas and co-workers found that tetrazole proline analogue **8** is considerably more enantioselective and reactive than proline for the amination of these challenging substrates with dibenzyl azodicarboxylate and used the transformation in a total synthesis of the cell adhesion inhibitor BIRT-377 (Scheme 74).[163,164]

6.1.4. Aza-Baylis–Hillman Reaction[165]

Highly functionalized allylic amines can be obtained from the aza-Baylis–Hillman reaction of activated alkenes with imines catalyzed by Lewis bases. Excellent enantioselective systems based on cinchona alkaloid-derived catalysts have been reported independently by Shi, Adolfsson, and Hatakeyama for the asymmetric version of this transformation with enone substrates. The demonstrated ability of cinchona alkaloid-derived catalysts to promote both Baylis–Hillman (section 2.3) and aza-Baylis–Hillman reactions highlights the impressive generality of this class of catalyst for enantioselective nucleophile–electrophile reactions. Shi and co-workers reported high enantioselectivity for the reaction of aryl *N*-Ts imines with methyl vinyl ketone catalyzed by *β*-isocupreidine.[166] Highest selectivities are observed with electron-rich benzaldimine electrophiles. A novel BINOL aminopyridine catalyst **45** has been reported for the aza-Morita–Baylis–Hillman reaction of methyl vinyl ketone and aromatic *N*-Ts imines that provides a comparable level of asymmetric induction to reactions catalyzed by *β*-isocupreidine (Scheme 75).[167]

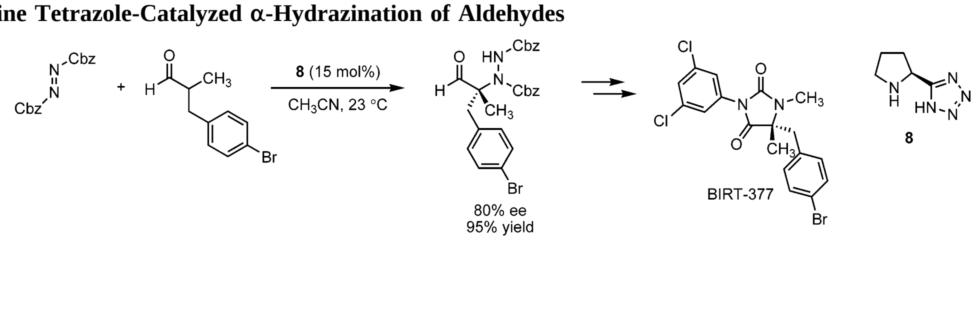
Reactions with methyl acrylate catalyzed by *β*-isocupreidine were described by Shi to be sluggish and only moderately enantioselective.[166a] On the other hand, aza-Baylis–Hillman reactions with hexafluoroisopropyl acrylate as the activated alkene partner proceed in high yield with aryl *N*-phosphinoyl imines.[168] *β*-Isocupreidine also participates in a one-pot, three-component aza-Baylis–Hillman reaction with benzaldehydes, tosylamine, and methyl acrylate in the presence of 2 mol % Ti(O-*i*-Pr)$_4$ (Scheme 76).[169]

Jacobsen and co-workers reported that thiourea catalyst **4b**, initially developed for the Mannich reaction of *N*-Boc imines and silyl ketene acetals (section 6.1.1), is optimal for the aza-Baylis–Hillman reaction of aromatic *N*-*p*-nitrobenzenesulfonylimines with methyl acrylate in the presence of DABCO.[170] The method provides unprecedented levels of enantioselectivity in reactions of acrylate derivatives, albeit in moderate yield (Scheme 77).

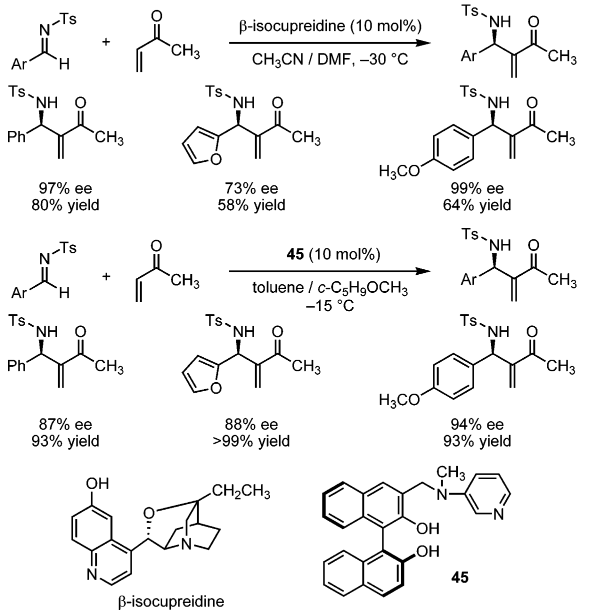
6.1.5. Biginelli Reaction

The Biginelli reaction, the multicomponent coupling of an aldehyde, (thio)urea, and *β*-ketoester, offers an efficient route to the preparation of 3,4-dihydropyrimidin-2-(1*H*)-ones

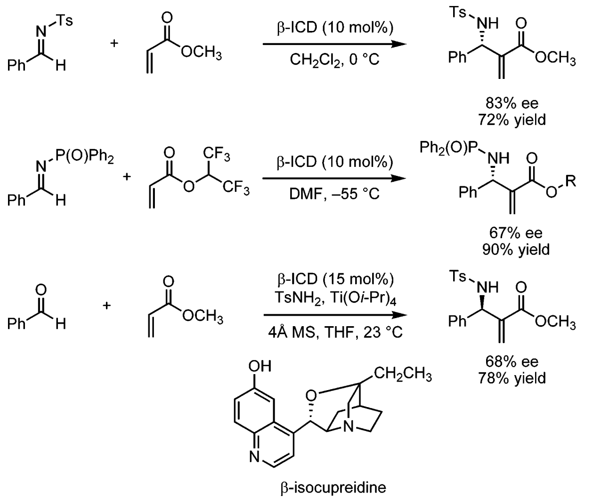
Scheme 74. Proline Tetrazole-Catalyzed α-Hydrazination of Aldehydes



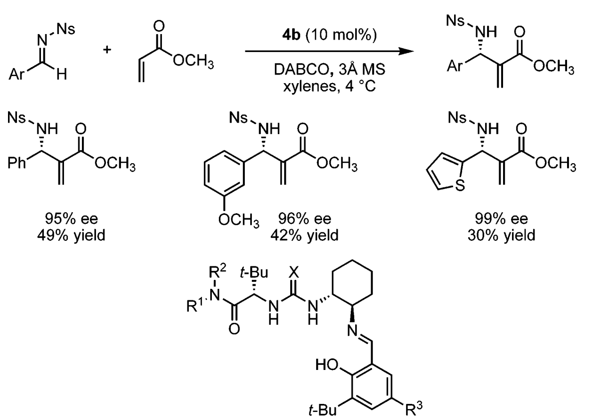
Scheme 75. Aza-Baylis−Hillman Reactions of *N*-Ts Imines



Scheme 76. Aza-Baylis−Hillman Reactions of Acrylates



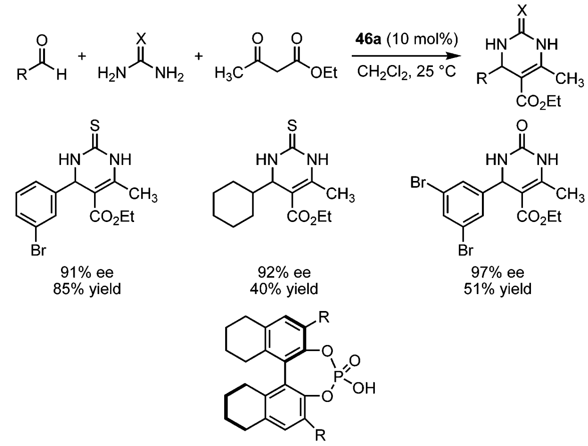
Scheme 77. Thiourea-Catalyzed Aza-Baylis−Hillman Reaction



4b: R^1 = Bn, R^2 = CH_3, R^3 = *t*-Bu, X = S

and related heterocyclic compounds. The reaction was originally reported to be catalyzed by Brønsted acids, where an *N*-acyliminium ion, generated in situ from the aldehyde and (thio)urea, undergoes electrophilic addition to the β-ketoester.[171] Despite the important position this reaction holds in heterocycle and diversity-oriented synthesis, the first examples of asymmetric catalytic Biginelli reactions were discovered only very recently. Gong and co-workers reported that H8-BINOL-based phosphoric acid **46a** catalyzes the reaction of aldehydes, ethylacetoacetate, and (thio)urea in high enantioselectivity (Scheme 78).[172]

Scheme 78. Phosphoric-Acid-Catalyzed Biginelli Reaction



6.1.6. Acyl-Mannich Reaction

N-Acyliminium ions generated in situ from an imine and an acylating agent have been subject to chiral catalyst-controlled Mannich reactions. The Jacobsen group reported recently that pyrrole-containing thiourea catalyst **47a** promotes addition of silyl ketene acetals to isoquinolines in the presence of 2,2,2-trichloroethyl chloroformate (Scheme 79).[173] The dihydroisoquinoline products were prepared in 60−92% ee and can be converted in a two-step process without racemization to 1-substituted tetrahydroisoquinoline derivatives.

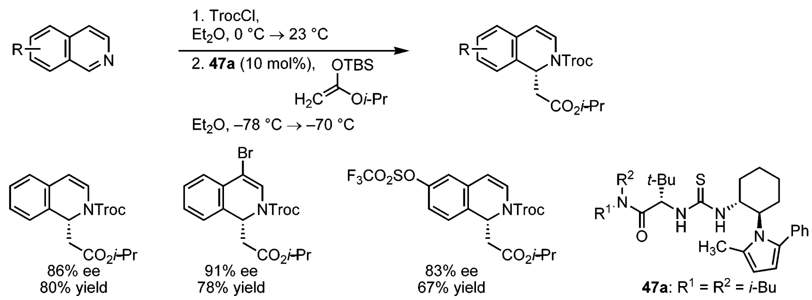
6.2. Friedel–Crafts Addition[60a]

6.2.1. Acyl-Pictet–Spengler Reaction

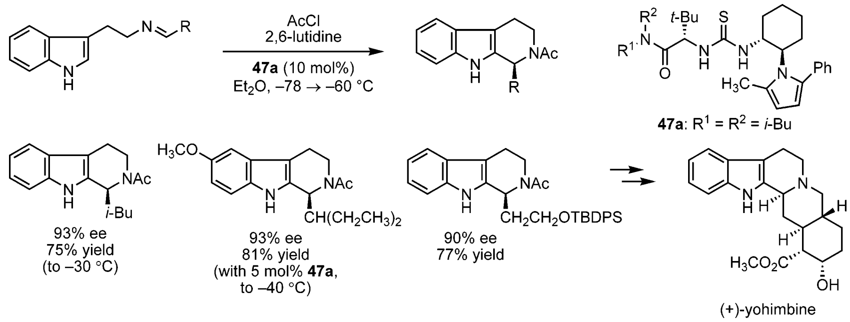
The acyl-Pictet−Spengler reaction, cyclization of electron-rich aryl or heteroaryl groups onto *N*-acyliminium ions, is a widely used method for the synthesis of tetrahydro-β-carbolines and tetrahydroisoquinolines. The Jacobsen group discovered that pyrrole-containing thiourea **47a** promotes the intramolecular addition of indoles to *N*-acyliminium ions generated in situ from imines and acetyl chloride (Scheme 80).[175] This thiourea-catalyzed acyl-Pictet−Spengler reaction has been used as an early and key step in an enantioselective total synthesis of the indole alkaloid (+)-yohimbine.[176]

Formal dehydration of hydroxylactams provides an alternative synthetic route to *N*-acyliminium ions. Jacobsen and co-workers have shown that hydroxylactams, in the presence of 2.0 equiv of TMSCl as a dehydrating agent, are substrates for thiourea **47b**-catalyzed enantioselective Pictet−Spengler cyclizations (Scheme 81).[177] Hydroxylactams prepared by imide alkylation undergo cyclization under even more facile reaction conditions than hydroxylactams prepared by imide reduction. These cyclizations generate highly enantioenriched products with fully substituted stereogenic centers. In order to explain the reactivity and enantioselectivity observed with thiourea **47**-catalyzed additions to *N*-acyliminium ions, the Jacobsen group proposed that the thiourea catalyst binds to the chloride counteranion of the charged electrophile. This

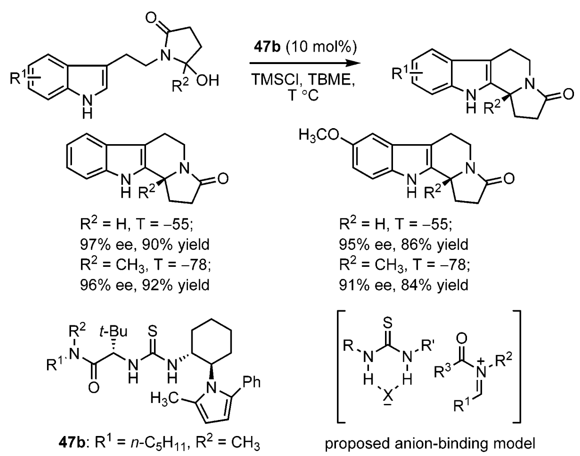
Scheme 79. Pyrrole Thiourea-Catalyzed Addition to *N*-Acyliminium Ions



Scheme 80. Pyrrole Thiourea-Catalyzed Acyl-Pictet−Spengler Reaction



Scheme 81. Pyrrole Thiourea-Catalyzed Cyclization of Hydroxylactams



proposal is consistent with the substitution and pronounced halide counteranion effects observed in the acyl-Pictet−Spengler and acyl-Mannich reactions (section 6.1.6). Anion binding by thioureas is well known in the context of biological and supramolecular systems.[127a,178]

6.2.2. Pictet–Spengler Reaction

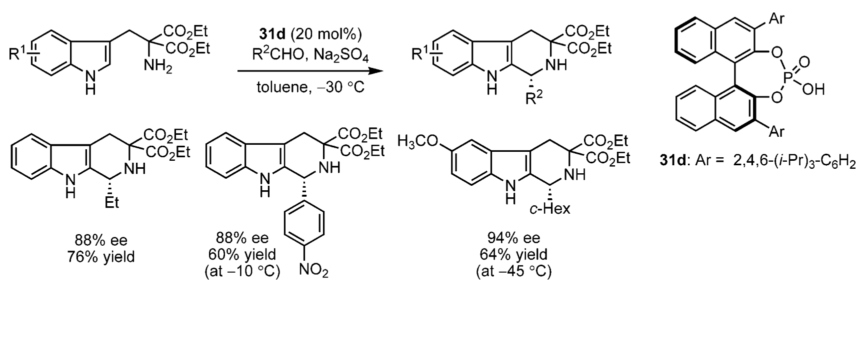
Recently, List and co-workers discovered that phosphoric-acid **31d** catalyzes the Pictet−Spengler cyclization of tryptamines with aliphatic and aromatic aldehydes (Scheme 82).[179] Electronically and conformationally biased tryptamines bearing gem-diester groups were found to undergo cyclization in the presence of 20 mol % **31d**, whereas simple tryptamine or phenethylamine-derived imines did not afford this desired cycloadducts. Highly enantioenriched tetrahydro-β-carbolines are generated from both aliphatic and aromatic aldehydes.

6.2.3. Intermolecular Additions

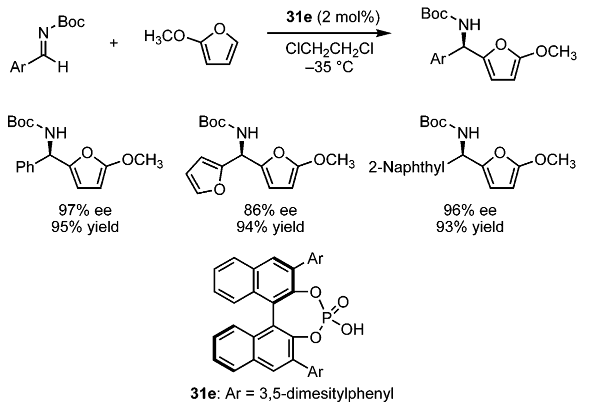
In a reaction related mechanistically to the Mannich reaction, Terada demonstrated that binapthyl monophosphoric-acid **31e** catalyzes addition of 2-methoxyfuran to electron-rich and electron-poor aromatic *N*-Boc aldimines in high yield and enantioselectivity.[180] The reaction can be performed on a gram scale with catalyst loadings as low as 0.5 mol %, and the catalyst can be easily recovered and reused (Scheme 83). The researchers further demonstrated the synthetic utility of the transformation by elaborating the furan-containing products to γ-butenolides in a two-step high-yielding sequence.

The mechanism for direct alkylation of diazoacetates via C−H bond cleavage of *N*-protected aldimines shares similarities to the mechanism for the Friedel−Crafts addition reaction of furans with the same electrophiles. Terada and co-workers found that reaction of *tert*-butyl diazoacetate and an aryl *N*-benzoyl imine with catalytic phosphoric-acid **31b** led to formation of highly enantioenriched α-diazo-β-amino

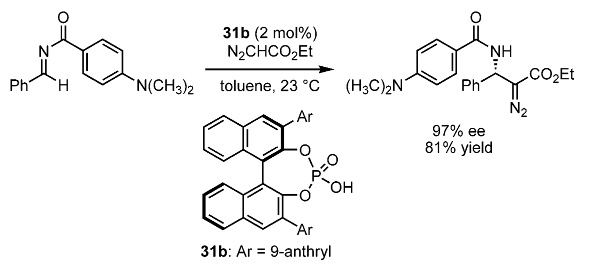
Scheme 82. Phosphoric-Acid-Catalyzed Pictet−Spengler Reaction



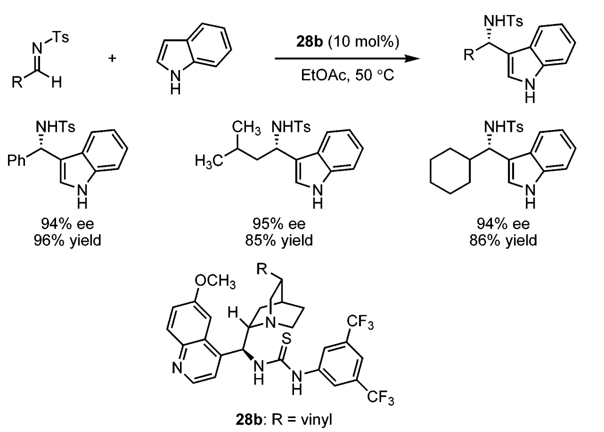
Scheme 83. Enantioselective Addition of 2-Methoxyfuran to *N*-Boc Imines



Scheme 84. Enantioselective Synthesis of α-Diazo-β-amino Esters



Scheme 85. Friedel−Crafts Addition of Indoles to Imines



acids (Scheme 84).[181] The diazo functional group can be readily reduced or oxidized to provide β-amino acid derivatives in high optical purity. A model for bifunctional activation by the phosphoric-acid catalyst has been proposed. Terada suggests that the phosphoric acid protonates the *N*-benzoyl imine electrophile and that the resulting phosphate anion serves to deprotonate the diazo ester−imine adduct, thereby preventing aziridine formation, a pathway often seen under Lewis-acid-catalyzed conditions.

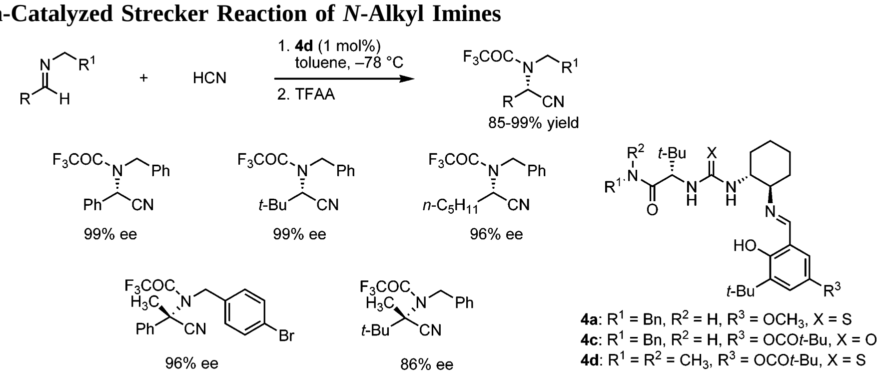
The enantioselective Friedel−Crafts addition of indoles to imines represents a powerful C−C bond-forming reaction for the stereoselective construction of indole-containing natural products. Deng and co-workers investigated thiourea **28b** for the transformation with aromatic and aliphatic *N*-Ts imines (Scheme 85).[182] Uniformly high enantioselectivity is observed for an impressive range of indole and imine reaction partners. Deng's 6′-OH catalysts **QD-1** and quinidine were both significantly less reactive for the Friedel−Crafts transformation than **28b**, highlighting the efficacy of the thiourea for electrophile activation via dual H-bond donation.

6.3. Strecker Reaction[63,183]

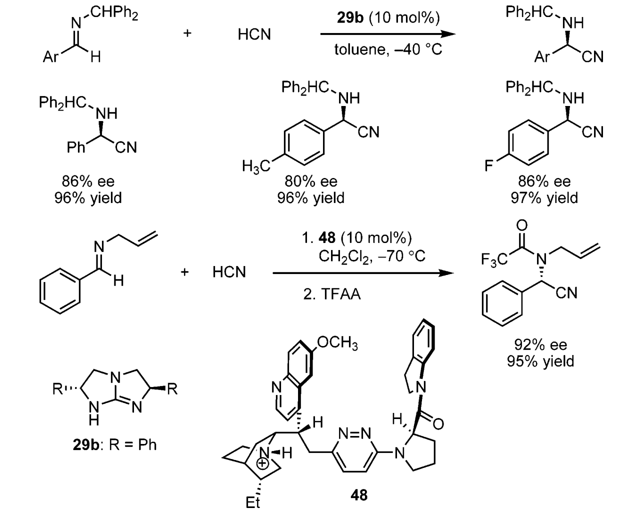
In 1998, the Jacobsen group reported that thiourea Schiff base **4a** promotes the highly enantioselective Strecker reaction of *N*-allyl imines (Scheme 6).[11] The thiourea catalyst **4a** was discovered through a combinatorial library synthesis of potential tridentate Schiff base ligands for a metal-catalyzed Strecker reaction. In evaluating the ligands in the absence of metal cocatalysts, urea derivatives with the general structure **4** were observed to induce good reactivity and moderate levels of asymmetric induction. Systematic optimization led to identification of **4a** and subsequently of **4c** and **4d** as remarkably general catalysts for the Strecker reaction.[12,184] With catalyst loadings as low as 0.1 mol %, catalyst **4d** promotes addition of HCN to aliphatic and aromatic aldimines as well as to methylketimines in high enantiomeric excess (Scheme 86). Furthermore, the catalyst can be reused without loss of either activity or enantioselectivity, and the catalyst can be immobilized on a polystyrene bead to facilitate Strecker product purification by simple filtration and solvent removal without impacting the enantioselectivity of the reaction. A very recent investigation by List and co-workers identified a related thiourea Schiff-base catalyst for acylcyanation of *N*-benzyl imine derivatives.[185]

The first highly enantioselective example of catalysis by synthetic chiral guanidinium derivatives was reported by Corey and Grogan in 1999 in the context of the Strecker reaction of aldimines.[186] The researchers demonstrated that C_2-symmetric bicyclic guanidine **29b**, previously studied in the context of phase-transfer catalysis, catalyzes the addition of HCN to *N*-benzhydrylimines in 50−88% ee at 10 mol % loading (Scheme 87). Access to aryl glycine derivatives is possible from the enantioenriched aminonitrile products by cleavage of the benzhydryl protecting group and hydrolysis of the nitrile functionality without erosion in enantioselec-

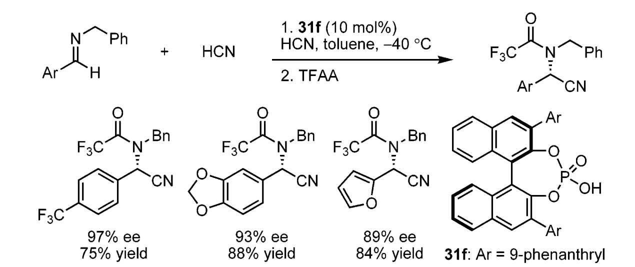
Scheme 86. Thiourea-Catalyzed Strecker Reaction of *N*-Alkyl Imines



Scheme 87. Guanidinium and Ammonium Catalysts for the Strecker Reaction



Scheme 88. Enantioselective Strecker Reaction Catalyzed by a Phosphoric Acid



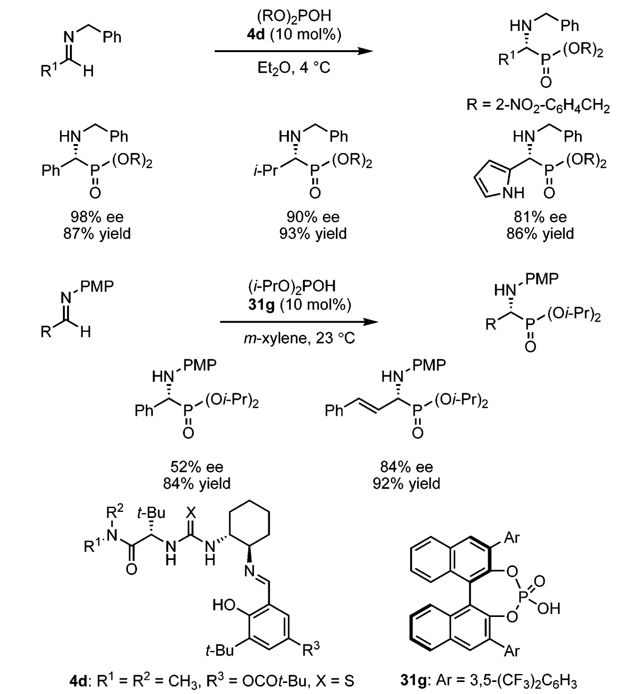
tivity. Enantioselective access to α-amino nitriles has also been accomplished with ammonium catalyst **48**, which promotes the Strecker reaction of aromatic *N*-allyl imines.[187] Catalyst **48**, derived from a bis-cinchona alkaloid ligand for osmium-catalyzed dihydroxylations, contains a protonated quinuclidine moiety for H-bond activation of the imine substrate.

Aromatic *N*-benzyl aldimines are substrates for highly enantioselective hydrocyanation with chiral phosphoric-acid catalyst **31f** (Scheme 88).[188] The importance of subtle changes in catalyst structure is highlighted by the dramatic differences in enantioselectivity that Rueping and co-workers observed in their catalyst optimization studies depending on the size and electronic nature of the 3,3′-substituents.

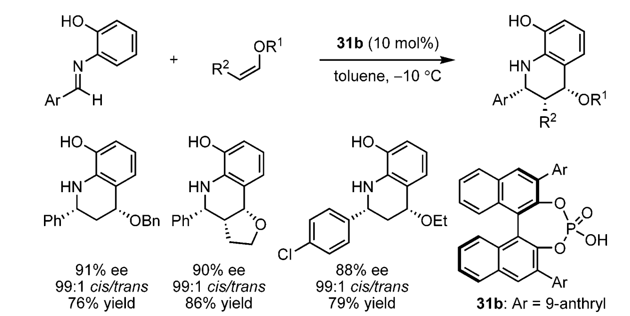
6.4. Hydrophosphonylation

The enantioselective addition of phosphites to imines provides an efficient route to α-amino phosphonic acids of biological relevance as inhibitors of proteolytic enzymes. The Strecker thiourea catalyst **4d** has been shown by Joly and Jacobsen to promote addition of di(2-nitrobenzyl)phosphate, in addition to HCN, to *N*-benzyl imines. Aliphatic and aromatic *N*-benzyl imines undergo highly enantioselective addition in the presence of 10 mol % of thiourea **4d**.[189] Deprotection of the enantioenriched α-amino phosphonates was shown to generate α-amino phosphonic acids in excellent yields and ee's. The significantly more Brønsted-acidic catalyst, phosphoric-acid **31g**, has also been shown to catalyze enantioselective hydrophosphonylation of imines. Aromatic and α,*β*-unsaturated *N*-PMP imines undergo addition with diisopropyl phosphate in good enantioselectivity (Scheme 89).[190]

Scheme 89. Enantioselective Additions of Phosphonates to Imines



Scheme 90. Phosphoric-Acid-Catalyzed Inverse Electron-Demand Aza-Diels−Alder Reaction

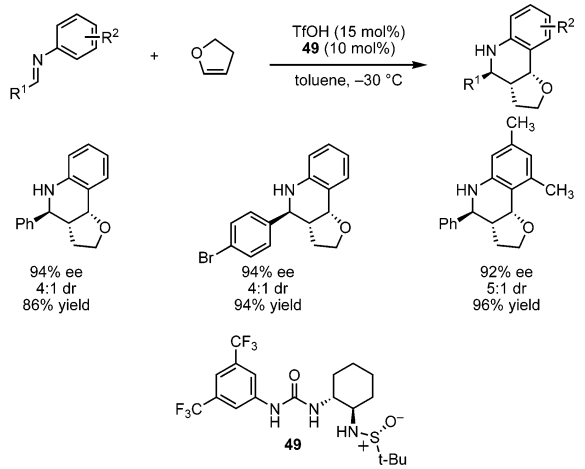


6.5. Aza-Diels−Alder Cycloaddition[152]

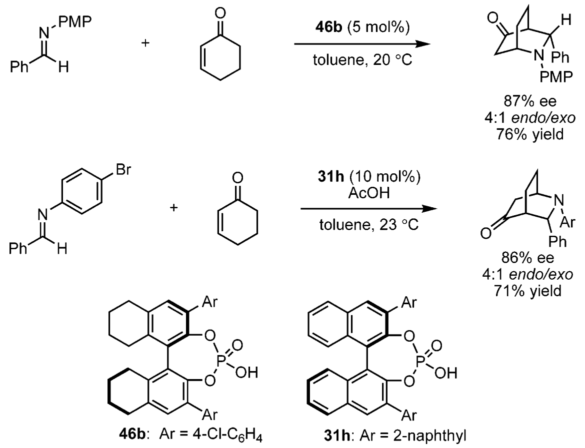
Enantioenriched tetrahydroquinolines can be prepared efficiently by inverse electron-demand aza-Diels−Alder reactions of an azabutadiene and an electron-rich alkene (Povarov reaction). Akiyama and co-workers have shown that *N*-aryl imine electrophiles that contain an *ortho*-hydroxy directing group participate in chiral phosphoric-acid-catalyzed inverse electron-demand aza-Diels−Alder reactions with vinyl ethers (Scheme 90).[191] The method, which is mechanistically related to the Mannich reaction, is highly enantioselective and cis-diastereoselective for reaction of aromatic imines with acyclic or cyclic vinyl ethers.

Jacobsen and co-workers found that sulfinamide **49** catalyzes the Povarov reaction in high enantioselectivity. In contrast to the diastereoselectivities observed in the phosphoric-acid-catalyzed system reported by Akiyama, trans products were found to dominate in reactions of aromatic *N*-aryl imines promoted by **49** (Scheme 91).[192] A mechanism of catalysis involving an anion-binding model analogous to that invoked for the acyl-Pictet−Spengler reaction (Scheme 81) is proposed. In the case of the Povarov reaction, the urea/strong acid system is proposed to generate an active electrophilic species consisting of a protioiminium electrophile with a catalyst-bound sulfonate counterion.

Scheme 91. Urea-Catalyzed Povarov Reaction



Scheme 92. Direct Aza-Diels−Alder Reactions of Cyclohexenone

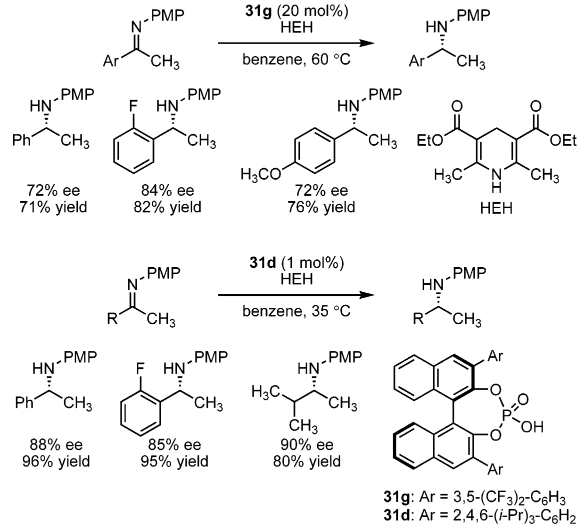


Chiral phosphoric acids have also been shown to catalyze direct aza-Diels−Alder reactions of cyclohexenone and aromatic *N*-aryl imines (Scheme 92).[193] In independent studies Gong and Rueping identified *N*-PMP and *N*-*p*-bromophenyl imines as effective substrates for the cycloaddition. Good enantio- and endo/exo-selectivity in favor of the endo isoquinuclidine products is observed with phosphoric-acid derivatives **46b** and **31h**. While the reaction times in Gong's report are on the order of 4 days, Rueping reports that the addition of 20 mol % acetic acid to the phosphoric-acid-catalyzed reaction conditions significantly improves the rate of the cycloaddition reactions, perhaps by increasing the rate of formation of the reactive dienol nucleophile.

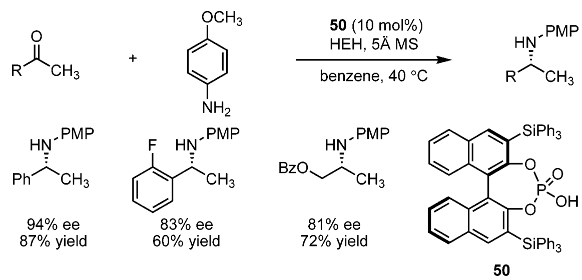
6.6. Reduction[194]

On the basis of their observation that diphenylphosphate catalyzes the reduction of *N*-PMP imines with Hanztsch's ester, Rueping and co-workers investigated the use of chiral binapthyl-derived phosphoric acids for an enantioselective organocatalytic reduction of imines.[195] Chiral phosphoric acid **31g** proved to be most enantioselective, allowing for the reduction of a range of aromatic methyl ketimine substrates in 70−84% ee (Scheme 93).[196] List and co-workers subsequently reported that improved reaction efficiency and enantioselectivity can be obtained with 1 mol % of phosphoric acid catalyst **31d**.[197] These reports provided the first indication that phosphoric acid catalysts can induce enantioselectivity in nucleophilic additions to ketimine substrates, including dialkyl ketimines.

Scheme 93. Enantioselective Transfer Hydrogenations of *N*-Aryl Imines



Scheme 94. Phosphoric-Acid-Catalyzed Enantioselective Reductive Amination



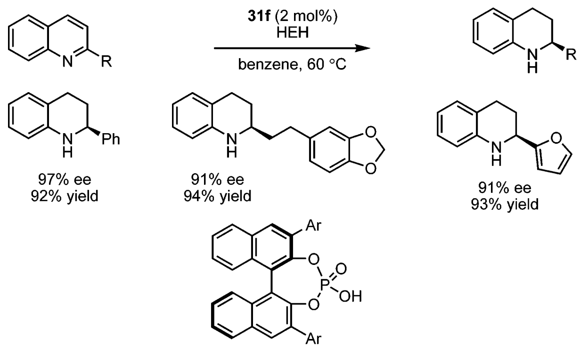
In their study of phosphoric-acid-catalyzed reductions of imines, List and co-workers reported one example wherein the imine substrate is generated in situ and undergoes reduction in good yield and enantioselectivity. A comprehensive examination of enantioselective reductive aminations of aryl and alkyl ketones with anilines was reported shortly thereafter by MacMillan and co-workers.[198] The reactions require methyl ketone partners, but the substrate scope is otherwise remarkably general, even for 2-butanone-derived imines, and the method provides a highly efficient route to chiral amine derivatives (Scheme 94). Phosphoric-acid-catalyzed reductive aminations of racemic α-branched aldehydes that undergo rapid racemization under the reaction conditions were reported very recently by List.[199]

The asymmetric reduction of heteroaromatic compounds represents an attractive route to enantioenriched heterocycles from abundant and inexpensive feedstocks. Chiral phosphoric acid **31f** has recently been shown to catalyze the reduction of quinolines to tetrahydroquinolines using the Hantzsch dihydropyridine ester under mild reaction conditions (Scheme 95).[200] Enantioselectivities for alkyl and aryl 2-substituted quinolines are uniformly high, providing direct access to enantioenriched tetrahydroquinoline alkaloids. Benzoxazines, benzothiazines, and benzoxazinones are also suitable substrates for the enantioselective hydrogenation methodology.[201]

6.7. Amidation

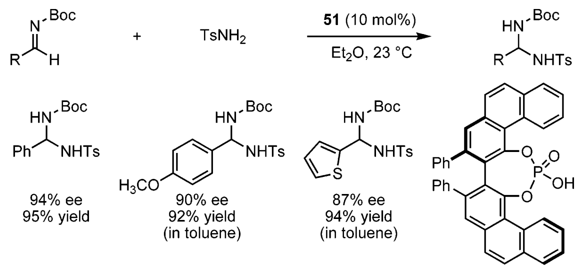
The hindered vaulted biphenanthrol (VAPOL)-derived phosphoric acid **51** was identified by Antilla and co-workers for addition of aryl sulfonamides to aromatic *N*-Boc imines

Scheme 95. Asymmetric Transfer Hydrogenation of Heteroaromatic Compounds



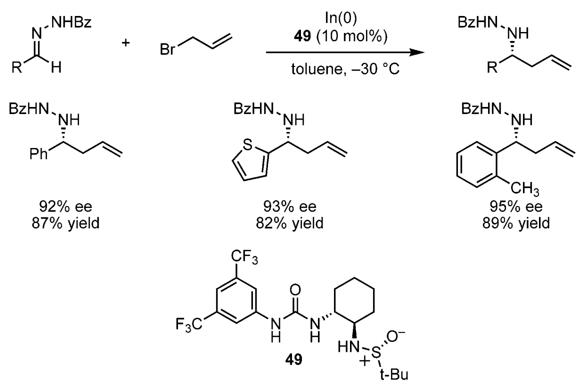
31f: Ar = 9-phenanthryl

Scheme 96. Enantioselective Amidation of *N*-Boc Imines



51

Scheme 97. Urea-Catalyzed Allylation of Hydrazones



to generate chiral *N*,*N*′-aminals (Scheme 96).[202] In this reaction, binapthyl-derived phosphoric-acid catalysts provided only modest enantioselectivity. Protected aminals find application in the development of useful drug candidates from biologically active peptides.[203]

6.8. Allylation[204]

Imine allylation represents a powerful strategy for the synthesis of enantioenriched amines, and considerable effort has been devoted to the development of enantioselective versions of this transformation.[205] The Jacobsen group found that urea **49** catalyzes enantioselective addition of in situ generated allylindium reagents to aromatic *N*-acylhydrazones (Scheme 97).[206] Allyl indium reagents are remarkably mild and functional group tolerant organometallic reagents and may thus be particularly well suited for catalysis by H-bond donors. The Lewis-basic sulfinamide moiety of the catalyst was found to be crucial for the attainment of high enantioselectivity. An X-ray crystallographic analysis of **49** revealed that the sulfinamide N−H participates in an H-bond to the C═O of the urea in the solid-state structure. This interaction may serve to increase the Lewis acidity of the urea functionality and rigidify the catalyst structure.

7. Conclusion

Over the past 10 years, a remarkable number of new enantioselective reactions subject to H-bond donor catalysis have been identified, providing solutions to challenging transformations of importance to asymmetric synthesis. This rapid progress can be attributed both to the discovery of diverse H-bond donor motifs for catalysis and to the design of novel catalyst frameworks to encompass those motifs. Given the range of different acidities and structures for the various H-bond donor catalysts and the different classes of electrophile amenable to asymmetric catalysis by these donors, it is clear that a great number of new discoveries are yet to come.

Without question, discovery of new reactivity is outpacing mechanistic understanding of these H-bond donor catalysts. The fact that both phosphoric acids and thiourea derivatives, which reside on opposite ends of the spectrum of the pK_a scale of known H-bond donor catalysts, are capable of mediating enantioselective transformations of prochiral iminium and *N*-acyliminium ion intermediates is truly unexpected. While most Brønsted-acid catalysts are thought to promote reactions by electrophile activation via direct H-bond donation, the basic mechanisms of activation and stereoinduction in reactions of iminium and *N*-acyliminium ions are almost certainly more complicated. Elucidation of these and other fundamentally distinct modes of activation will likely inspire the design of new H-bond acid catalysts and suggest new reactions and reaction partners for enantioselective catalysis.

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