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Review

Recent Developments in Enantioselective Transition Metal Catalysis Featuring Attractive Noncovalent Interactions between Ligand and Substrate

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ABSTRACT: Enantioselective transition metal catalysis is an area very much at the forefront of contemporary synthetic research. The development of processes that enable the efficient synthesis of enantiopure compounds is of unquestionable importance to chemists working within the many diverse fields of the central science. Traditional approaches to solving this challenge have typically relied on leveraging repulsive steric interactions between chiral ligands and substrates in order to raise the energy of one of the diastereomeric transition states over the other. By contrast, this Review examines an alternative tactic in which a set of attractive noncovalent interactions operating between transition metal ligands and substrates are used to control enantioselectivity. Examples where this creative approach has been successfully applied to render fundamental synthetic processes enantioselective are presented and discussed. In many of the cases examined, the ligand scaffold has been carefully designed to accommodate these attractive interactions, while in others, the importance of the critical interactions was only elucidated in subsequent computational and mechanistic studies. Through an exploration and discussion of recent reports encompassing a wide range of reaction classes, we hope to inspire synthetic chemists to continue to develop asymmetric transformations based on this powerful concept.

KEYWORDS: *enantioselective catalysis, transition metal catalysis, ligand, noncovalent interactions, density functional theory*
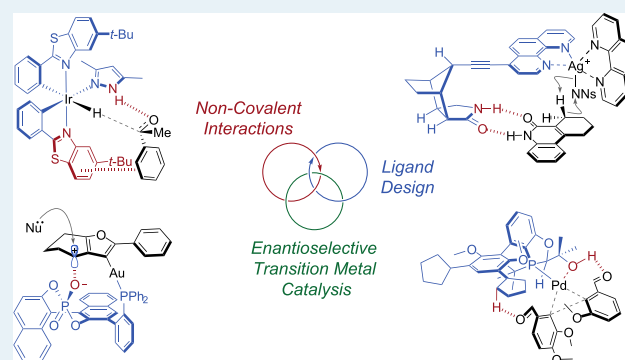
1. INTRODUCTION

The necessity for synthetic chemists to be able to access enantiomerically pure material remains as crucial as it has ever been. Pressure, both ethical and financial, to make chemical processes as environmentally sustainable as possible is only increasing, and the environmental impact of a putative process is now an important consideration when weighing up competing synthetic routes. For asymmetric synthesis, catalysis is an obviously beneficial strategy since only a fractional amount of chiral material should be required to induce enantioenrichment in a much larger amount of product.[1] While the initial challenges faced by the pioneers of this general strategy were significant, over the years, transition metal complexes, typically bearing chiral ligands, have become the central workhorses of asymmetric synthesis.[2−4] Since the early 2000s, organocatalysis has risen quickly as an alternative branch of asymmetric synthesis, which can offer complementary activation strategies and new opportunities for asymmetric induction. It can sometimes overcome some of the disadvantages of using transition metals, namely that the most useful ones are often the least abundant and costliest. Enzymes have been used for many years to carry out

asymmetric chemistry, but traditionally the range of reactions and substrates amenable to this approach was relatively narrow. This is changing rapidly with the widespread application of directed evolution, allowing enzymes to be applied to challenging reactions never seen before in Nature.[5] Despite these advances, the remarkable and diverse reactivity, coupled with the redox capability enjoyed by many transition metals makes them still as valuable as ever for those engaged in the design of new catalytic asymmetric chemical methods. A key feature of transition metals are the opportunities for control of both reactivity and selectivity offered by the metal−ligand partnership. A multidentate chiral ligand complexed with a transition metal constitutes the prototypical strategy, forming the basis of many successful reactions. The most

common strategy in ligand design is to incorporate steric bulk at particular points to exert influence at the transition state for the enantiodetermining step, through steric repulsion. While translating this into high enantioselectivity often involves a degree of trial and error, privileged ligand scaffolds have proven to be effective in a multitude of processes and are returned to time and again.[6]

A variation of this venerable strategy is to consider the use of attractive interactions as a design element.[7] One could imagine that drawing the substrate close to the chirality of the ligand scaffold, as opposed to pushing it away, could be more effective for stereoinduction and may allow for leaner, less extended ligand structures. Attractive Non-Covalent Interactions (NCIs) have long been integral to the mechanisms of enzyme catalysis and their application to chemical catalysis has dramatically accelerated over the past two decades.[7−11] The combination of the diverse reactivity of transition metals with ligands capable of not only ligating and modulating the reactivity at the metal but also engaging in attractive noncovalent interactions with the substrate concurrently could prove to be a remarkably powerful strategy for developing new enantioselective reactions. Ambitions toward such systems have been apparent since the 1980s; for example, the early work of Ito and Hayashi using bifunctional ligands in the gold-catalyzed asymmetric aldol reaction was highly influential.[12] Their parallel research with palladium in pi-allyl chemistry[13] also demonstrated that multifunctional ligands could provide an alternative mode of stereoinduction to those based purely on sterics, as in the classic Trost ligand (Figure 1, upper panel).[14] Interestingly,
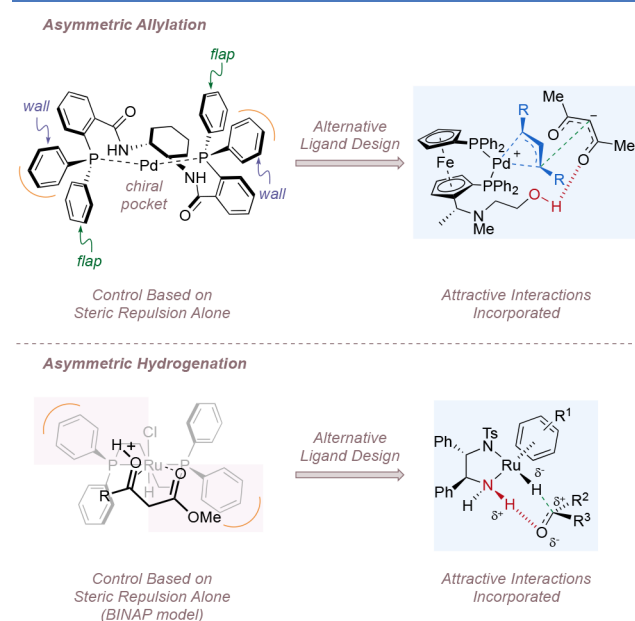

Figure 1. Illustrative comparisons of chiral ligand strategies based on sterics (left) and those which also incorporate attractive NCIs (right).

recent computational studies suggest that in some cases attractive NCIs between ligand and nucleophile may actually be in operation using the Trost ligand, although the original design was likely to be based solely on steric considerations.[15] In the 1990s the development of diamine ligands for asymmetric transfer hydrogenation served to highlight how powerful the ligand-substrate NCIs could be; the hydrogen bond between the N−H of the ligated diamine and the ketone

undergoing reduction being a crucial aspect for both reactivity and selectivity (Figure 1, lower panel).[16]

In certain particularly striking examples, the unmasking of groups capable of engaging in noncovalent interactions on an already chiral ligand scaffold can result in a complete switch in the sense of reaction enantioinduction. Pioneering examples in this area include a report from Zhou and Li examining a silver-catalyzed 1,3-dipolar cycloaddition reaction[17] and another from Aït-Haddou and Balavoine in the context of a palladium-catalyzed allylation reaction.[18] In both cases, seemingly innocuous changes to the chiral scaffold revealed functionality capable of hydrogen bond donation, and a resulting reversal in enantioselectivity was observed. For example in Zhou and Li's 1,3-dipolar cycloaddition, the replacement of a dimethylamino group in **L1** with an amino group in **L2** is proposed to turn "on" a hydrogen-bonding interaction between the ligand and a suitable substrate, transitioning from a purely steric control model to one in which noncovalent interactions were the primary determinant of the stereochemical outcome (Figure 2). Such an imaginitive yet unconventional approach to
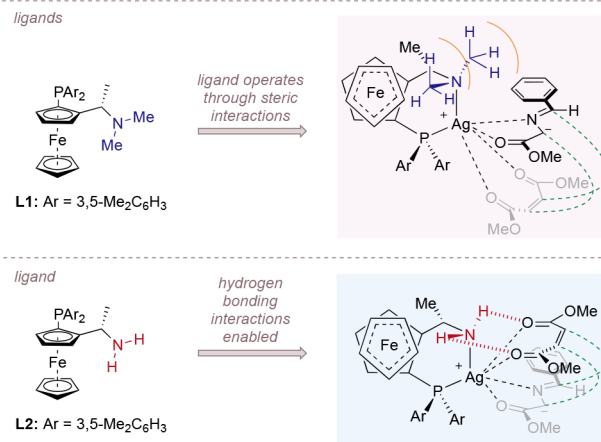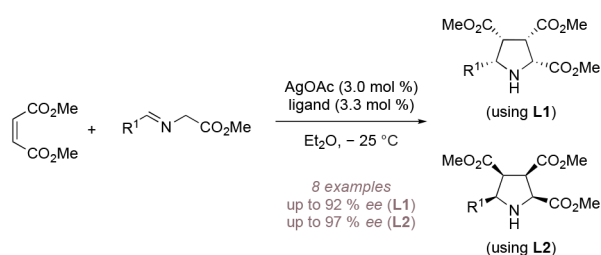

Figure 2. Reversal of enantioselectivity following the unveiling of hydrogen-bond-donating groups on a chiral ligand scaffold.

reversing reaction enantioselectivity could be of particular use in cases where the antipode of a privileged chiral ligand scaffold is not readily available from the chiral pool.

The development of organocatalysis since the early 2000s has driven a far improved practical understanding of how discrete NCIs can be productively harnessed in the context of small-molecule catalyst scaffolds. These insights have fed back into strategies involving transition metals. As a result, design strategies whereby an attractive ligand−substrate interaction is proposed are now more widespread. In parallel to this, the greater prevalence of mechanistic insight obtained through DFT calculation has revealed the importance of attractive NCIs even in systems where they had perhaps not been

anticipated, such as in the previously mentioned Trost ligand.[19] The insights gained from such studies can be highly instructive in formulating new approaches and are likely to become more routine as time progresses.

This Review will cover key advances made in the past decade (2010–2020) in which attractive NCIs between ligand and substrate are proposed or implicated. This will include both examples where the NCI was part of the original design plan as well as those where subsequent analysis suggested their importance. In order to retain focus, this Review will cover only examples in which the ligand is reasonably expected to remain fully coordinated to the metal center throughout the catalytic cycle. As such it will not cover the extensive developments involving chiral counterions for transition metals. This is an area of exciting growth, which in many cases likely involves networks of NCIs between metal, counterion, and substrate and which have been subjected to focused review elsewhere.[20–22] While not discussed in detail, relevant examples will be referred to as appropriate in order to provide context.

The Review sections will be divided based on the type of bond being formed, with some further subdivision based on reaction type in the case of C−C bond formation. It will refer to representative key examples from pre-2010 at the beginning of each section, for context. There are several particularly relevant reviews which cover previous literature and will be of interest to the reader. Those to highlight include an early 1992 review from Ito and Sawamura,[23] a broad 2014 review from Raynal and co-workers covering various aspects of supramolecular catalysis,[24] including examples with ligand–substrate interactions, as well as a perspective article from Reek and Dydio published in 2014.[25] With the relatively broad remit of the defined topic, it will not be feasible to include every single example which falls under the definition, but we have selected examples which we feel are important, inspiring, or unusual. In each instance, we have sought to depict a diagram showing the proposed interactions involved, alongside several representative examples from the reaction scope, for maximum clarity to the reader. We hope that this survey will provide guidance and inspiration for those seeking to involve NCIs in the design of ligand systems for enantioselective transition metal catalysis.

2. CARBON−CARBON BOND-FORMING REACTIONS

2.1. Asymmetric Aldol and Mannich Reactions. An early and highly influential example which embodies the theme of this Review is the gold-catalyzed aldol reaction reported by Ito, Sawamura, and Hayashi in 1986 (Figure 3a).[12,23] The original publication describes the reaction between various aldehydes and methylisocyanoacetate in the presence of a gold(I) source and ligands **L3** and **L4** (Figure 3b) to form 5-alkyl-2-oxazoline-4-carboxylate products. The reaction conditions are mild, and the products are formed in excellent yield, with good diastereoselectivity and high enantioselectivity. The authors proposed that the pendant amino group attached to the ferrocene ligand scaffold serves to deprotonate the acidic α-position of the gold-coordinated methylisocyanoacetate, forming an ion-paired ammonium enolate. Both the length of the amino linker and the nature of the basic group itself were of great importance in achieving high stereoselectivity: increases or decreases in length from the optimal 2-(dialkylamino)ethyl spacer led to significant decreases in enantioselectivity.[26] Further, extensive variation of the nature
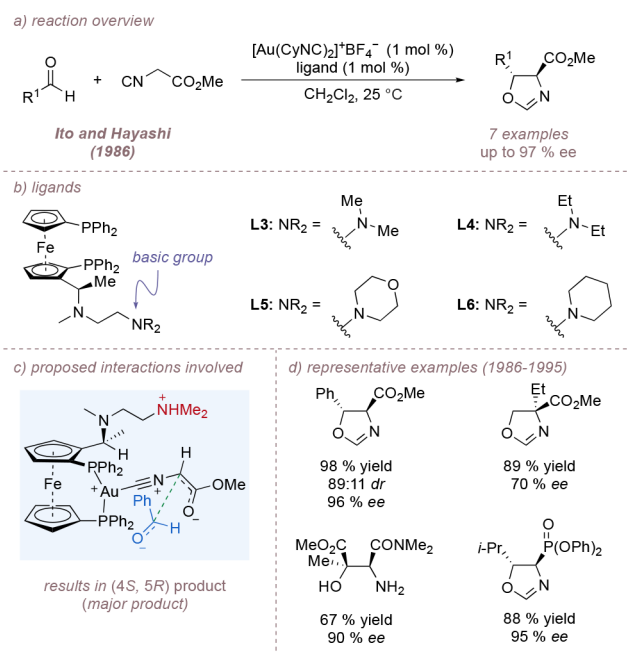

Figure 3. Enantioselective gold-catalyzed aldol reaction reported by Ito and Hayashi.

of the pendant basic group demonstrated that the incorporation of morpholino (**L5**) or piperidino (**L6**) moieties in place of simple dimethyl or diethyl groups led to significant increases in enantioselectivity with previously challenging substrates such as acetaldehyde.[26] In the initial proposal advanced by the authors, the ammonium enolate attacks the gold-coordinated aldehyde in an intramolecular fashion with the ion-pairing interaction between the ligand and enolate being a crucial aspect. In subsequent mechanistic investigations, Togni and Pastor provided evidence to suggest that there is no coordination of the aldehyde to the gold center and that the basic amino group is indeed free to deprotonate the isonitrile pronucleophile to form the proposed ion-paired ammonium enolate. The electrostatic interaction between the ammonium group of the ligand side chain and the enolate effectively shields one face of the complex due to steric bulk, forcing electrophiles to attack from the other open face (Figure 3c). For a full account of the proposed mechanism of this seminal transformation, the reader is directed to the original publication from Togni and Pastor.[27]

The practical utility of the approach was emphasized by further expansion to the original substrate scope in modifications to both the nucleophilic and electrophilic components. This included α-ketoesters[28] and aldehydes bearing aromatic rings other than simple phenyl groups.[29,30] Modifications to the pro-nucleophile included α-substitution of the isonitrile[31] and replacement of the ester group with amides,[28,32] Weinreb amides,[33] or even phosphonate esters (Figure 3d).[34,35] In a related study, an analogous silver(I) system using the same ligand was also found to mediate the reaction.[36]

In 2011, 25 years after Ito and Hayashi's seminal report, Dixon and co-workers revisited the same reaction in the first of a series of related publications (Figure 4a). While Dixon's catalytic system was structurally very different, in both cases attractive noncovalent interactions are thought to play a critical role in determining enantioselectivity.[37] The initial report

a) reaction overview

Dixon (2011)

*epi-cinchonine-derived ligand

R[1] = H
8 examples
up to 96 % ee

R[1] ≠ H
8 examples
up to 98 % ee

b) example ligand

Brønsted base

MeO

Lewis base

epi-quinine-derived ligand

c) proposed interactions involved (2016)

further applications - representative examples

d)

(Ar = 4-MeC$_6$H$_4$)

Dixon 2014
78 % yield
9:1 dr
98 % ee

e)

Dixon 2015
76 % yield
9:1 dr
98 % ee

f)

(Ar = 4-ClC$_6$H$_4$)

Dixon 2016
80 % yield
89 % ee
(following deprotection)

g)

Dixon 2018
99 % yield
>19:1 dr
94 % ee

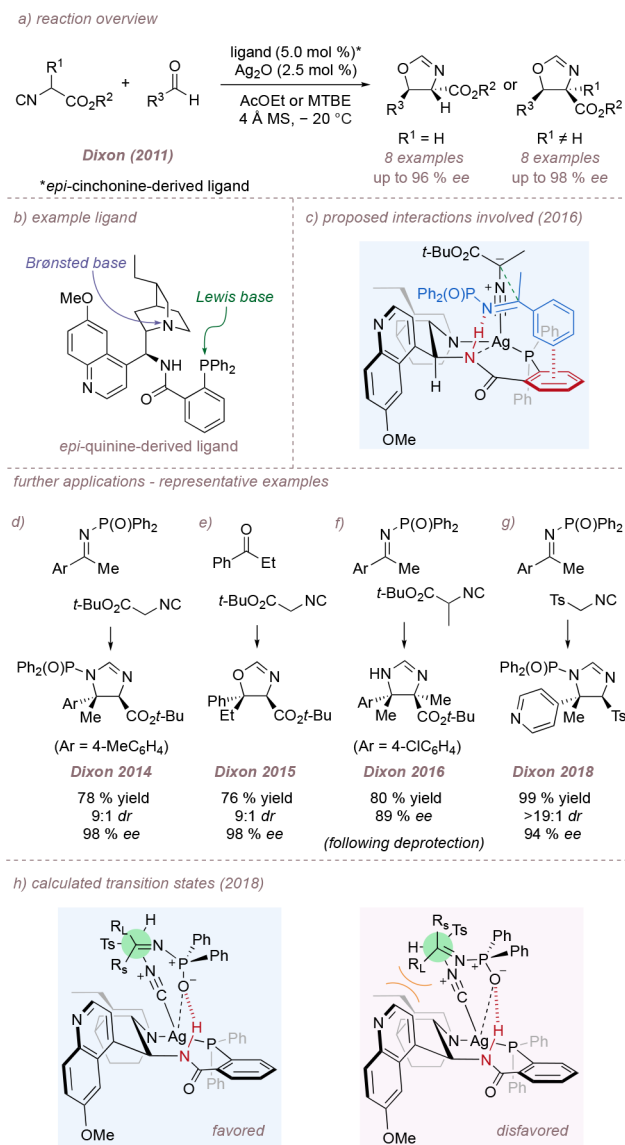h) calculated transition states (2018)

favored

disfavored

Figure 4. Enantioselective aldol and Mannich reactions using a bifunctional ligand for silver catalysis.

introduced bifunctional ligands derived from the *epi*-cinchona scaffold (Figure 4b) which incorporate a Lewis basic phosphine to ligate silver(I), leaving the Brønsted basic quinuclidine nitrogen to function as a base and deprotonate the isonitrile. Under the optimized conditions, a variety of aldehydes were reacted with a glycine-derived isonitrile leading to products formed in good yields and with good diastereoselectivities and enantioselectivities. α-Substitution of the isonitrile was tolerated to afford products bearing a quaternary α-stereocenter, and interestingly, the facial selectivity of the nucleophile in these cases was reversed in comparison to the unsubstituted isonitriles. In a closely related system, an enantioselective aldol reaction with ketone substrates was also achieved (Figure 4e).[38] Further examples using this methodology to construct challenging quaternary carbon centers have been described. For example, the group reported a catalytic asymmetric Mannich-type addition to N-diphenylphosphinoyl (DPP) protected imine electrophiles to form imidazolines bearing a quaternary carbon stereocenter at the β-position (Figure 4d).[39] α-Substitution of the isonitrile

subsequently allowed access to imidazolines bearing two adjacent quaternary stereocenters (Figure 4f).[40] Variation in the pronucleophile component was also studied, and p-toluenesulfonyl isocyanide (TosMIC) was a competent pronucleophile for the Mannich transformation with a variety of DPP-protected imines (Figure 4g).[41]

Detailed ^{31}P and ^{1}H NMR studies along with X-ray crystallographic data provided the basis of a stereochemical model for ketimine substrates (Figure 4c).[40] Silver is ligated by the *epi*-quinine-derived ligand via the amide nitrogen, the phosphorus atom, and also the quinuclidine nitrogen. The remaining coordination site on the metal is occupied by the isonitrile. In the enantiodetermining step, two NCIs between the ligand and electrophile are suggested. The first is a hydrogen bond between the ketimine lone pair and the carboxamide N−H of the bifunctional ligand. This hydrogen bond activates the ketimine and orients it such that the large group on the electrophile points away from the ester group of the isonitrile and the bulky quinuclidine and quinoline portions of the ligand. Further organization may arise from C−H/π interactions (arranged in a "T"-shaped geometry) between the aromatic ring on the substrate and the carboxamide aromatic ring of the ligand. In the more recent report using TosMIC as the pronucleophile, DFT was used to rationalize the formation of the major enantiomer (Figure 4h).[41] In the two lowest-energy transition states, in which the ketimine adopts the E-configuration, the strongly hydrogen bond-accepting phosphine oxide interacts with both silver and the amide of the ligand through hydrogen bonding.

In related studies using modified cinchona alkaloid ligands in conjunction with transition metals, Nakamura and co-workers investigated the direct asymmetric Mannich-type reaction of α-isocyanoacetates with ketimine electrophiles to afford valuable α,β-diamino acid precursors (Figure 5a).[42] In this catalyst design, a picolinamide motif is incorporated into the *epi*-cinchonine scaffold, and fine-tuning of the picolinamide ring

a) reaction overview

Nakamura (2014)

17 examples
up to 99 % ee

b) ligand

tuning of picolinamide group
(improved diastereoselectivity)

c) proposed interactions involved

d) representative examples

62 % yield
92:8 dr
99 % ee

46 % yield
81:19 dr
95 % ee

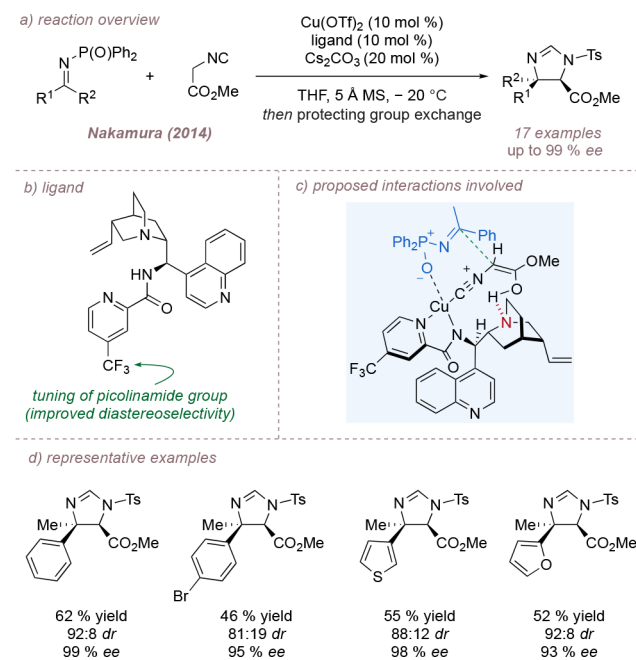55 % yield
88:12 dr
98 % ee

52 % yield
92:8 dr
93 % ee

Figure 5. Enantioselective Mannich reaction using a bifunctional ligand for copper catalysis.

substitution provided optimal stereoselectivity (Figure 5b). The reaction proceeds with excellent stereocontrol, and a variety of ketimines with predominantly aromatic substituents are tolerated (Figure 5d). The major diastereomer obtained under these conditions is the *syn* product, complementing Dixon's methodology which affords predominantly the *anti* product. A transition state model was suggested to rationalize the stereochemical outcome (Figure 5c). In contrast to the tetrahedral geometry around silver, the copper is square planar, coordinated by the substrate, the picolinamide group, and the oxygen atom of the DPP-protected ketimine. The quinuclidine portion of the ligand is proposed to be free to interact through hydrogen bonding with the isocyanoacetate ketene hemiacetal generated *in situ*, guiding the latter's attack onto the ketimine electrophile. Unfavorable steric interactions between the nucleophile and the bulky imine protecting group are minimized in the transition state, resulting in the (4*R*, 5*R*) stereochemistry observed in the products. Subsequently, the enantioselective synthesis of imidazolines bearing fully substituted vicinal *α*- and *β*- stereocenters was achieved by replacing copper(II) with nickel(II) as the catalytic metal and using an *epi*-cinchonidine-derived ligand functionalized with a picolinamide group.[43]

In an earlier, related publication, Nakamura and co-workers had investigated the application of a similar system to the vinylogous Mannich reaction using ketimine electrophiles and siloxyfuran pronucleophiles (Figure 6a).[44] Initial experiments
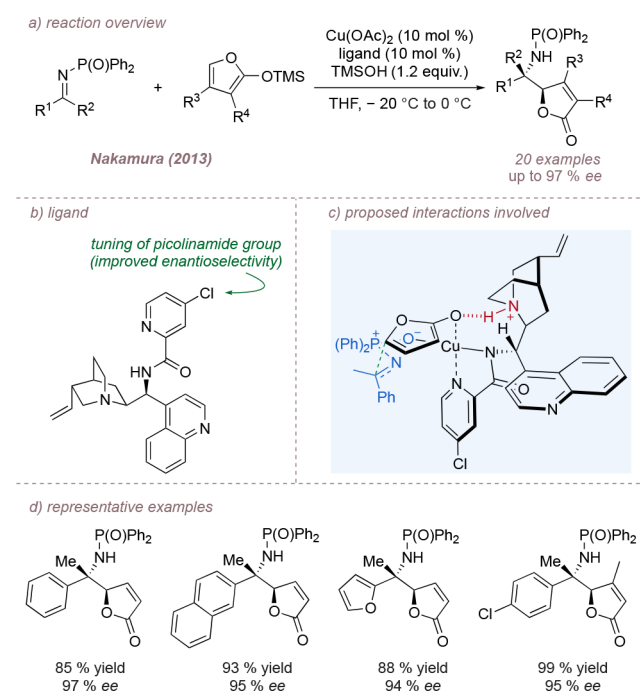

Figure 6. Enantioselective Mannich reaction with siloxyfurans under copper catalysis.

identified Cu(OAc)$_2$ as the optimal Lewis acid in conjunction with an *epi*-cinchonidine-derived ligand, again with optimized picolinamide substitution (Figure 6b). Under the carefully chosen conditions, a variety of ketimine electrophiles were investigated with the reaction proceeding with excellent control over all aspects of selectivity (Figure 6d). In order to explain the stereochemical outcome of the reaction, the authors proposed a transition state model (Figure 6c). As with

the previous example, the copper is square planar, ligated by both nitrogen atoms of the picolinamide and by the oxygen atoms of the DPP-protected ketimine and the dienolate, respectively. A hydrogen bonding interaction with the protonated quinuclidine then guides the nucleophile to attack the less sterically hindered face of the coordinated ketimine.

Hong and co-workers designed a bifunctional salen ligand to achieve asymmetric nitroaldol reactions (Figure 7a).[45] The
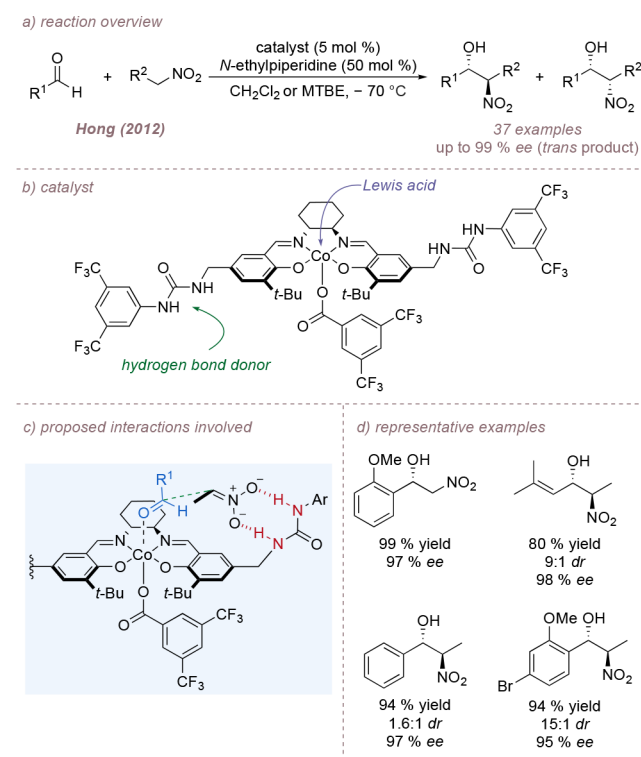

Figure 7. A bifunctional salen ligand for enantioselective nitroaldol reactions.

bifunctional catalyst possesses a Lewis-acidic cobalt(III) site coordinated by a modified salen ligand bearing remote hydrogen-bond-donating urea groups (Figure 7b). The cobalt coordinates the electrophilic aldehyde, activating it toward nucleophilic attack while one of the pendant urea groups is thought to engage the nitronate nucleophile via two-point hydrogen bonding (Figure 7c). While the combined yields and enantioselectivities of the isolated *syn* and *anti* products were mostly very good, the diastereomeric ratio was found to be sensitive to the nature of the aldehyde substituent (Figure 7d). Various mechanistic studies supported the proposal outlined by the authors. Control experiments where the urea moieties were either methylated or removed resulted in poor outcomes and association through hydrogen bonding between a 2-nitropropanoate anion, and a simple urea model system was also inferred from ^{1}H NMR experiments. Mechanistic studies supported a catalytically active monometallic species in which the terminal urea groups are free to interact with the anionic nucleophile.

2.2. Asymmetric 1,2- and 1,4-Additions. Catalytic 1,2- and 1,4-additions are routinely used to construct C−C bonds with one or multiple stereocenters in an atom-economic and highly enantio- and diastereoselective fashion.[46,47] Metal catalysts bearing functionalities that can interact with the reactive species via noncovalent interactions have been shown

to provide an attractive and practical approach to organize the reactants in a specific spatial arrangement. An early pioneering example of a hydrogen bond-directed 1,2-addition incorporating a transition metal catalyst was reported by Hoveyda, Snapper, and co-workers in 1999.[48] The enantioselective synthesis of α-amino acid precursors was achieved via the addition of cyanide to protected imines,[48] catalyzed by titanium-tripeptide Schiff base complexes (Figure 8a,b).
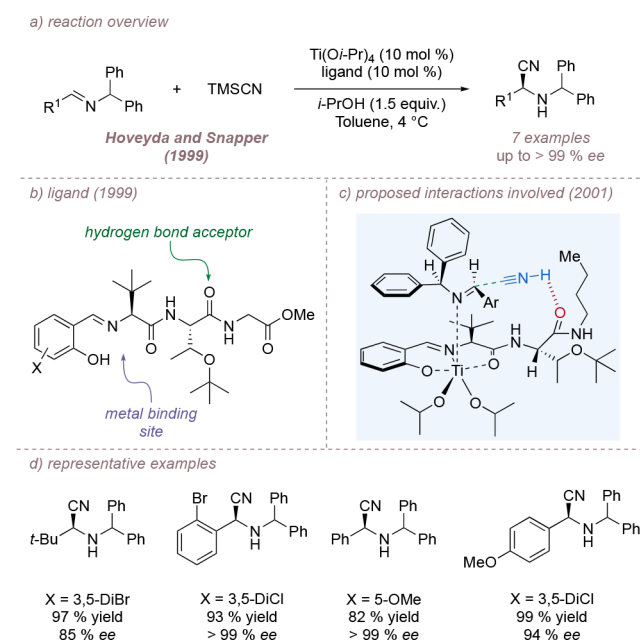

Figure 8. Asymmetric 1,2-cyanation using a chiral peptide ligand for titanium.

Shortly after, the same groups used an identical catalyst system to perform regio- and enantioselective 1,2-addition to unsaturated imines.[49] A detailed mechanistic study indicated a highly organized transition state, in which the peptidic segment of the chiral ligand hydrogen bonds to the incoming HCN (generated *in situ*) and delivers it to the activated Ti-complexed imine (Figure 8c).[50] In the original report, small modifications to the aromatic group of the ligand enabled the efficient conversion of various imine substrates in very high ee (Figure 8d).

In 2013, Sawamura and co-workers reported the copper-catalyzed enantioselective addition of alkynes to aldehydes (Figure 9a).[51] Prolinol-based hydroxyamino phosphines **L7** and **L8** were used as chiral ligands on the basis that the hydroxyl group should enable tridentate ligation of copper, thereby allowing for the monomerization of a copper(I)/acetylide complex (Figure 9b). DFT experiments indicated the occurrence of a nonclassical sp³-CH···O hydrogen bond between the pyrrolidine ring and the carbonyl oxygen, in addition to a key hydrogen bond between the ligated hydroxyl group and the aldehyde. This two-point hydrogen bonding interaction was proposed to be key to orientating the carbonyl group of the aldehyde (Figure 9c). In 2018 the same authors expanded the scope of the reaction to include α-ketoester substrates using the same ligands (Figure 9d).[52] DFT calculations indicated that steric repulsions between catalyst and substrate did not play a significant role in the enantioinduction, but the enantioselectivity was determined by attractive catalyst−substrate interactions. These included
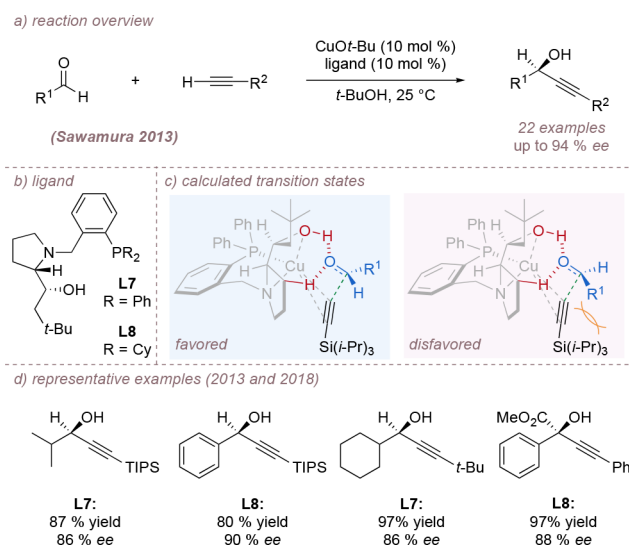

Figure 9. Asymmmetric 1,2-alkynylation reactions using prolinol-based hydroxyamino phosphines as ligands.

the two-point hydrogen bond, which had been observed previously, as well as dispersive attractions between the *P*-cyclohexyl groups and the ketoester. When this level of theory was applied to the previous report, it indicated similar attractive dispersion interactions between the cyclohexyl moiety of the aldehyde and the *P*-phenyl groups of the ligand.

An elegant and unusual approach came from Meggers, Gong, and co-workers who in 2013 reported a catalytic, asymmetric 1,4-addition of indoles to β-nitroacrylates to form all-carbon, quaternary stereocenters (Figure 10a).[53] Inspired by thiourea organocatalysts, an inert chiral-at-metal iridium-(III) complex was employed, bearing a coordinated 5-amino-3-(2-pyridyl)-1H-pyrazole which acts as a hydrogen bond donor
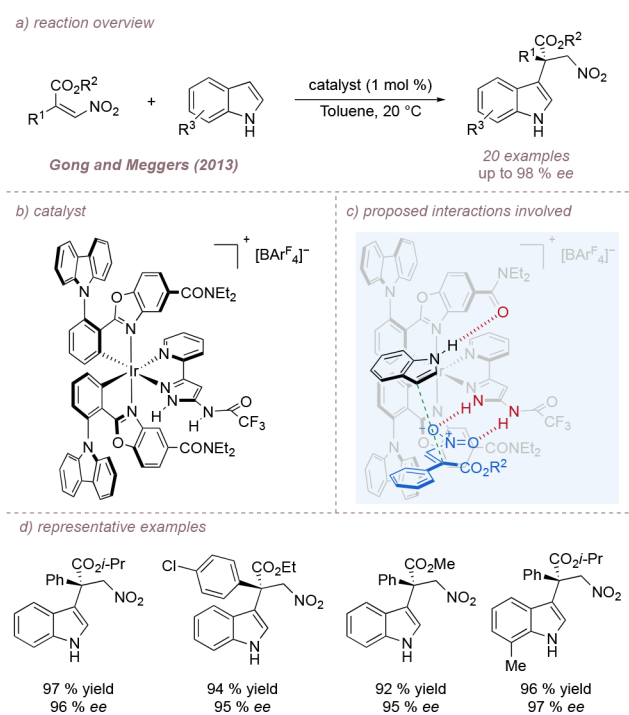

Figure 10. Asymmetric 1,4-addition to nitroalkenes using a chiral-at-metal bifunctional catalyst.

to the nitroalkene. In addition, one of the benzoxazole ligands bears an *N,N*-diethylcarboxyamide substitutent, which serves as a hydrogen bond acceptor for the incoming indole nucleophile and renders the complex bifunctional (Figure 10b,c).[54−56] As a result, both reactants are activated and preorganized for C−C bond formation to afford products with excellent enantioselectivity (Figure 10d). See section 3 for the application of this system to transfer hydrogenation and for further discussion. Subsequently the Meggers group expanded the scope to *α*-nitroacrylate substrates, thereby creating two consecutive stereocenters.[57] In this case a modified catalyst was used, and while good to excellent enantioselectivities could be obtained, there was little discrimination between the diastereomers of the product. The authors have also reported asymmetric 1,4-addition of 2,5-disubstituted pyrroles at the *β*-position using nitroacrylates as electrophiles.[58] In 2016, the same authors reexamined the asymmetric 1,4-addition of indoles to *β,β*-disubstituted nitroalkenes and increased the efficiency of the catalyst by cyclizing the pendant carboxamide groups into lactams.[59] The resulting reduction in conformational freedom reduced the entropic penalty of hydrogen bonding, and further optimization replaced the pyridylpyrazole ligand with a bispyrazole, rendering the catalyst C_2-symmetric, with two catalytic sites per iridium complex. Using these optimized ligands, 1,4-additions could be catalyzed with catalyst loadings as low as 0.05 mol % while maintaining high enantioselectivity.

Shortly after, the same authors reported different catalysts for addition of 3-substituted indoles to *α,β*-unsaturated 2-acyl imidazoles (Figure 11a).[60] Chiral-at-metal, bis-cyclometalated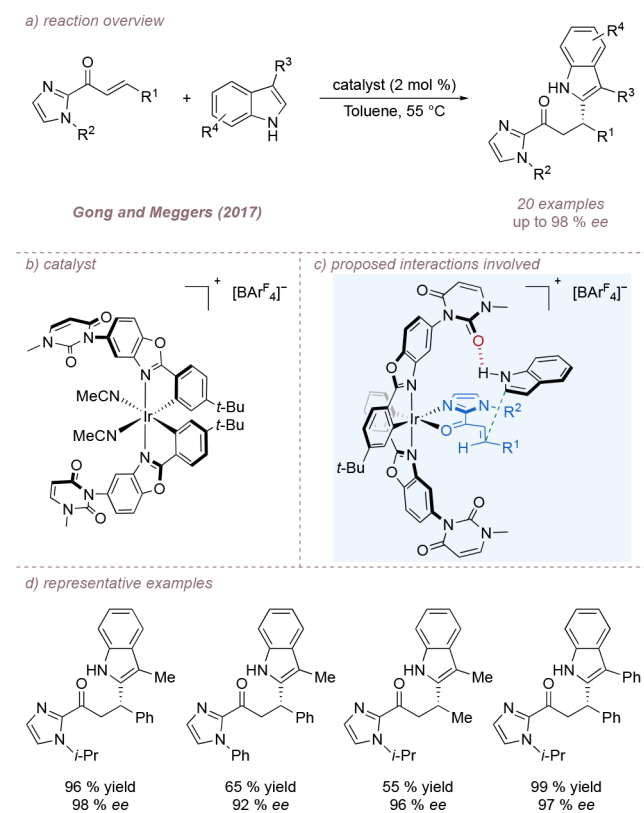 iridium complexes bearing two labile acetonitrile molecules (Figure 11b) meant that the iridium(III) complex could combine electrophile activation via metal coordination with nucleophile activation through hydrogen bonding. The new ligand introduced *N*-methyl uracil moieties which could form strong hydrogen bonds with the indole nucleophile to activate it (Figure 11c). Using this system, a range of alkylated indoles were obtained with excellent enantioselectivities (Figure 11d). Although various experiments supported the hydrogen bonding hypothesis, the authors found that an *N*-protected indole substrate experienced only slightly reduced ee but at a much reduced yield. Therefore, steric effects were also considered to play an important role in the asymmetric induction, while the hydrogen bonding/Lewis acid catalysis was thought to primarily increase reactivity.

Further demonstrating the utility of this class of catalyst, the same authors also reported the use of related complexes to serve as chiral Brønsted base/hydrogen bonding donor catalysts (Figure 12a,b).[61] Within the context of an asymmetric

Figure 11. Asymmetric 1,4 addition of 3-substituted indoles using a dual hydrogen bond/Lewis acid catalyst.
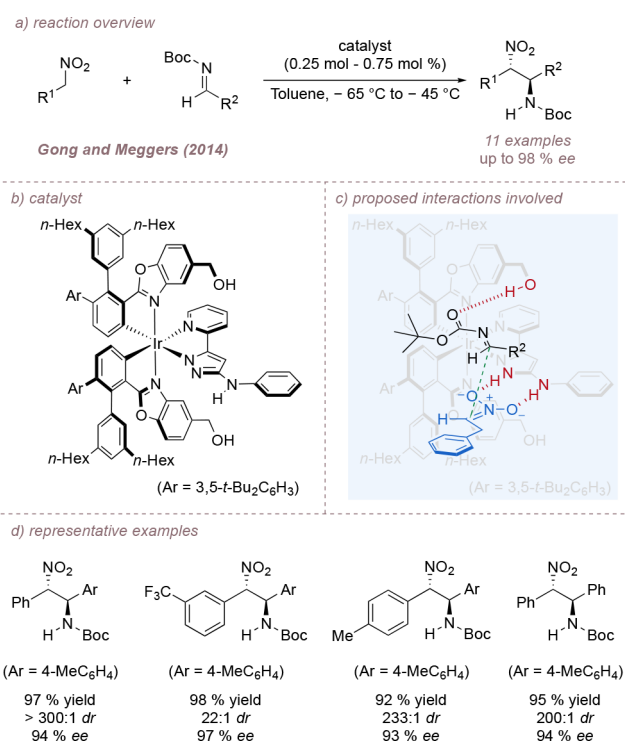

Figure 12. Asymmetric aza-Henry additions via chiral Brønsted base/hydrogen bonding dual activation.

aza-Henry reaction, the deprotonated, coordinated pyrazolato unit could serve as a base, forming a hydrogen bond donor once protonated. The pendant hydroxyl group on the cyclometallating ligand is thought to provide organization through hydrogen bonding with the imine (Figure 12c). A range of 1,2-diamine derivatives were formed in excellent yield and ee (Figure 12d), and the complexes were also able to catalyze sulfa-Michael reactions (not shown). The scope was expanded to include asymmetric sulfa-Michael additions to *α,β*-unsaturated *γ*-oxoesters and the aza-Henry reaction between isatin-derived ketimines and aryl nitromethanes.[62,63]

Also in a chiral-at-metal approach, Gladysz and co-workers in 2015 reported the synthesis and purification of chiral-at-metal cobalt(III) complexes which bear chiral 1,2-diphenyle-thylenediamine (DPEN) ligands and explored their application

as chiral hydrogen bond donor catalysts for asymmetric Michael additions (Figure 13a,b).[64] This built on prior work in
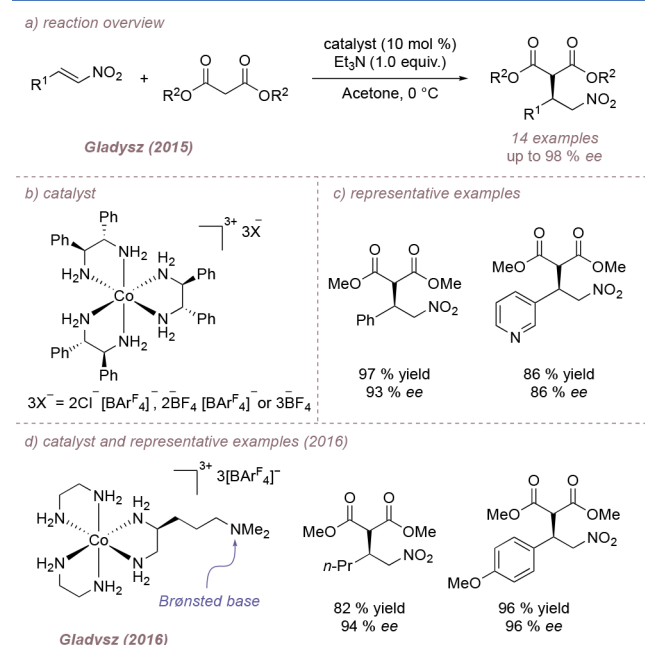

Figure 13. Asymmetric 1,4-addition of dialkyl malonates to nitroalkenes using chiral-at-cobalt complexes.

which purely chiral-at-metal cobalt complexes bearing achiral ethylenediamine ligands had shown promise in asymmetric Michael additions, presumably as a result of hydrogen bond donation from the ligating amino groups.[65] These new diastereomeric complexes were found to catalyze the Michael addition of malonate esters to nitroalkenes with up to 98% ee (Figure 13c). In 2016, the authors built upon their prior work through the incorporation of an additional amine functionality onto one of the ligands to introduce bifunctionality (Figure 13d).[66] The new class of catalysts incorporated one enantiopure ω-dimethylaminoalkyl-substituted ligand to form diastereomers which could be separated on chiral-phase columns. These complexes catalyzed the addition of dialkyl malonates to nitroalkenes with excellent yields and enantiose-lectivities, while the chiral but monofunctional $[Co(en)_3]^{3+}$ analogue gave <10% ee. It was proposed that the malonate esters could simultaneously interact with the protonated dimethylamino groups and the proximal N−H donor sites. In 2020, the same authors reported an interesting study involving the combination of the chiral $[Co((S,S)-dpen)_3]^{3+}$ cations with chiral monoanions or dianions.[67] These diastereomeric salts could catalyze the addition of 1,3-dicarbonyl compounds to trans-β-nitrostyrene and di-tert-butylazodicarboxylate with significant variation in enantiose-lectivity, although the performances of the matched catalysts only occasionally exceeded those from their report in 2015. Recently, the same authors have also investigated a range of lipophilic $[M(en)_3]^{n+}[BAr^F_4]^-$ salts with a variety of metal centers.[68]

Concurrently with the above work, the Gladysz group were developing ruthenium complexes for asymmetric 1,4-additions (Figure 14a).[69,70] After the modest results with the [Co-(en)_3]^{3+} complex the authors devised an approach whereby the hydrogen bond donor N−H groups were more remote from the metal. The catalysts were formed through the complex-
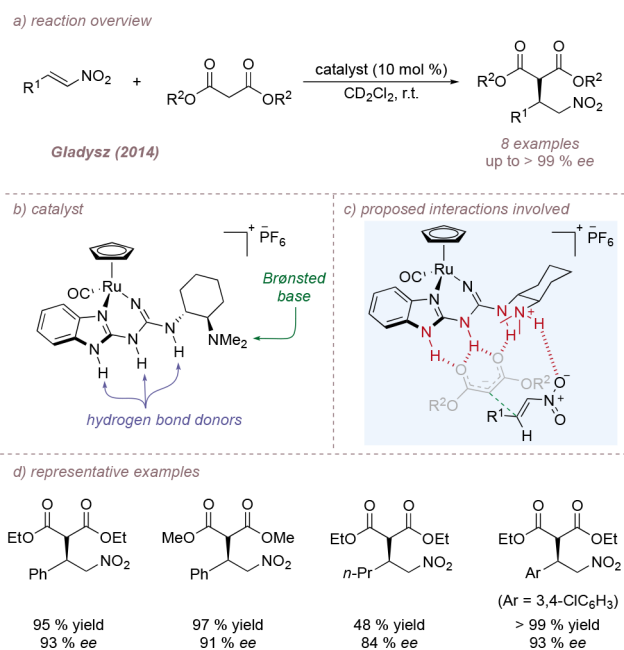

Figure 14. Asymmetric 1,4-addition of nitroalkenes catalyzed by ruthenium-GBI catalysts.

ation of ruthenium with 2-guanidinobenzimidazole (GBI) (Figure 14b). Following calculations, it was proposed that the complex and the malonate readily associate via NH···O hydrogen bonds, while the tertiary amine acts as a Brønsted base.[71] Once protonated, this can hydrogen bond with the nitroalkene (Figure 14c). These diastereomeric complexes could catalyze the addition of malonate esters to nitroalkenes with high yields and enantioselectivities while the free GBI ligand alone exhibited modest reactivity, highlighting the importance of the metal center for preorganization (Figure 14d). The importance of the Brønsted basic component was confirmed empirically in a report shortly later, when a sterically bulky pentaphenylcyclopentadienyl ruthenium 2-GBI complex was synthesized bearing no basic nitrogens, in which enantioselectives were significantly lower.[72]

Mechler and Peters recently reported the diastereodivergent, asymmetric 1,4-addition of oxindoles to nitroolefins (Figure 15a).[73] Notably, their strategy was able to overcome inherent diastereoselectivity to access the typically less favored product diastereomers. The authors developed a polyfunctional catalyst which comprises a nickel(II)-bis(phenoxyimine), bearing free hydroxyl groups, and an axially chiral bisimidazolium motif which serves as a linker between the phenoxyimines (Figure 15b). The authors proposed that the ligated nickel metal serves as a Lewis acid to promote oxindole enolization, while the free hydroxyl groups aid in controlling the reactive conformation of the oxindole-nickel adduct via hydrogen bonding. Furthermore, the bisimidazolium linker was proposed to activate the nitroolefin through dual hydrogen bond donor interactions in addition to electrostatic interactions (Figure 15c). The "unnatural" diastereomer could be accessed in up to 80:20 unnatural:natural ratio with a (1S,2R)-1,2-diphenyl-2-amino-ethanol motif incorporated into the catalyst (Figure 15b). By varying the iminoalcohol to a (1R,2S)-norephedrine-like structure, or to (R)-1-phenyl-2-aminoethanol, the naturally favored diastereomer could be accessed with good disastereo- and enantioselectivity. Interestingly, changing the iminoalcohol
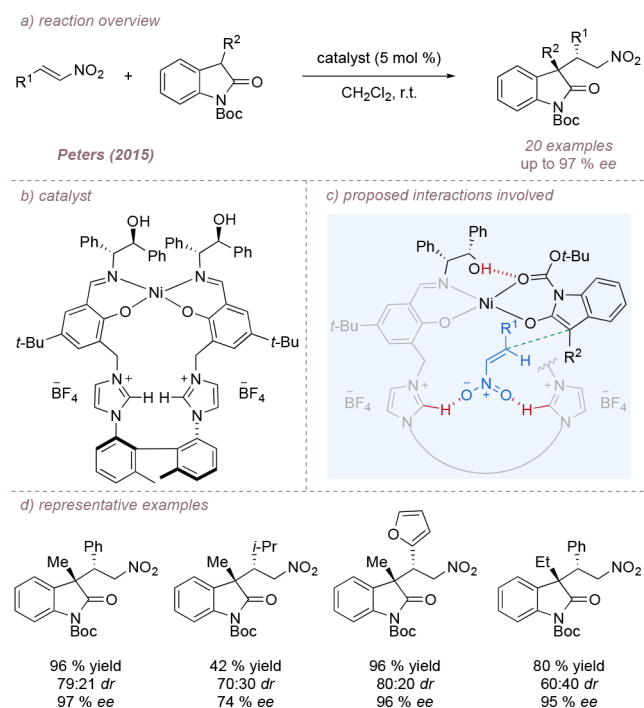
Figure 15. Asymmetric 1,4-addition of oxindoles to nitroolefins using a polyfunctional nickel catalyst.

Figure 16. Asymmetric 1,4-addition of oxindoles to maleimides using a bimetallic, multifunctional cobalt complex.

motif did not change the enantioselectivity of the reaction, strongly indicating that the axially chiral bisimidazolium backbone plays the dominant role in the enantiocontrol of the system. This was confirmed when the imidazolium was replaced with achiral linkers, as the enantioselectivity was both reversed and diminished. Thus, the imidazolium motif controls the configuration of the stereocenter generated at the nitroolefin, while the iminoalcohol side arm predominantly determines the new stereocenter formed at the oxindole (Figure 15d).

In 2019, Peters and co-workers reported a related dinuclear catalyst for the asymmetric 1,4-addition of oxindoles to maleimides (Figure 16a).[74] Two Lewis acidic cobalt centers are used in combination with a linker which comprises an enatiopure BINOL backbone and two triazolium moieties (Figure 16b). The authors speculated that the triazolium heterocycles would constitute stronger hydrogen bond donors than the imidazolium rings of the previous catalyst.[75,76] In this case, using cobalt as the metal led to improved reaction outcomes compared to nickel. Initial experiments focused on monometallic complexes and mechanistic experiments suggested more than one catalyst species was involved in the rate-determining step. For this reason, tethered bimetallic designs were investigated, ultimately leading to the catalyst shown, which gave excellent results (Figure 16c). Various control experiments exploring replacement of the triazolium unit resulted in poor yield and stereoselectivity, suggesting the triazolium is essential for high reactivity, most likely due to the strongly polarized C−H hydrogen bond donors.

Shortly after, the same authors described the development of a novel catalyst for the asymmetric 1,4-addition of prochiral 1,3-dicarbonyl substrates to β-substituted nitroolefins, again providing the typically rare diastereomer products (Figure 17a).[77] Impressively, α,β-disubstituted nitroolefins could be used, and the third contiguous stereocenter formed in such cases could be controlled via diastereoselective nitronate
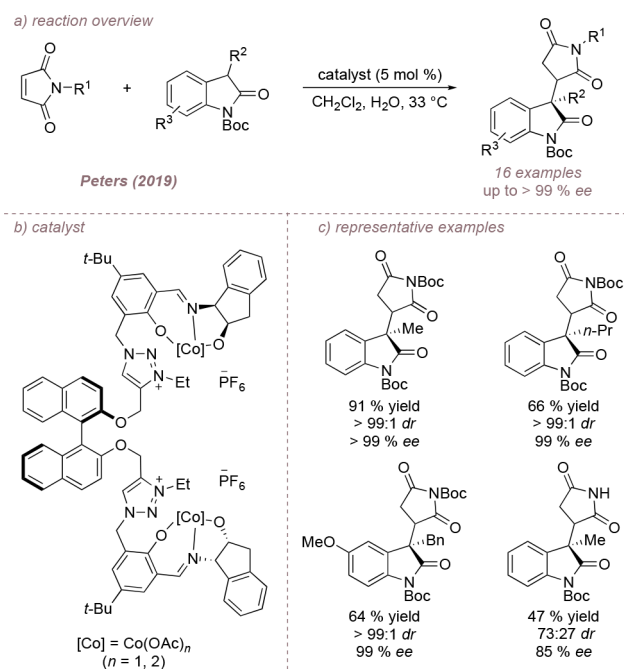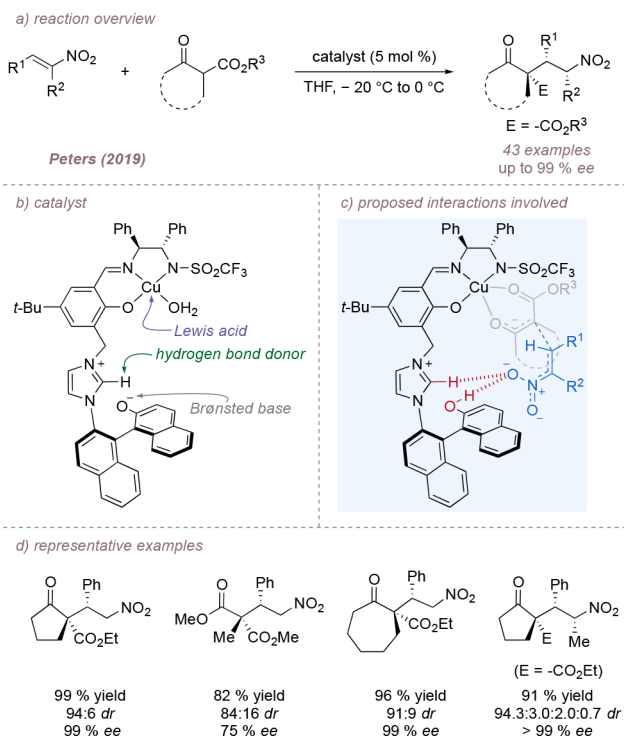

Figure 17. Further developments in asymmetric 1,4-addition reactions using a copper catalyst.

protonation. The new ligands developed for this task were based on copper and contain an axially chiral binaphthyl unit bearing both an imidazolium moiety and a phenolic hydroxyl (Figure 17b). All of these elements were crucial to form the unnatural diastereomers in high yield and with high enantioselectivity (Figure 17d). It was proposed that these motifs were responsible for hydrogen bonding with the nitroolefin during both the 1,4-addition and the nitronate

protonation, thus allowing the ligand to control the configuration at all three of the stereocenters formed. A detailed mechanistic study suggested that there was a key interplay between the Lewis acidic nature of the copper metal center and the basic nature of the aryl oxide to form the enolate, while the nitroolefin is activated by hydrogen bonds with the imidazolium unit and the newly formed phenolic −OH. This network of finely tuned OH···O and CH···O hydrogen bonds was responsible for spatially organizing the nitroolefin during C−C bond formation (Figure 17c). This was confirmed empirically, as the presence of both the −OH group and imidazolium was essential for high stereoselectivity. It was proposed that proton transfer from the naphthol to the nitronate follows to complete product formation, rendering the protonation step diastereoselective.

A powerful example of an asymmetric 1,4-addition reaction was reported by Zhu and co-workers with the addition of α-isocyanoacetates to β-aryl-α,β-alkynic ketones for the synthesis of axially chiral 3-arylpyrroles (Figure 18a).[78] The reaction was
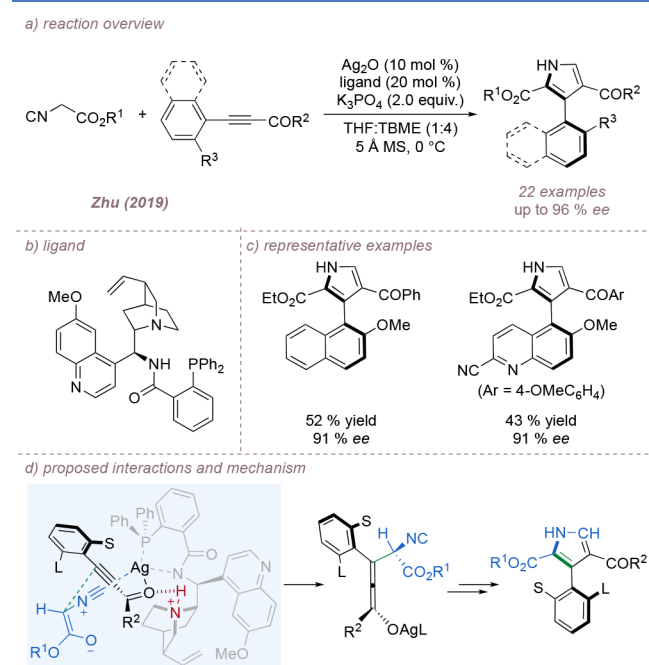

Figure 18. Asymmetric synthesis of 3-arylpyrroles via asymmetric 1,4-addition.

catalyzed by silver oxide with a phosphine ligand derived from *epi*-quinine, as utilized by Dixon (Figure 18b, see section 2.1 also).[37,38] This reaction constitutes a catalytic enantioselective version of the Yamamoto-de Meijere pyrrole synthesis, wherein the 3-arylpyrroles are formed *de novo* and possessing a chiral C−C axis.[79,80] A range of axially chiral 3-arylpyrroles could be synthesized with generally excellent enantioselectivities (Figure 18c). The authors proposed a stereochemical model implicating the (Z)-enolate of α-isocyanoacetate. The reaction components are thought to coordinate to silver via a carbonyl oxygen and a divalent isocyanide carbon atom, with the ligand coordinating via the amide nitrogen and phosphorus (Figure 18d). A hydrogen bond between the protonated quinuclidine of the ligand and the oxygen atom of the ketone were proposed to add further organization in the transition state.

2.3. Asymmetric Allylation Reactions. Transition metal-catalyzed asymmetric allylation reactions are now common-

place in organic synthesis, with applications in natural product synthesis and pharmaceuticals driving research in the area over half a century since foundational work by Tsuji in the 1960s using palladium as catalyst.[81−83] In a typical outer-sphere asymmetric allylation mechanism, the incoming nucleophile attacks the electrophilic, metal-complexed π-allyl ligand from the face opposite to the metal center. For this reason, sterically encumbered C_2-symmetric ligands are often utilized to project outward, transferring chiral information in the transition state. However, approaches which incorporate attractive noncovalent interactions between ligand and substrate have been shown to be viable remarkably early on for this reaction type. Important early work was covered in detail by the 1992 review from Sawamura and Ito, with key examples being discussed briefly here to provide context for subsequent developments (Figure 19a,b).[23] The earliest reports came from Kumada and co-
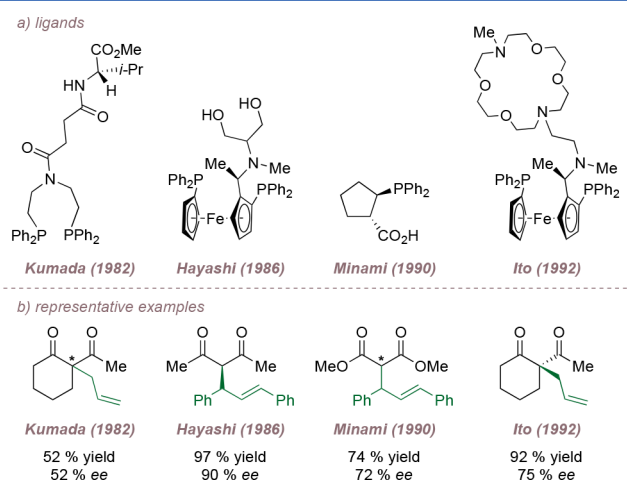

Figure 19. Seminal developments in asymmetric allylation using ligand designs which incorporate NCIs.

workers in 1982, whereby chiral amides were affixed to a bidentate phosphine backbone via an alkyl chain—the long reach hypothesized to place the chiral center close to the incoming prochiral nucleophile.[84] It was suggested that a hydrogen-bonding interaction between the chiral amide and the enolate nucleophile was responsible for enantioselectivities of up to 52% ee. This was followed in 1986 by Hayashi and co-workers, whereby chiral ferrocenylphosphine ligands were modified with hydroxyalkylamino groups that could hydrogen bond with the deprotonated malonate or alkyl isocyanide nucleophiles.[13,85] Enantioselectivities of up to 92% ee were obtained, suggesting that attractive NCIs were viable for achieving the highest levels of enantioinduction. Alternative ligand scaffolds were developed by Minami and co-workers which comprised chiral cycloalkylphosphines bearing a carboxylic acid group on the ring or in the β-position.[86,87] These ligands were able to catalyze the addition of malonate or phosphonoacetate nucleophiles to allylic acetates. While similar in design, it was proposed that the ligand would act in an opposite fashion to the ligands designed by Kumada and Hayashi, with the carboxylate group exerting electronic repulsion onto the incoming, negatively charged nucleophile. This ligand scaffold was later followed by an acyclic analogue which also proved to be an efficient ligand for asymmetric allylation reactions.[88,89] Modifications to the Hayashi ligands were made by Ito and co-workers in 1992, whereby the

hydrogen bond donors were replaced with a crown ether.[90,91] These macrocycles were proposed to form a ternary complex with the countercation of the deprotonated nucleophile, thereby transferring the chiral information from the backbone of the bidentate ligand to the incoming prochiral nucleophile.

Further important developments in asymmetric allylation reactions involving NCIs have come from List and co-workers who since 2007 have reported various important asymmetric allylation reactions of α-branched aldehydes and ketones via the concept of counteranion-directed catalysis using chiral phosphates together with palladium catalysis.[92−94] As defined in the Introduction, this Review will only focus on examples where the ligand remains fully complexed to the metal throughout the catalytic cycle.

In 2012, Ooi and co-workers reported an ion-paired chiral ligand for the asymmetric synthesis of α-nitrocarboxylates through palladium-catalyzed allylation (Figure 20a).[95] The
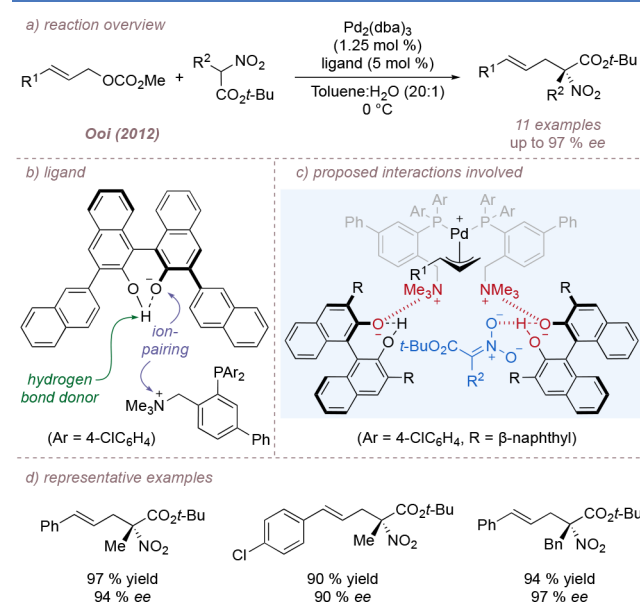

Figure 20. Enantioselective formation of quaternary stereocenters using an ion-paired ligand.

conceptually novel ligand design was based on an achiral, phosphine ligand bearing a remote quaternary ammonium functionality that was ion-paired with a chiral BINOL-derived anion (Figure 20b). Appropriate positioning of the cationic group on the ligand was very important as demonstrated with variants of this ligand. ^{1}H NMR experiments, kinetic studies, and nonlinear effect experiments were used to elucidate the reaction mechanism. These suggested a rate-limiting carbon−carbon bond formation in which two ion-paired ligands are present on a single palladium(II) metal center. The authors proposed that the nitronate anion likely engages in hydrogen bonding with the phenolic hydroxyl of the binaptholate anion in the transition state (Figure 20c) since racemic product was obtained if this hydroxyl was methylated. The elaborate network of noncovalent interactions in the transition state proved crucial for enantiofacial discrimination of the prochiral anionic nucleophile during its addition to the π-allyl complex and a good substrate scope was obtained in this challenging reaction (Figure 20d). This study was highly influential in that it provided a powerful demonstration that chirality can be associated with the primary ligand structure through ion-

pairing interactions. What is more remarkable is that here the chiral component likely resides between the ligand and the substrate, interacting with each through attractive noncovalent interactions.

The authors further demonstrated the general application of this idea in enantioselective allylation of benzofuran(3H)-ones to construct quaternary stereocenters with excellent enantio-control (Figure 21a).[96] In a modification compared with the
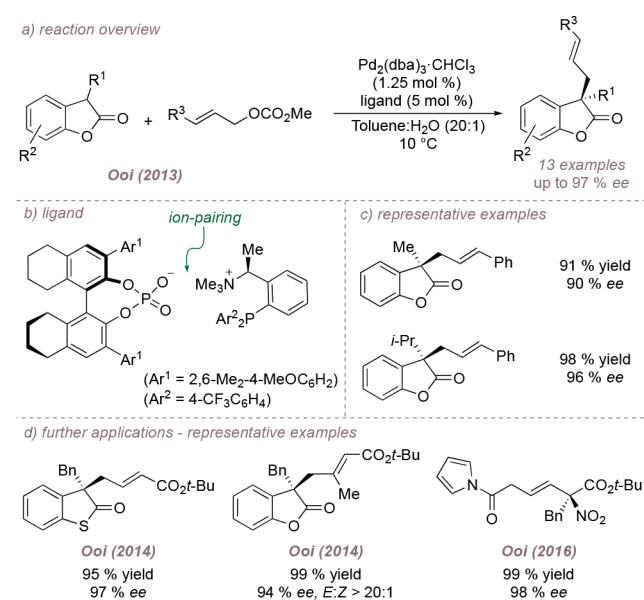

Figure 21. Further developments in asymmetric allylation using ion-paired ligands for palladium.

first report, an octahydrobinaphthol-derived chiral phosphate (Figure 21b) was used as the chiral anion as the more nucleophilic binaptholates were observed to react with the palladium-allyl complex in this case. Emphasis was placed on the modular approach to the synthesis of these ligands, meaning that changes to the chiral anion and cationic ligand could be made in tandem and large libraries of chiral ligands quickly accessed for optimization. This was exemplified when the scope of the reaction was expanded to include simple allylic carbonates, such as cinnamyl methyl carbonate. Structural tuning of the ammonium-phosphine was also important: appending an electron-withdrawing 4-trifluoromethyl phenyl group led to enhanced reactivity and incorporation of a stereocenter at the benzylic carbon of the ammonium-phosphine moiety improved selectivity. With the new catalyst system the authors were able to catalyze the addition to a range of simple carbonates with high yields and excellent enantioselectivities (Figure 21c). The benefits of the modular catalyst system were further emphasized in 2014, when the same group reported the *in situ* generation of ion-paired chiral ligands to quickly identify the optimal ligand system to allow the asymmetric allylation of benzo[*b*]thiophen-2(3H)-ones (Figure 21d, left).[97] Ion-exchange under phase-transfer conditions precluded the requirement for the preparation of individual ion-paired ligands, allowing for rapid combinatorial ligand screening. This modular approach was used again in 2014 to enable *E*-selective and enantioselective allylic alkylation of prochiral benzofuranones with 1,2-disubstituted allylic carbonates (Figure 21d, middle).[98] The rapid, combinatorial screening process allowed for subtle changes

in ligand design to be quite noticeably observed. This was demonstrated again in 2016, when complexes in a 1:2:3 ratio of palladium metal:ammonium phosphine:chiral phosphoric acid proved optimal for the enantioselective allylation of α-nitrocarboxylates with functionalized allylic carbonates (Figure 21d, right).[99] This suggested that there could potentially be three molecules of chiral phosphate involved in the enantiodetermining step.

In 2013, Liao and co-workers developed a palladium-catalyzed allylic alkylation of indoles in which hydrogen bonding was proposed to play an important role (Figure 22a).[100] The optimal phosphine ligand incorporated two chiral
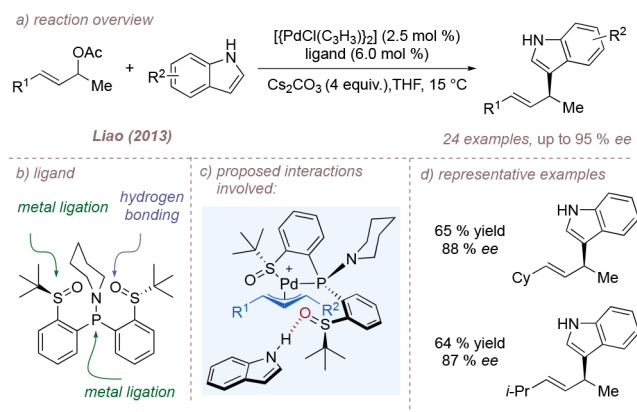
Figure 22. Asymmetric allylation of indoles using a bifunctional ligand acting as a hydrogen bond acceptor.

tert-butylsulfinyl groups, which were postulated to each have a different role to play (Figure 22b).[101] One is thought to serve as a ligand for palladium through sulfur, while the other acts as a hydrogen bond acceptor to interact with the indole N−H in the transition state (Figure 22c), a hypothesis supported by control experiments and NMR titrations. The reaction could be applied efficiently to a variety of 1-aryl,3-methyl-allylic acetates with good regio- and enantioselectivity (Figure 22d). It is expected that the DYKAT pathway occurs via the stereospecific oxidative addition of the acetate to generate a diastereomeric allyl palladium species. Reversible nucleophilic displacement by the palladium(0) species could then interconvert the mismatched diastereoisomer in a proposed epimerization process to the favored isomer, prior to trapping with the indole.[102]

Another noteworthy example of hydrogen-bond-directed enantioselective allylic alkylation was reported by Sawamura, who developed a protocol for the regio- and enantioselective addition of terminal alkynes to allylic phosphates using copper catalysis (Figure 23a).[103] Saturated N-heterocyclic carbene (NHC) ligands with a chiral backbone were able to direct the incoming alkyne to give the branched product, forming a stereogenic center. A phenolic hydroxy group at the *ortho*-position of the N-aryl groups of the NHC ligand proved crucial for high enantioselectivity (Figure 23b). An attractive Li$^+$-bridging interaction between the phenolic oxygen and the phosphate assisted the diastereoselective π-coordination of the alkene moiety toward the lithium (alkynyl)(aryloxo)cuprate (Figure 23c). Li$^+$ assisted allylic oxidation, followed by isomerization, and reductive elimination afforded the tertiary alkyl products. A similar methodology was implemented by the same group in the formation of quaternary stereogenic centers
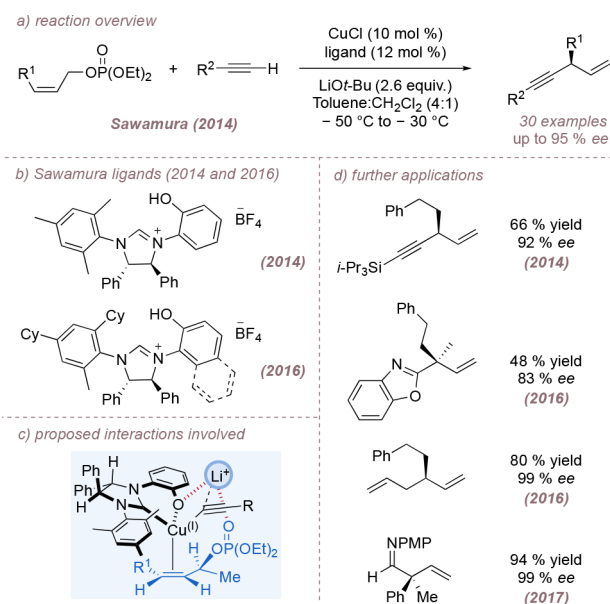
Figure 23. Copper-catalyzed enantioselective allylation reactions using bifunctional NHC ligands.

via the allylic alkylation of azoles in 2016 (Figure 23d second row) for which a modified catalyst was used (Figure 23b).[104] Shortly after, Sawamura disclosed conditions for the allyl−allyl coupling between allylic boronates and Z-aliphatic allylic phosphates using similar ligands for copper (Figure 23d).[105] A noncovalent interaction was not proposed in the reaction mechanism, but both reaction yield and enantioselectivity showed a marked increase when one N-aryl group contained phenolic functionality. In 2017, Sawamura and co-workers used the same ligand design for the regio- and enantioselective three-component coupling of isocyanides, hydrosilanes, and γ,γ-disubstituted allylic phosphates/chlorides for the enantioselective synthesis of α-quaternary formimides (Figure 23d).[106] It was proposed that reaction proceeds via a lithium aryloxo(formimidoyl)cuprate species followed by an S$_N$2′ reaction with the allylic substrate. As before, naphtholic and phenolic functionality on the NHC proved to be essential and was attributed to an O···Li$^+$···O ionic bridge that is formed between the ligand hydroxyl group and the hydrosilane reagent, forming a hydrosilicate species.

2.4. Asymmetric Cycloaddition Reactions. Cyclo-additions, whether pericyclic or proceeding by stepwise mechanisms, constitute one of the most important reaction classes in organic chemistry. While aspects of regioselectivity can in many cases be predicted and in some situations influenced, control of the absolute stereochemistry can prove more involved. In the following section, we discuss several examples in which carefully engineered NCIs between ligands and substrates in transition metal-catalyzed cycloaddition reactions have addressed this challenge in a variety of scenarios.

Major breakthroughs in enantioselective cycloadditions came with the application of Lewis-acidic metal catalysts bearing chiral ligands. In an early contribution, which is very pertinent to the topic of this Review and is thus included for context, Narasaka studied the Diels−Alder reaction of cyclopentadiene with a dienophile (Figure 24a).[107] The latter is capable of two-point binding to a Lewis-acidic titanium complex and addition of a chiral diol (Figure 24b) provided a
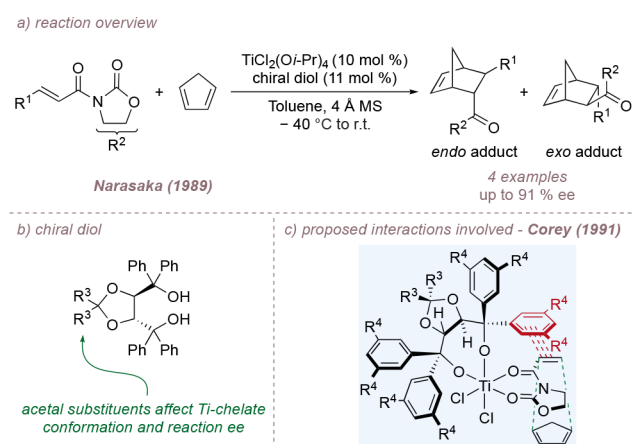
Figure 24. Enantioselective Diels−Alder cycloaddition reactions investigated independently by Narasaka and Corey.

Figure 25. Enantioselective synthesis of highly substituted pyrrolidines using a PyBidine ligand.

chiral environment in which the cycloaddition could take place, imparting enantioselectivity in the product. With optimization, high enantioselectivities could be obtained with a small selection of dienophiles. The system was later studied further by Corey who hypothesized that in the optimal chiral complex geometry, one of the benzhydryl aromatic groups on the diol would be well-placed to engage in π−π donor−acceptor interactions with the coordinated α,β-unsaturated carbonyl component of the dienophile.[108] As a result, in the transition state leading to the major enantiomer, the diene is forced to attack from the accessible bottom face of the s-trans configured dienophile. (Figure 24c). In an elegant study lending support to this hypothesis, Corey systematically varied the electron density on the aromatic arms of the ligand.[108] A series of catalyst analogues differing in the donating ability of the aromatic ring (R^4 = Me or CF_3 or Cl) demonstrated that increased π-basicity led to improved enantioselectivity in a similar system (Figure 24c). Steric effects may have also contributed to the observed trends in enantioselectivity. Since the publication of this report, Corey has developed novel catalysts to perform enantioselective Diels−Alder reactions.[109,110] While these catalysts do not involve transition metals and thus fall outside the scope of this Review, it is of note that noncovalent interactions including formyl hydrogen bonding and attractive π−π interactions between catalyst and substrate are critical to achieving high enantioselectivities with these systems.

In 2010 Arai and co-workers investigated novel bis-(imidazolidine)pyridine (PyBidine) ligands for [3 + 2] cycloaddition reactions involving iminoesters and the synthesis of pyrrolidine rings bearing four stereocenters was accomplished with good yield and near-perfect stereoselectivity (Figure 25a,b).[111] While the initial stereochemical model relied on steric arguments alone, in a later publication in which the reaction scope was expanded, the model was refined on the basis of DFT calculations.[112] In the lowest-energy endo-activation mode, the iminoester engages the copper in two-point binding. The incoming nitroalkane is spatially oriented and activated as a result of a key hydrogen bond with an acidified N−H of the coordinated imidazolidine, as shown for a simplified catalyst (Figure 25c). Various control experiments suggested the importance of the hydrogen bonding not only for enantioselectivity but also for effective reactivity, and selected representative examples are shown (Figure 25d).
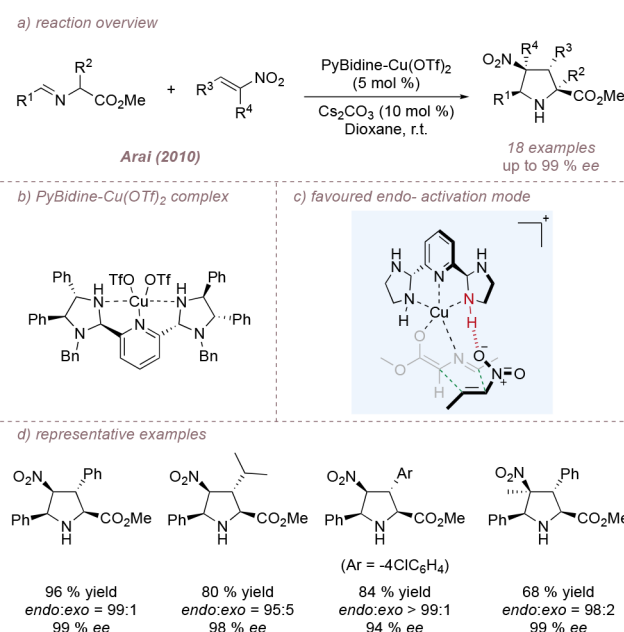
Since the first reports, PyBidine ligands and closely related scaffolds have found wider use in the application to other classes of transition metal-catalyzed asymmetric transformations.[113−115]

In 2011, Gong and co-workers employed noncovalent interactions to control enantioselectivity in the silver-catalyzed synthesis of the structurally related 4,5-dihydropyrroles.[116] The work bears a resemblance to the gold and silver-catalyzed aldol reactions discussed previously, differing primarily in the mode of nucleophilic attack of the enolate (1,4- as opposed to 1,2-attack). Here, reaction of α-substituted isocyanoacetates with 2-oxobutenoate esters affords 4,5-dihydropyrroles via a Michael addition-cyclization sequence (Figure 26a). A bifunctional ligand proved to be optimal (Figure 26b), and the authors proposed a transition state model where both stereocenters are set simultaneously (Figure 26c). The isocyanoacetate coordinates to silver, acidifying the α-proton and enabling deprotonation by the weakly basic acetate counterion. While the "soft" phosphorus atom on the ligand binds to the silver, the hydroxyl functionality on the naphthol ring group is free and well positioned to hydrogen bond to the newly formed enolate. Activation of the oxobutanoate ester is achieved through two-point binding to silver, which also restricts the conformational freedom of the electrophile ensuring that only the Re-face is attacked. While the overall yields and enantioselectivities of the major products were very good, the diastereoselectivities were moderate, although significant enantiomeric excesses were observed for the minor diastereomers also (Figure 26d). This example provides a nice demonstration in showing that chiral ligands need not be complicated to achieve high levels of enantiocontrol in challenging processes.

Several approaches to chiral pyrrolidines and their derivatives have already been outlined. In all cases, multiple stereocenters are set in a single transformation and such a rapid increase in complexity is very attractive. The following work from Ooi and co-workers is yet another fine example of this and is of particular note since a single chiral ligand orchestrates
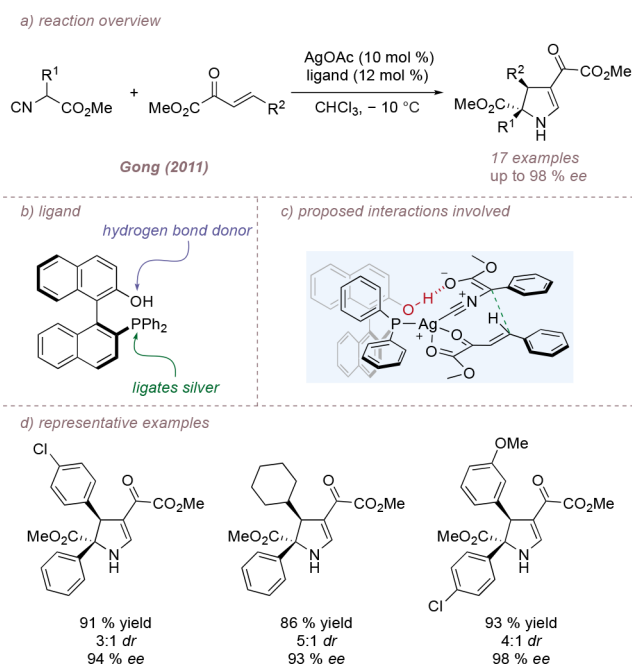
Figure 26. Enantioselective synthesis of 4,5-dihydropyrroles using a bifunctional ligand for silver.

Figure 27. Ooi's enantioselective synthesis of densely functionalized pyrrolidines using cationic phosphine ligands for palladium

the formation of three contiguous stereocenters of which two are vicinal quaternary centers. While most of the examples above have involved the combination of an iminoester and a substituted alkene, Ooi's disconnection is distinct, relying instead on π-allyl chemistry to form a C−N and a C−C bond in sequence.[117] The transformation begins with the oxidative addition of the palladium(0) into the C−O bond of a racemic 5-vinyloxazolidinone (Figure 27a). Loss of carbon dioxide then affords the Ns-stabilized nitrogen anion and a cationic π-allyl system. The nosylate anion selectively attacks one of the faces of the prochiral conjugated alkene acceptor following which ring-closure occurs through attack of the newly formed carbanion onto the electrophilic π-allyl system. The source of the chirality in the process is the unconventional chiral phosphine ligand **L9** containing a triarylphosphine in which one of the aromatic rings is functionalized with a side arm attached to a chiral cation based on the Maruoka scaffold (Figure 27b).[118] The anion associated with the ammonium salt was also found to play an important role to play in determining stereoselectivity, iodide being optimal. The authors advance the following argument in order to rationalize the reaction stereochemistry. The nosylate anion formed from the ring-opening of the oxazolidinone is proposed to ion pair with the remote ammonium moiety of the chiral ligand (Figure 27c). It is here that the nature of the achiral anion originally associated with the ammonium cation is important. It was hypothesized that the nosylate might preferentially associate with the cationic palladium reducing its availability for nucleophilic attack. However, the presence in the reaction mixture of anions such as iodide which have strong affinity for monocationic palladium leave the N-nosyl anion free to ion-pair with the chiral cation instead. As a result of its proximal chiral environment the anionic nitrogen selectively attacks one prochiral face of the trisubstituted alkene acceptor to form a stabilized anion. In the ring-closing step, which defines the stereochemistry at both quaternary centers, the chiral ligand controls the planar chirality of the π-allyl system while also
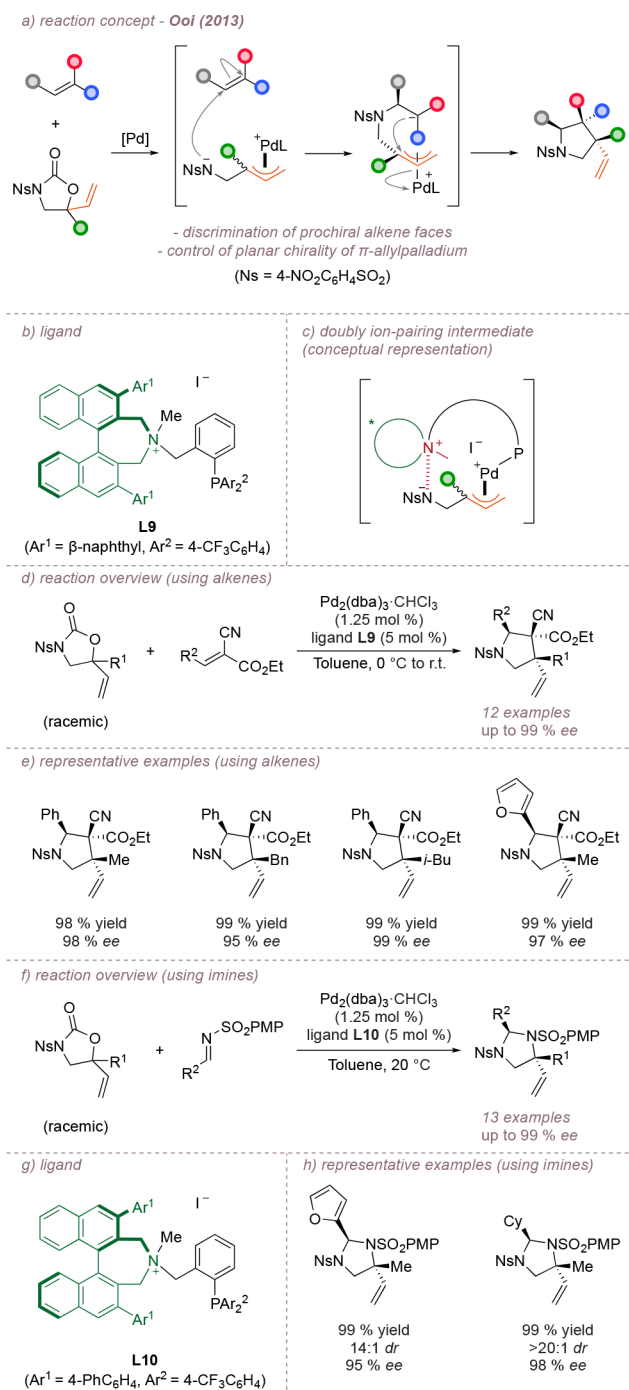
controlling which face of the prochiral carbanion this system is attacked by. Under the optimized conditions, variation on both the substituted alkene and the racemic oxazolidinones led to the efficient synthesis of several highly congested pyrrolidine cores in excellent yield and stereoselectivity (Figure 27d,e) In later work, the same group reported a related reaction in which an imine was used in place of the alkene component to afford chiral imidazoline products (Figure 27f−h).[119] These reports are ground-breaking in that they constitute relatively rare cases of the use of ion pairing interactions between ligand and substrate to realize enantiocontrol.

A long-standing interest of the Tang research group has involved the incorporation of "side arms" into BOX-type ligands in order to improve the efficiency or stereoselectivity of reactions catalyzed by the resulting metal complexes.[120] A recent example nicely showcases how attractive NCIs can sometimes be operative in unexpected situations. Sun, Li, Tang, and co-workers used a trisoxazoline (TOX) ligand bearing an Indane-derived side arm to direct enantioselective nickel-catalyzed [3 + 3] cycloadditions of azomethine imines with cyclopropane diesters, in which attractive π–π interactions are proposed to play an important role (Figure 28a,
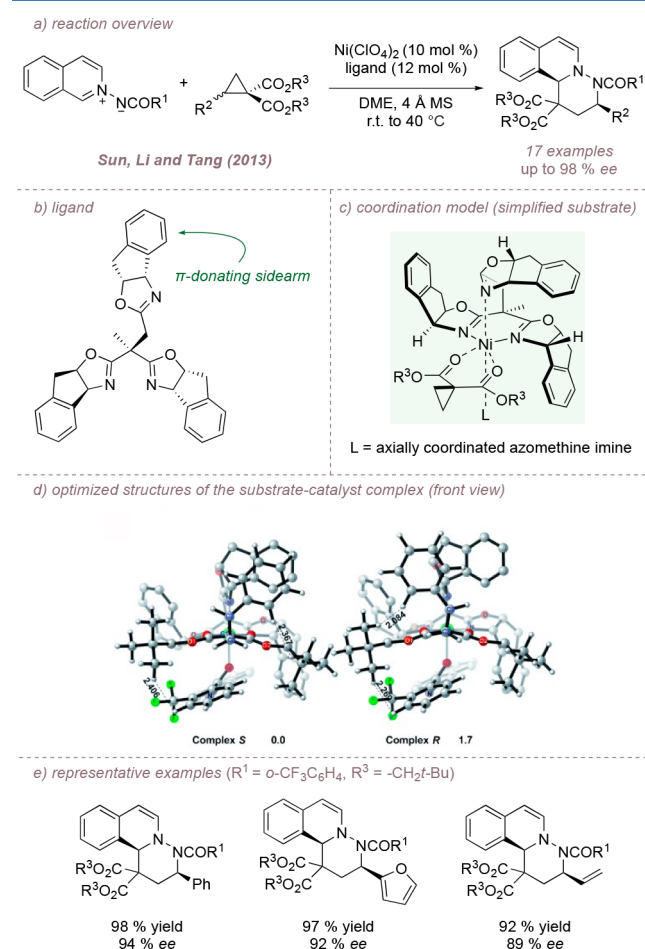

a) reaction overview

Sun, Li and Tang (2013)

17 examples
up to 98 % ee

b) ligand

π-donating sidearm

c) coordination model (simplified substrate)

L = axially coordinated azomethine imine

d) optimized structures of the substrate-catalyst complex (front view)

Complex S   0.0   Complex R   1.7

e) representative examples (R[1] = o-CF₃C₆H₄, R³ = -CH₂t-Bu)

98 % yield   97 % yield   92 % yield
94 % ee   92 % ee   89 % ee

Figure 28. Enantioselective [3 + 3] cycloaddition involving proposed attractive π–π interactions. Reproduced with permission from ref 121. Copyright 2013 Wiley-VCH.

b).[121] In a simplified system, the proposed coordination of the catalyst with a substrate is shown (Figure 28c). For certain functionalized cyclopropanes, π–π attractive interactions between the designed side arm and the unsaturated substituents on the ring were crucial to obtaining high levels of stereoselectivity in the reaction. DFT calculations suggested that under the reaction conditions a kinetic resolution occurs. Thus, when 2.2 equiv of racemic phenylcyclopropane diester is used, the complex between the (S)-cyclopropane and the chiral catalyst is favored over the (R)-cyclopropane complex by 1.7 kcal mol⁻¹. These same π–π interactions also stabilize the (S)-transition state by 1.4 kcal mol⁻¹. Such interactions are precluded in the transition state involving the (R)-cyclopropane because, in this case, the rings are misaligned. The

(R)-cyclopropane transition state is further disfavored as a result of steric clashing between the ester and aromatic substituents on the adjacent three-membered ring. Axial coordination of an azomethine imine molecule at the metal center prevents rotation of the ester to relieve this strain (Figure 28d, reproduced with permission). Various control experiments supported the hypothesis of the π–π attraction being important for attaining high enantioselectivity. Under the reaction conditions, excellent enantioselectivities were obtained for a number of structurally interesting products (Figure 28e).

Sawamura's work on asymmetric alkynylation reactions using chiral prolinol-phosphine ligands has been discussed earlier in this Review (section 2.2). These ligands have also found application to enantioselective copper-catalyzed alkyne-nitrone couplings (Kinugasa reactions) to afford β-lactams (Figure 29a).[122] The reaction has a broad scope and accesses

a) reaction overview

Cu(OTf)₂ (10 mol %)
ligand (10 mol %)

Et₂NH (1.0 equiv.)
Toluene, – 40 °C

Sawamura (2017)

33 examples
up to > 99 % ee

b) representative examples

(Ar = 1-naphthyl)

79 % yield   91 % yield   50 % yield   76 % yield
89:11 dr   90:10 dr   72:28 dr   87:13 dr
91 % ee   99 % ee   98 % ee   98 % ee

c) ligand

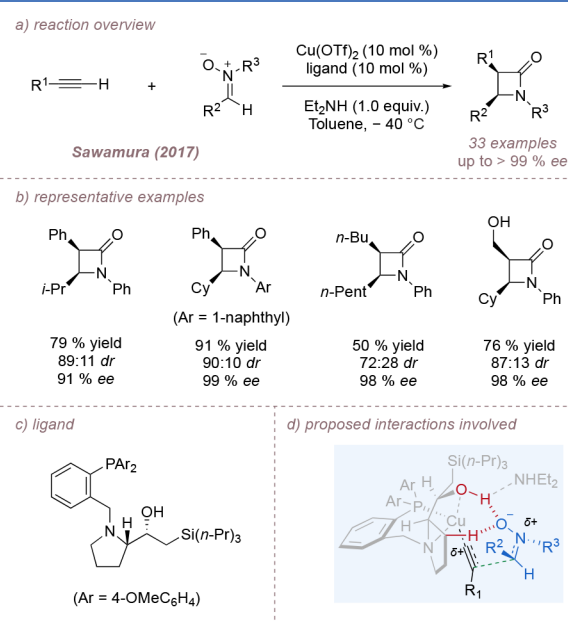(Ar = 4-OMeC₆H₄)

d) proposed interactions involved

Figure 29. Enantioselective Kinugasa reaction employing a chiral prolinol-phosphine ligand.

β-lactams bearing alkyl groups at the C–3 position (Figure 29b) using the ligand shown (Figure 29c). According to the authors' mechanistic proposal, the nitrone interacts with the copper complex through two hydrogen bonds: one conventional hydrogen bond involving the free prolinol hydroxyl group and a less conventional C–H···O hydrogen bond from the prolinol backbone. These interactions orient the nitrone such that in the bond-forming step, steric repulsion between the alkyne substituent and the N-aryl group is minimized (Figure 29d). The second stereocenter is set in a diastereoselective protodemetalation step during which catalyst turnover occurs. Subsequently, the methodology was expanded to the synthesis of α-alkylidene-β-lactams.[123]

The Baik and Yoon laboratories have together published two very recent reports in which enantiocontrol is exerted in excited-state [2 + 2] cycloaddition reactions. These works are remarkable since they showcase enantiocontrol in primary photoreactions, in which it is typically very challenging to achieve stereoselectivity due to the short lifetimes and extreme reactivities associated with the intermediates involved.[124] In

the first publication, Baik, Yoon, and co-workers studied an intramolecular cycloaddition reaction of 3-alkoxyquinolone substrates catalyzed by a chiral-at-iridium octahedral complex under photochemical conditions (Figure 30a,b).[125] On the
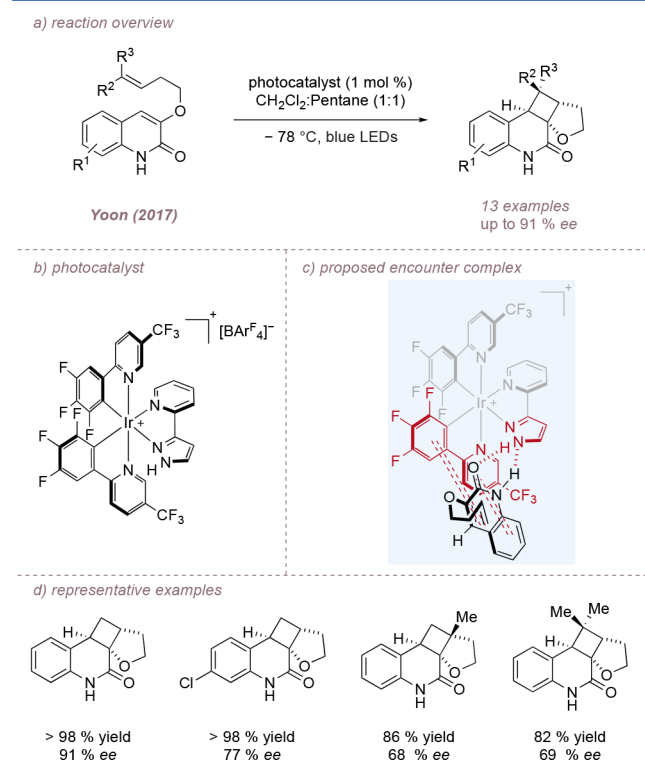

Figure 30. Enantioselective intramolecular [2 + 2] cycloaddition using a chiral-at-iridium photocatalyst.

basis of detailed studies involving mechanistic, spectroscopic, and DFT experiments, the authors proposed a Dexter energy transfer mechanism where an electron from the α-HOMO of the excited photocatalyst moves into the α-LUMO of the substrate. Simultaneously, there is electron transfer in the other direction from the quinolone to the β-LUMO of the metal complex. In this system, DFT reveals that three attractive noncovalent interactions in the encounter complex are critical to achieving high enantioselectivity and a productive reaction (Figure 30c). The first two interactions are between the substrate and the pyrazole-derived ligand. There is a hydrogen bond between the quinolone and the pyrazole N−H, and an unusual attractive interaction is proposed between the N−H of the quinolone amide and the π-system of the pyrazole. Any substrate modifications which could alter these contacts led to large decreases in observed ee. The final interaction is a π−π interaction between a cyclometalated phenylpyridine ligand and the substrate. The stacking ensures that there is the correct orbital overlap between the photocatalyst and substrate for the energy transfer and also shields the *Re*-face of the quinolone from intramolecular attack. Selected examples from the substrate scope are shown (Figure 30d).

The second, closely related publication is a very thorough study and demonstrates how subtle changes in the noncovalent interactions between catalyst and substrate can lead to a fundamentally different reaction mechanism and outcome. In this work, the authors describe an *inter*molecular [2 + 2] cycloaddition reaction between 3-alkoxy quinolones and (primarily) maleimides (Figure 31a).[126] The system is very
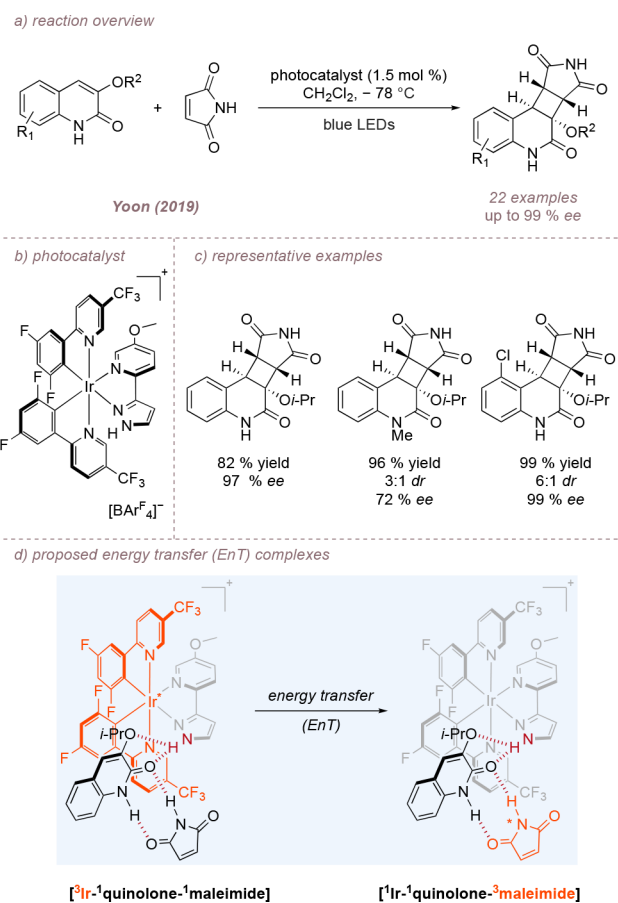

Figure 31. Enantioselective intermolecular [2 + 2] cycloaddition using a chiral-at-iridium photocatalyst.

similar to the intramolecular one with only a minor variation in the photocatalyst (Figure 31b) and conditions. Experimental evidence showed that in this second system, intermolecular energy transfer occurred from the excited iridium photocatalyst, which is also binding the quinolone, to the maleimide. The triplet maleimide state then engages the bound quinolone in a cycloaddition reaction before the former has a chance to escape from the solvent cage. Since the quinolone is interacting with the photocatalyst through hydrogen bonding, the reaction takes place within a chiral environment. Central to the success of this reaction is the fact that Dexter energy transfer from the excited iridium to the quinolone, which proceeded so efficiently in the previous example, is now disfavored. DFT revealed that this was as a direct consequence of a difference in structure in the quinolone-photocatalyst complex. In this case, the pyrazole N−H engages the quinolone carbonyl and also the alkoxy side chain in hydrogen bonding. However, the "unusual" interaction between the quinolone N−H and the pyrazole π-system is now absent. Evidence supporting the loss of this interaction was observed when *N*-methylation of the quinolone did not lead to a significant decrease in enantioselectivity (Figure 31c). As a consequence of the substrate's altered binding poise, the orbital overlap between the cyclometalating ligand of the photocatalyst and the aromatic quinolone system is poor, which in turn limits the efficiency of the intramolecular Dexter energy transfer between these two components. As a result, the cyclometalated ligand orbitals are now available to interact with the approaching maleimide ensuring intermolecular energy transfer to this

species instead. Representations of the complexes involved in the energy transfer are shown above (Figure 31d). The results presented in this work are significant since they counter the view that in order to perform asymmetric primary photoreactions some kind of association is required between the chiral catalyst and the substrate prior to the reactant excitation and bond-forming events.

Returning to the synthesis of pyrrolidines, in 2019 Zhang and co-workers used a ligand design approach to tackle the enantioselective 1,3-dipolar cycloaddition reaction between methacrylonitriles and iminoesters (Figure 32a).[127] The
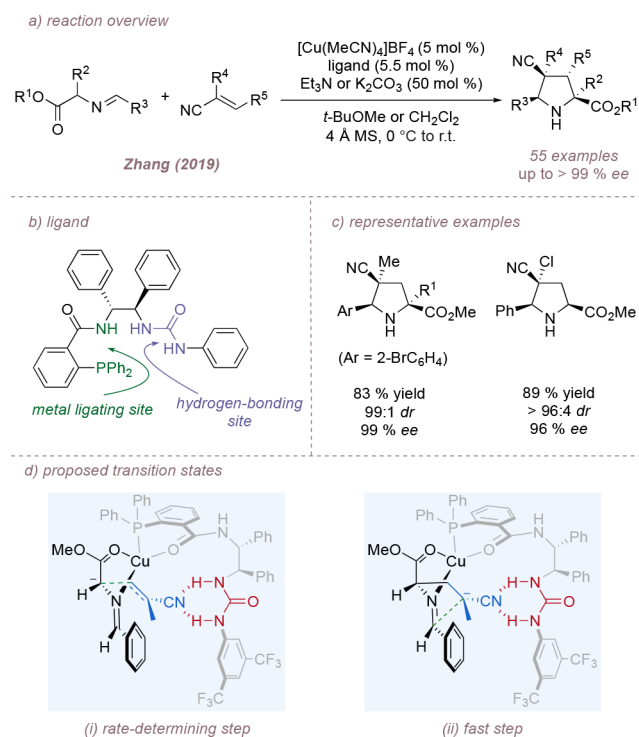

Figure 32. Enantioselective synthesis of pyrrolidines using a designed bifunctional phosphine ligand.

authors synthesized a ligand possessing a bidentate metal-coordinating site linked to a thiourea group via a chiral diphenyldiethylenediamine linker (Figure 32b). Under the optimized reaction conditions a variety of iminoester and acrylonitrile derivatives were converted to highly substituted chiral pyrrolidine products bearing up to three stereocenters, with excellent stereoselectivity (Figure 32c). DFT calculations revealed that in the enantiodetermining step, the iminoester coordinates to the copper center via two-point binding and the enolate adds in a conjugate fashion to the electrophile. The latter interacts with the urea portion of the ligand through hydrogen bonding which stabilizes the negative charge on the intermediate. In the second (fast) step, attack of the nitrile anion back into the iminoester C=N π^* orbital forms the second stereocenter (Figure 32d). It is notable that during optimization, other privileged chiral ligands were also tested but none could match the combination of high yields and selectivity displayed by the novel ligand. This work provides a clear demonstration of the advantages of rational incorporation of attractive noncovalent interactions between ligands and substrates to enhance enantioselective catalysis.

In a more recent example, Toste and Sigman studied an asymmetric γ,δ-selective Diels−Alder reaction between cyclopentadiene and conjugated dienophiles catalyzed by a Lewis-acidic gold(III) complex (Figure 33a).[128] The reaction is
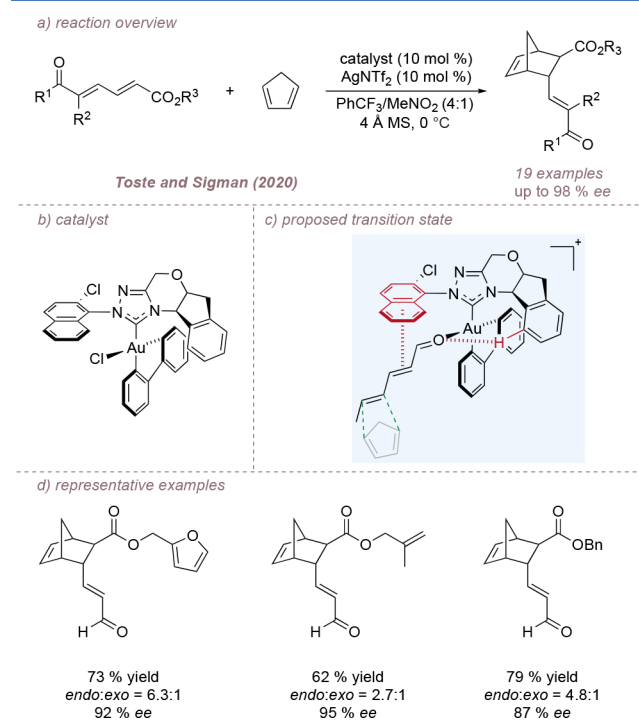

Figure 33. Enantioselective and regioselective gold(III)-catalyzed Diels−Alder reactions.

intriguing, first as a result of the atypical regioselectivity and also as it is an example of the use of gold(III) as opposed to gold(I) in enantioselective catalysis. Various NHC ligands were evaluated and the catalyst shown was identified as optimal (Figure 33b). DFT calculations suggested that in the lowest-energy transition state, two important attractive noncovalent interactions are at play (Figure 33c). The first is a $\pi−\pi$ interaction between the aromatic ring on the ligand and the α,β-alkene. The second involves the $C(sp^2)$-H bond on the other aromatic ring of the NHC and the aldehyde oxygen. Together, these two interactions ensure excellent enantioselectivity despite the site of reaction being far from the source of chirality. The stereochemical model was unable to explain the results obtained when some of the other ligands in the library were employed. Therefore, the authors turned to multivariate linear regression (MLR) analysis which identified three factors determining the stereoselectivity—large proximal bulk to the gold center, substituent shape, and an interaction energy term which was presumed to comprise of the attractive noncovalent interactions previously identified. Under the final optimized conditions, a range of substrates underwent the transformation with moderate to excellent ee (Figure 33d).

2.5. Cross-Couplings and Miscellaneous C−C Bond-Forming Reactions. In 2013, Zhou and co-workers developed a Heck-type asymmetric arylation of γ-butyrolactone-derived silyl enol ethers using novel chiral phosphine ligands **L11** and **L12** (Figure 34a,b).[129] Surprisingly, DFT calculations probing the transition state of the reductive elimination step suggested that the H_1 and H_8 protons of the naphthalene ring of **L11** form double hydrogen bonding
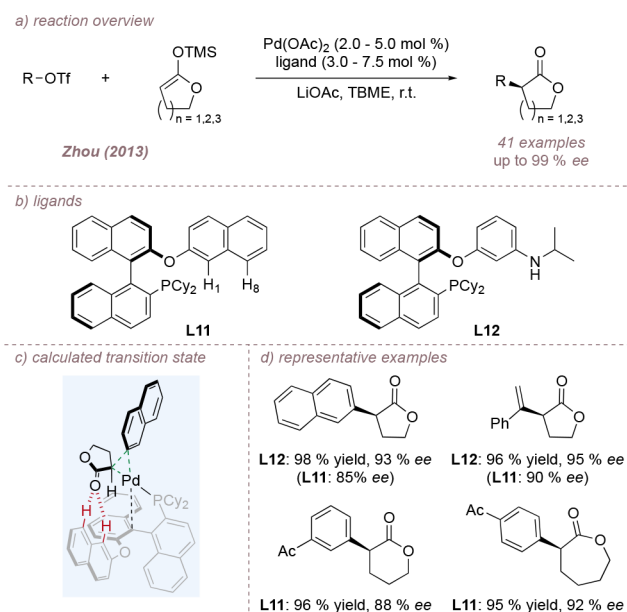
Figure 34. Palladium-catalyzed arylation and vinylation of enolates.

Figure 35. Asymmetric alkylation of propargylic alcohols using a multifunctional ligand for ruthenium.

interactions with the carbonyl oxygen of the substrate, which stabilizes the pathway leading to the major enantiomer (Figure 34c). In the transition state leading to the minor enantiomer, these hydrogen bonds were absent. On the basis of this insight, ligand **L12** was synthesized, where the naphthalene ring was replaced by an aniline group in which the N−H bond occupies a similar position to the naphthalene H_8. It was expected that based on its improved hydrogen bond-donating ability, this new ligand might lead to increases in ee. In general, this proved to be the case, although in many instances, the differences in enantioselectivity were modest (Figure 34d). Overall, excellent yields and enantioselectivities for the arylation and vinylation of silyl enol ethers were obtained. Interestingly, the reaction with β-substituted γ-butyrolactones proceeded efficiently giving only the trans isomer. Simultaneously, the same group reported the related asymmetric arylation of cyclic ketones via tin enolates generated in situ from acetyl enol ethers.[130] Both **L11** and **L12** gave excellent results in this reaction, and DFT calculations suggested that an analogous hydrogen bonding interaction between the ligand and substrate was once again essential in obtaining high enantioselectivities.

In 2015 Nishibayashi and co-workers reported the diastereo- and enantioselective alkylation of propargylic alcohols with enecarbamates (Figure 35a).[131] The authors designed a novel hybrid catalyst which contained a thiolate-bridged diruthenium complex linked to a phosphoramide based on (R)-BINOL (Figure 35b). It was hypothesized that the phosphoramide could activate enecarbamates through hydrogen bonding and also control the facial selectivity of nucleophilic attack onto a ruthenium-allenylidene intermediate. Optimal length of the chain linking the two catalyst components was crucial, and NMR studies suggested a dual hydrogen bonding interaction between the phosphoramide and the carbamate of the substrate (Figure 35c). It was proposed that this arrangement facilitated highly enantioselective C−C bond formation, and various control experiments provided support for this. The substrate scope was in general broad (Figure 35d).

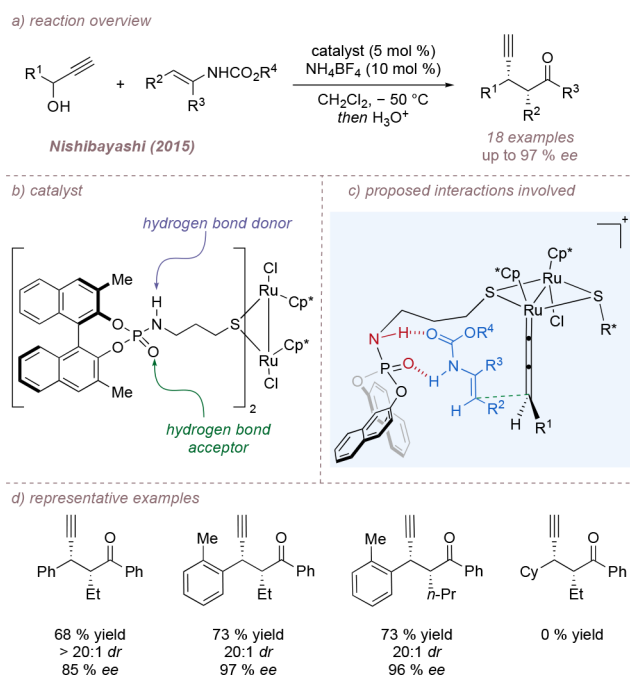In 2016, Miller and co-workers demonstrated that attractive NCIs could induce stereocontrol at a distal position in the desymmetrization of diarylmethanes (Figure 36a).[132] Copper-catalyzed Ullman cross-coupling of malonate nucleophiles was carried out on a prochiral substrate bearing two remote aryl bromides and proceeded enantioselectively using a peptide ligand **L13** (Figure 36b). This resulted in the formation of a new stereocenter quite some distance from the site of reaction. The guanidine of **L13** was proposed to act as a ligating site for copper, and the terminal carboxylate was found to be crucial for high selectivity. Careful studies suggested that the trifluoroacetamide groups on the substrate are deprotonated to form the corresponding Cs-salt. Kinetic studies and solvent effects suggested that **L13** interacts with the substrate at both ends. At the site of the reaction, N-coordination to copper facilitates oxidative addition into the carbon−bromine bond. Importantly, the distant deprotonated amide is proposed to interact with the terminal carboxylate group of the peptide through a Cs-bridge, with the Cs^+ cation associated with the deprotonated trifluoroacetamide (Figure 36c). This complex assembly, governed by NCIs, is thought to be responsible for the high stereoselectivity of the desymmetrization reaction. Furthermore, kinetic resolution could be achieved and it was revealed that a trifluoroacetamide was not required at the distant position for high k_{rel}, leading the authors to propose that in these cases, a cation-π interaction is binding the remote parts of the catalyst and substrate (Figure 36d). In the following year, Miller and co-workers demonstrated that this concept could be applied to desymmetrization of the same substrates via catalytic C−O bond formation, again using copper.[133] With the newly optimized peptide ligand **L14**, phenols could be used as nucleophiles in place of malonates, resulting in excellent enantioselectivity in the coupled products (Figure 36e).

Over the years, the group of Huw Davies has pioneered the use of rhodium catalysts to enable a wide variety of C−H insertion reactions of transition metal carbenes, while simultaneously developing innovative strategies for control of both site-selectivity and enantioselectivity.[134] In 2017, Davies

a) reaction overview

Miller (2016)

Cu(MeCN)$_4$BF$_4$ (5 mol %)
ligand **L13** (10 mol %)
Cs$_2$CO$_3$ (3.2 equiv.)
DMF:Toluene, r.t.

11 examples
> 98 % *ee*

b) ligand

interacts with substrate

ligand for Cu

L 13

c) proposed interactions involved

d) representative examples

R^1 = Et; 46 % yield, > 98 % *ee*
R^1 = *i*-Pr; 48 % yield, > 98 % *ee*

(*kinetic resolution*)
k_{rel} = 10.3

(*kinetic resolution*)
k_{rel} = 1.2

e) C-O bond formation - optimal ligand and representative examples

L 14

R^1 = 4-OMe; 68 % yield, 92 % *ee*
R^1 = 2-*t*-Bu; 43 % yield. 98 % *ee*
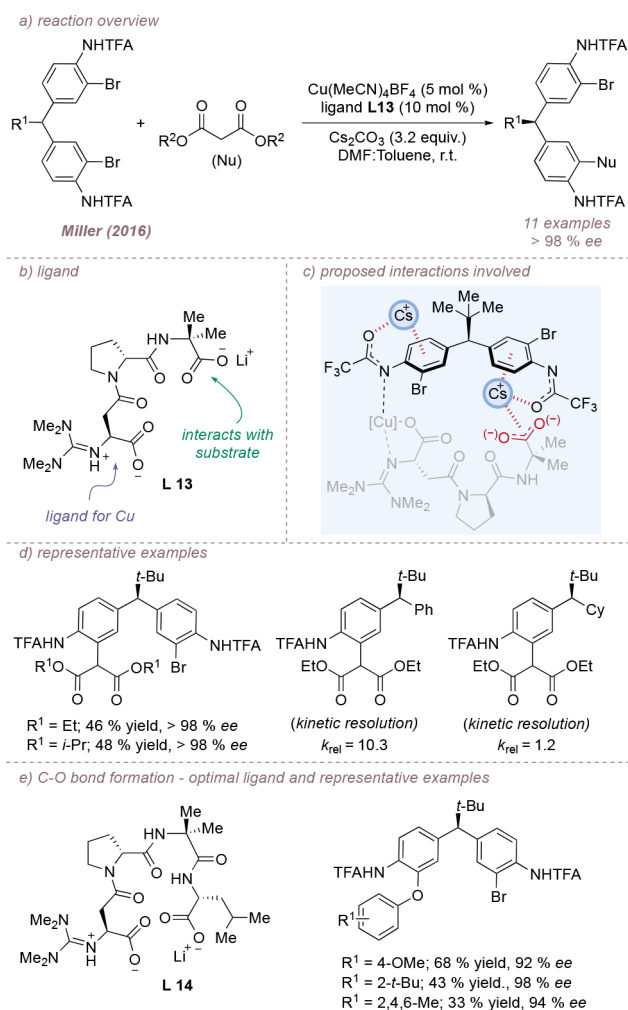R^1 = 2,4,6-Me; 33 % yield, 94 % *ee*

Figure 36. Desymmetrization of diarylmethanes via Ullman coupling using a peptide ligand for copper.

and co-workers reported the site-selective and enantioselective functionalization of nonactivated, tertiary C−H bonds (Figure 37a).[135] By using a modified carbene reagent and a Rh$_2$(*S*-TCPTAD)$_4$ catalyst (Figure 37b), site-selective functionalization at the most accessible tertiary C−H bond was achieved, which had previously been inaccessible using more sterically demanding catalysts.[136] X-ray and computational studies demonstrated that the catalyst adopts a structure of approximately C_4-symmetry with a relatively shallow pocket formed of phthalimido groups, enabling the most accessible tertiary C−H bonds to approach the rhodium-bound carbene. Computational studies revealed that, even though the catalyst is quite rigid, when the carbene is bound to the complex there is a change in the ligand orientation, where one of the phthalimido group bends to engage in attractive π−π interactions with the aryl ring on the carbene. This π-stacking interaction is proposed to act as an important stabilizing interaction and favors attack of the alkane substrate on the opposite face of the carbene (Figure 37c, reproduced with permission). Excellent site-selectivity could be achieved for a variety of simple as well as more elaborate substrates (Figure 37d). It is possible that similar stabilizing interactions are responsible for the observed enantioselectivity in other related C−H functionalization reactions.[134]
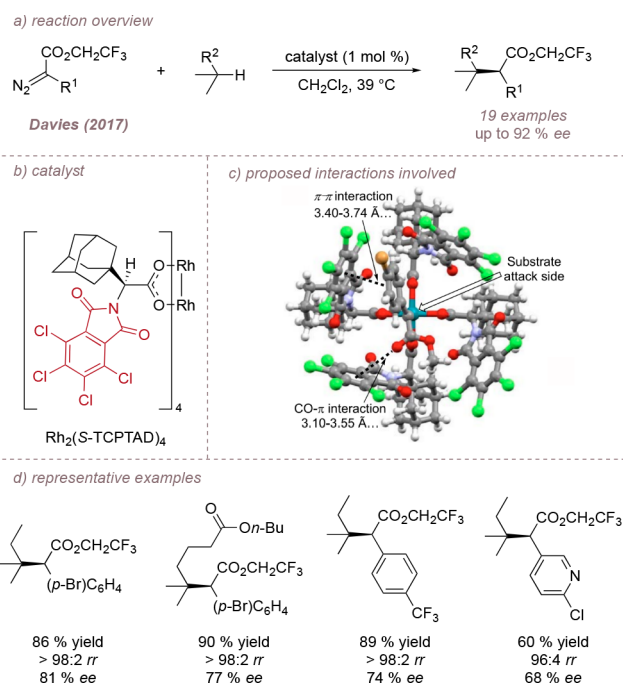
a) reaction overview

catalyst (1 mol %)
CH$_2$Cl$_2$, 39 °C

Davies (2017)

19 examples
up to 92 % *ee*

b) catalyst

Rh$_2$(*S*-TCPTAD)$_4$

c) proposed interactions involved

π-π interaction
3.40-3.74 Å...

Substrate attack side

CO-π interaction
3.10-3.55 Å...

d) representative examples

86 % yield
> 98:2 *rr*
81 % *ee*

90 % yield
> 98:2 *rr*
77 % *ee*

89 % yield
> 98:2 *rr*
74 % *ee*

60 % yield
96:4 *rr*
68 % *ee*

Figure 37. Site- and enantioselective functionalization of non-activated, tertiary C−H bonds. Reproduced with permission from ref 135. Copyright 2017 Springer Nature.

In addition to rhodium, cobalt has also proven to be a highly effective metal for promoting a variety of carbene transfer reactions.[137] The group of Zhang has studied asymmetric cobalt-catalyzed cyclopropanation reactions extensively and in doing so has developed a new family of chiral D_2-symmetric cobalt(II) porphyrin catalysts.[138] In a study from 2010, the group reported the efficient cyclopropanation of a range of electronically distinct alkenes using a cobalt(II) complex based on the chiral ChenPhyrin ligand (Figure 38a,b).[139] Under the optimized reaction conditions, a range of alkenes could be converted to valuable cyclopropane products in very good yield and with excellent control over all aspects of selectivity (Figure 38c). A dual hydrogen bonding interaction between the chiral cyclopropyl amide N−H groups of the ligand backbone and the hydrogen bond-accepting substituents of the postulated metallocarbene intermediate was proposed to contribute to the overall efficiency of the process through the stabilization of the highly reactive species (Figure 38b). In subsequent publications, the nature of the hydrogen bond-accepting groups on the metallocarbene precursor was varied to enable the efficient enantioselective cyclopropanation of alkenes using α-ketodiazoacetates[140] (Figure 38d, left and centre) as well as an enantioselective intramolecular cyclization reaction using α-methoxycarbonyl-α-diazosulfone precursors (Figure 38d, right).[141]

Since the early 2000s, there has been significant interest in gold catalysis.[142,143] A well-documented challenge that must be overcome when considering enantioselective catalysis using gold(I) is the adoption of a linear geometry at the metal in which the ligand and coordinated substrate are placed at 180° to each other. Thus, in a conventional chiral ligand strategy based on steric repulsion, the stereochemical information may be rather far removed from the site of substrate coordination.[144] Chemists have devised ingenious approaches to tackle this challenge, some of which rely on attractive noncovalent
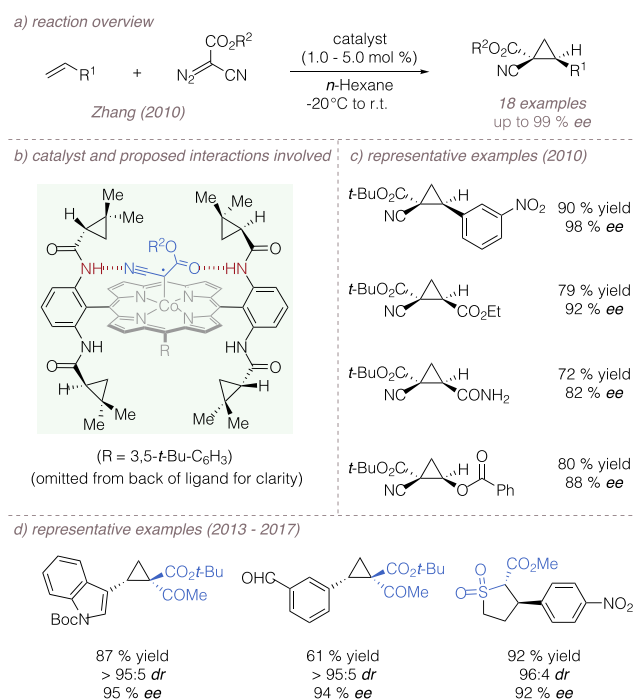
Figure 38. Enantioselective cobalt-mediated carbene transfer reactions.

Figure 39. Gold(I)-catalyzed enantioselective synthesis of tetrahydrocarbinole scaffolds.

interactions. A landmark publication which offers an elegant and powerful solution to the above-mentioned problem is Toste and co-workers' report on asymmetric gold(I)-catalyzed hydroxyalkylation and hydroamination reactions, published in 2007.[145] While this work falls outside of the scope that we have defined for this Review (see Introduction), it is mentioned here for context. Due to the catalytically active gold(I) complex being cationic throughout the cycle, the authors reasoned that close association with a chiral anion might control enantioselectivity in the key transition state. The unique bifunctionality of chiral phosphates also leads to highly organized, ternary transition states in many cases, involving interactions with the substrate also. The concept of pairing a chiral anion with a reactive, cationic transition metal has had far-reaching implications, and has been reviewed extensively elsewhere.[21,146] Other solutions include the use of axially chiral digold complexes and monodentate phosphoramidite ligands.[147−149]

In 2017, Zhang and co-workers reported an asymmetric, gold(I)-catalyzed cyclization of allenes in which ligand-substrate NCIs play a role (Figure 39a). In this case, the nucleophilic component was a substituted indole and the electrophile a pendant *N*-allenamide attached to the C-3 position.[150] A number of bifunctional sulfinamide-phosphine (Sadphos) ligands have been developed in the Zhang laboratory, and a new variant was used here.[151] PC-Phos is a monodentate phosphine ligand loosely based on Xantphos but bearing a chiral sulfonamide attached via a further carbon stereocenter (Figure 39b). The phosphine ligates gold and the three Xantphos-derived fused rings ensure the correct distance and angle between the ligated gold and the sulfinamide. The latter, which is chiral at sulfur, is a good hydrogen bond donor. These combined features are proposed to ensure a high degree of organization and control in attack onto the complexed allene (Figure 39c). The sulfinamide N−H is proposed to engage in hydrogen bonding with the sulfonamide protecting
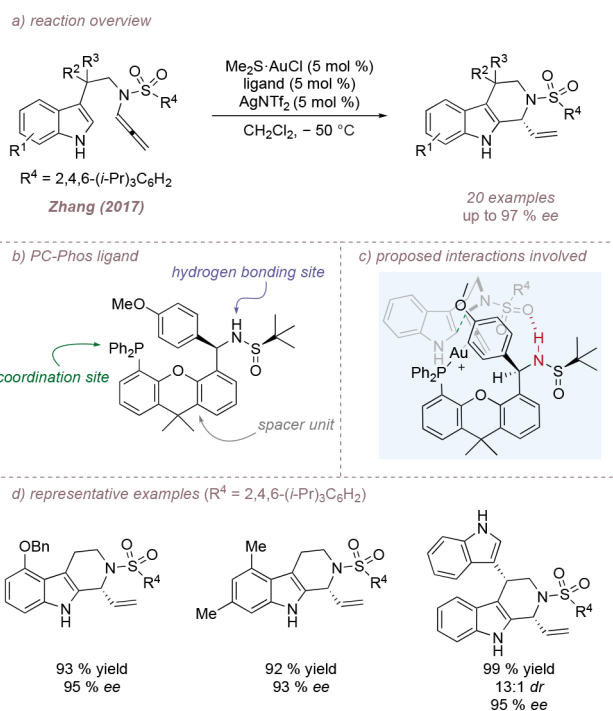
group of the allenamide, which orients the substrate for intramolecular attack onto the *Re*-face of the allenamide. A variety of substituents on the indole component were tolerated (Figure 39d). In addition, the authors disclosed efficient total syntheses of several alkaloid natural products using this methodology.

Very recently, Echavarren and co-workers reported a new ligand design for gold(I), which enabled the enantioselective cyclization of enynes (Figure 40a).[152] The authors developed ligands based on a modified JohnPhos scaffold, with a remote C_2-symmetric 2,5-diarylpyrrolidine which was anticipated to place the chiral information on the catalyst close to the site of enyne folding (Figure 40b). Following reaction optimization, the authors were able to catalyze the challenging 5-*exo*-dig cyclization of various 1,6-enynes with very high levels of enantioselectivity to afford formal [4 + 2] cycloaddition products (Figure 40c). The authors also noted the interesting result that in the formation of 1,2-dihydronaphthalenes the enantioselectivity of the transformation was reversed (Figure 40d). DFT calculations suggested that in both cyclization modes, attractive NCIs between aromatic rings play a major role in transition state stabilization. Specifically, $\pi-\pi$ interactions between the aryl ring of the substrate and both of the aryl rings of the pyrrolidine and the biphenyl are thought to be very important. The reversal in enantioselectivity arises as a result of different combinations of noncovalent interactions operating in each case. The calculated transition state for the synthesis of 1,2-dihydronapthalenes is shown (Figure 40e) along with representative examples (Figure 40f). In 2017, the same group had reported the enantioselective intermolecular [2 + 2] cycloaddition of terminal alkynes with alkenes using gold(I) catalysis utilizing chiral Josiphos ligands.[153] Once again, DFT suggested that stabilizing π-stacking interactions, as well as other steric and repulsive interactions, played an important role in the enantiodetermining step.
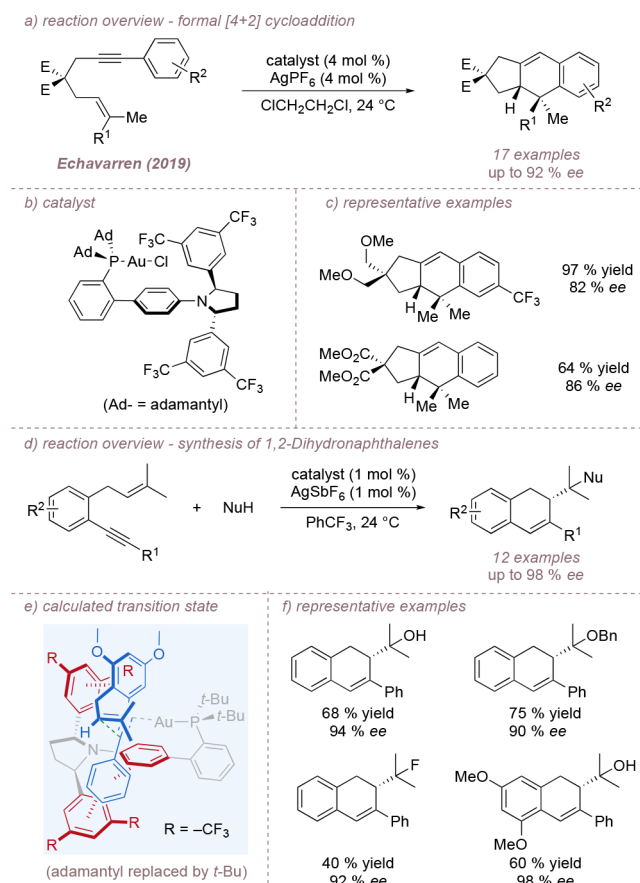
Figure 40. A new ligand design for gold(I) enabling enantioselective enyne cyclization.

Recently, Tang and co-workers reported an enantioselective Suzuki-Miyaura cross-coupling to access axially chiral tetra-*ortho*-substitut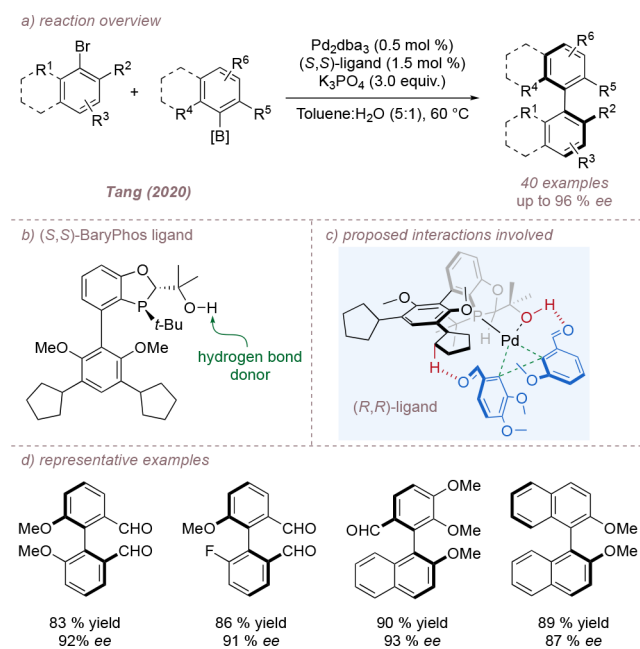ed biaryl molecules (Figure 41a).[154] The cross-coupling was enabled by a novel *P*-chiral monophosphorus ligand, BaryPhos, building on previous designs from the same group (Figure 41b).[155] A hydrogen bond donor was incorporated into the scaffold which was anticipated to allow for interaction with one of the coupling partners and provide organization during enantiodetermining reductive elimination. While the tertiary alcohol initially coordinates to the palladium center to form a five-membered oxapalladacycle, it is thought to act as an internal base, lowering the barrier to trans-metalation. On the basis of X-ray data, two significant noncovalent interactions were proposed to account for the stereochemical outcome: first, a weak CHO···H interaction between the oxygen of the formyl group of one component and an aliphatic hydrogen atom of the cyclopentyl ring. Second, a hydrogen bonding interaction between the tertiary alcohol and the formyl group of the second component (Figure 41c). The reaction scope was impressive although it is notable that all of the substrates possessed either a formyl group or an alkoxy group at the *ortho-* position of each fragment (Figure 41d). To demonstrate the utility of the methodology, the authors reported the first enantioselective synthesis of gossypol, a male contraceptive and antitumor agent.

Very recently, an enantioselective iridium-catalyzed hydro-arylation of vinyl ethers with heterobiaryl compounds was reported to form atropisomeric products (Figure 42a).[156]
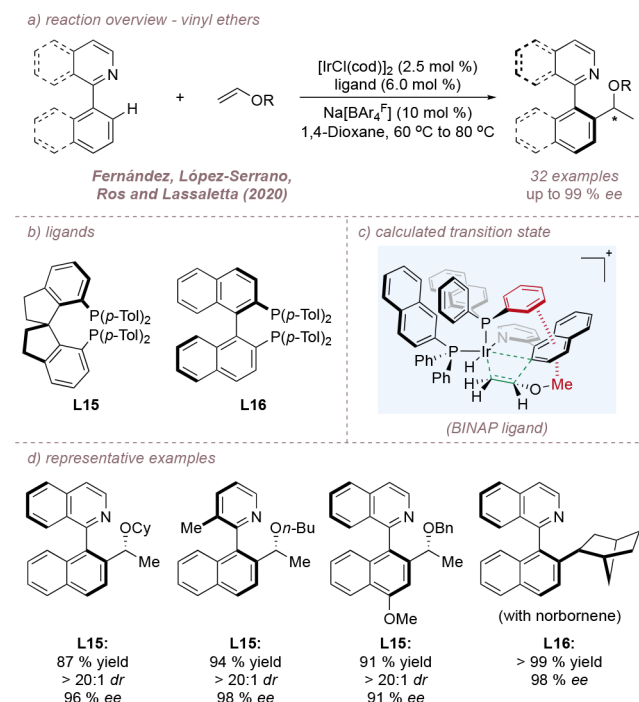

Figure 42. Iridium-catalyzed atroposelective C−C bond formation via C−H bond functionalization.

Biaryl spirodiphosphine ligand **L15** or (*p*-Tol)-BINAP **L16** were optimal, depending on substrate class (Figure 42b), giving excellent yields and a good level of regio-, diastereo-, and enantioselectivity for both acyclic alkenes (using **L15**) and norbornenes (using **L16**). Migratory insertion of the iridium−carbon bond to the vinyl ether was proposed to be the selectivity-determining step, and detailed DFT calculations implicated several NCIs as possibly contributing to the high selectivity, although the precise interplay was complex. An

Figure 41. A palladium-catalyzed enantioselective cross-coupling reaction for the synthesis of axially chiral biaryls.

attractive $\pi-\pi$ interaction between the substrate aryl ring and an aryl ring of the phosphine ligand was identified as being important in the lowest-energy transition state, and attractive dispersive interactions between the alkyl group of the enol ether and the same substrate aryl ring were also invoked (Figure 42c). Representative products are shown (Figure 42d).

Another recent example that highlights the important role that $\pi-\pi$ interactions between substrate and ligand can play was reported by Wencel-Delord, Colobert, and co-workers in the palladium-catalyzed direct arylation of cyclopropanes using a bidentate S/N ligand (Figure 43a,b).[157] Detailed DFT
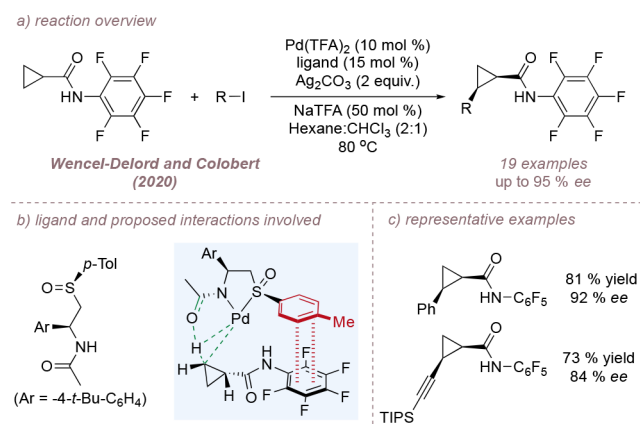

Figure 43. Palladium-catalyzed enantioselective arylation of cyclopropanes involving $\pi-\pi$ interactions.

calculations suggested that a $\pi-\pi$ interaction between the aromatic perfluoroarene of the substrate and the aromatic group on the ligand is important in precisely controlling substrate orientation. When the *N*-acetyl group of the palladium complex comes into close proximity with the substrate, C−H activation takes place via the CMD mechanism. Notably, iodoalkynes performed well in this reaction, enabling the efficient asymmetric alkynylation of cyclopropanes (Figure 43c).

3. HYDROGENATION REACTIONS

Attractive noncovalent interactions between metal and ligand have played an important role in the development of asymmetric hydrogenation reactions, where reactivity, chemoselectivity, and enantioselectivity can all be influenced. The prototypical example is the Noyori asymmetric hydrogenation using a ruthenium catalyst with diamine ligands (Figure 44a−d).[158−162] Complexation of the diamine to the metal significantly acidifies the N−H bonds and renders them to be effective hydrogen bond donors. One of these interacts with the heteroatom in the substrate activating the latter to hydride reduction from the metal hydride through a highly organized transition state, enabling the highly enantioselective hydrogenation of ketones and imines (Figure 44c). Following Noyori's influential work, there have been many reports in this area with new ligand and catalyst combinations to broaden the scope and understanding of this reaction, including those using other transition metals such as rhodium, iridium, iron, and osmium. Not surprisingly, there are several reviews detailing these transformations, and the broader application of the so-called "N−H effect".[16,163−167]

Focusing on the application of NCIs, there have been a number of examples of hydrogenation reactions where ligand−
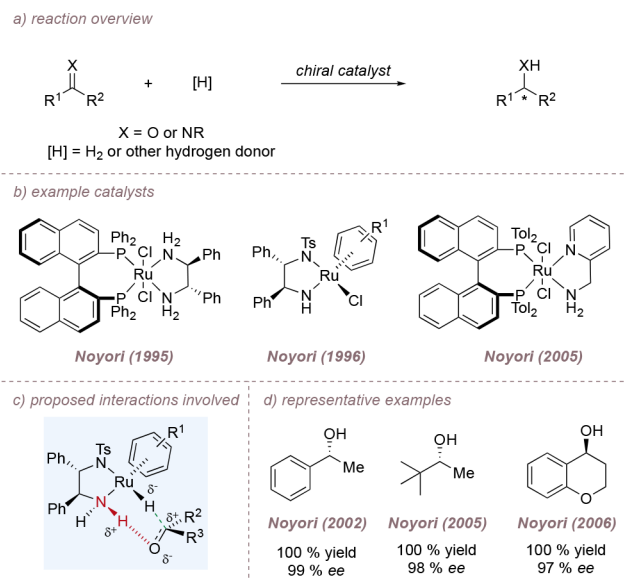

Figure 44. An overview of the Noyori asymmetric hydrogenation using diamine ligands.

ligand interactions are used to generate "supramolecular" catalysts *in situ*. For example, two monodentate phosphines may unite by virtue of a carefully designed interaction that occurs between the two.[24,168,169] As defined at the outset, this Review will not examine these but will focus on the recent reports which feature attractive NCIs between ligand and substrate.

In 2009, Reek and co-workers reported a highly efficient catalyst for the asymmetric hydrogenation of esters using a heterophosphine ligand system (Figure 45a).[170] Interestingly, heterocomplex [Rh(cod)**L17L19**] was formed efficiently from a nearly equimolar mixture of rhodium precatalyst, **L17**, and **L19** (Figure 45b). DFT calculations, IR studies, and control experiments suggested that a single hydrogen bond between the urea unit of **L17** and the N−H bond in **L19** (ligand−
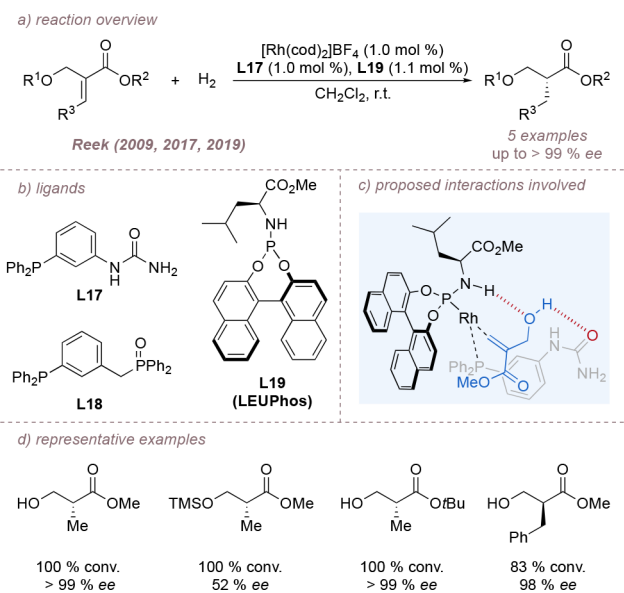

Figure 45. Enantioselective hydrogenation involving a ligand-substrate−ligand hydrogen bonding network.

ligand interaction) was important for selective formation of the heterocomplex. Crucially, an interaction between the hydroxyl group of the substrate with the ligand was thought to be involved. In later work, further NMR studies and DFT calculations suggested that in fact the −OH group of the substrate inserts into the ligand−ligand hydrogen bond, resulting in the formation of two independent hydrogen bonds between the substrate and the complex, as shown above (Figure 45c).[171,172] Based on this understanding, phosphine oxide ligand **L18** was developed, which is analogous to **L17** but possesses a stronger hydrogen bond acceptor (Figure 45b). The resulting catalyst experienced better turnover and higher product enantiomeric excess (>99%) were observed.[173] Removal of the key hydrogen bond through protection of the alcohol group resulted in a dramatic drop in selectivity (99% ee vs 52% ee, Figure 45d).

In 2011, Reek and co-workers reported an ingenious asymmetric hydrogenation using an achiral phosphine ligand fashioned around an anion binding motif in combination with a small chiral anion "cofactor" (Figure 46a).[174] The
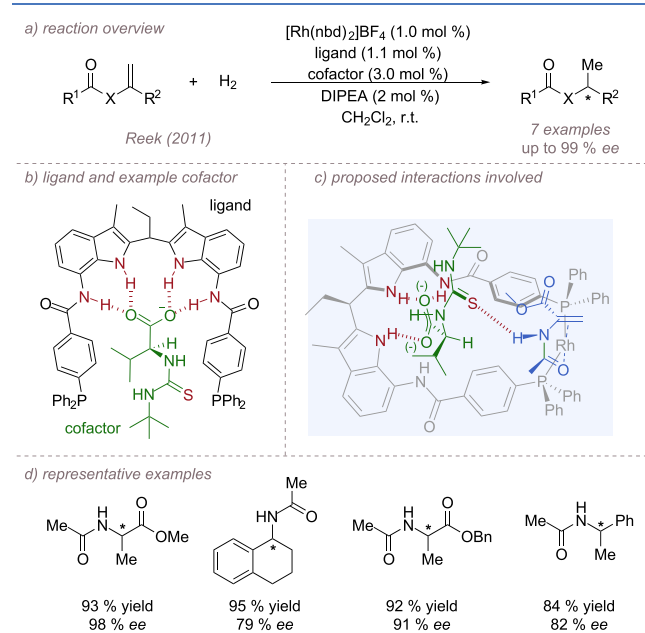
Figure 46. Reek's asymmetric hydrogenation using a chiral cofactor and an anion-binding bisphospine.

bisphosphine ligand used in this work is equipped with four N−H units organized to constitute an excellent binding site for a chiral carboxylate cofactor which also possesses a thiourea group (Figure 46b). DFT calculations suggested that in addition to the anticipated ligand−cofactor interaction, the thiourea unit of the cofactor also engages in hydrogen bonding interactions with the N−H of the enamide substrates (Figure 46c,d). Control experiments suggested that all of these interactions are crucial for the reactivity and reaction selectivity. This work is again illustrative of how influential a network of NCIs between multiple reaction components can be when the only chiral unit present in this system is the small chiral carboxylic acid cofactor, which can be easily varied for rapid reaction optimization.

Generally, the most active catalysts for asymmetric hydrogenation reactions are those based on precious metals such as ruthenium or rhodium and the development of earth-abundant

catalysts is a major goal. Iron has been one of the principal candidates investigated and a number of reports have demonstrated its potential, some of which have involved ligand−substrate noncovalent interactions.[175,176] In one leading family of catalysts, Morris and co-workers developed an iron(II) complex featuring a P−N−N−P tetradentate bis-imine ligand for the asymmetric transfer hydrogenation of ketones (Figure 47a).[177−179] A combination of NMR data, X-
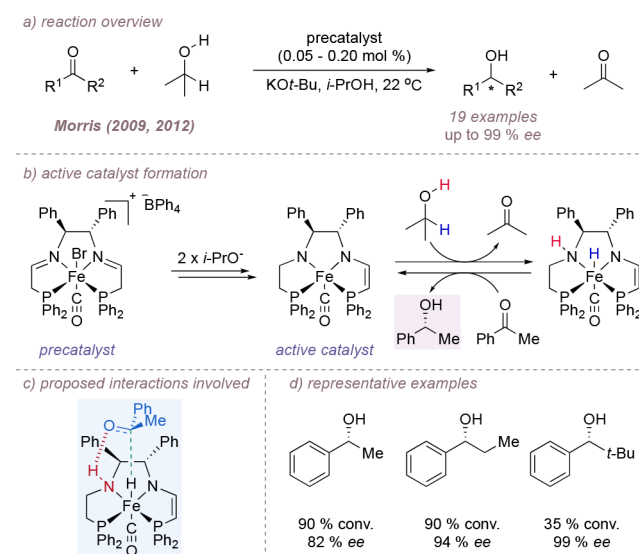
Figure 47. Morris's iron-catalyzed asymmetric transfer hydrogenation of ketones.

ray crystallography, and control experiments suggested that the ligand was hydrogenated at one imine, while the other was deprotonated in the reaction to form an amido-(ene-amido) complex (Figure 47b), the proposed active catalyst. Notably, control experiments demonstrated that independently synthe-sized bis(amine) and bis(amido) complexes were found to be inactive for hydrogenation. The authors propose that a hydrogen bonding interaction between the ketone oxygen and N−H of the ligand is important for the correct orientation of the carbonyl (Figure 47c). The H−N−Fe−H unit contained in the species derived from the active catalyst is highly reactive for the hydrogenation of ketones (Figure 47d). KIE studies suggested a stepwise hydride addition followed by proton transfer, rather than a concerted hydride/proton transfer mechanism. In subsequent work, the amido(imine)-diphosphine complex proposed to be the active catalyst was synthesized directly and shown to be more active. Multiple related ligands have also been developed.[180] In related work, the group of Mezzetti has developed a chiral macrocyclic ligand scaffold for iron which relies on hydrogen bonding interactions operating in a similar manner, and this is an area of rapid development.[181]

While ligand-based chirality is typically the most common strategy used to induce stereoselectivity, chiral-at-metal complexes constitute a less explored approach which has seen exciting developments in recent years.[182−184] In 2013, Gong, Meggers, and co-workers reported a highly enantiose-lective transfer hydrogenation of nitroalkenes catalyzed by a chiral-at-metal iridium catalyst (Figure 48a,b).[185] The iridium−metal center is itself inert and serves only as a chiral template. Importantly, one of its three ligands is an amidopyrazole which can act as a dual hydrogen bond
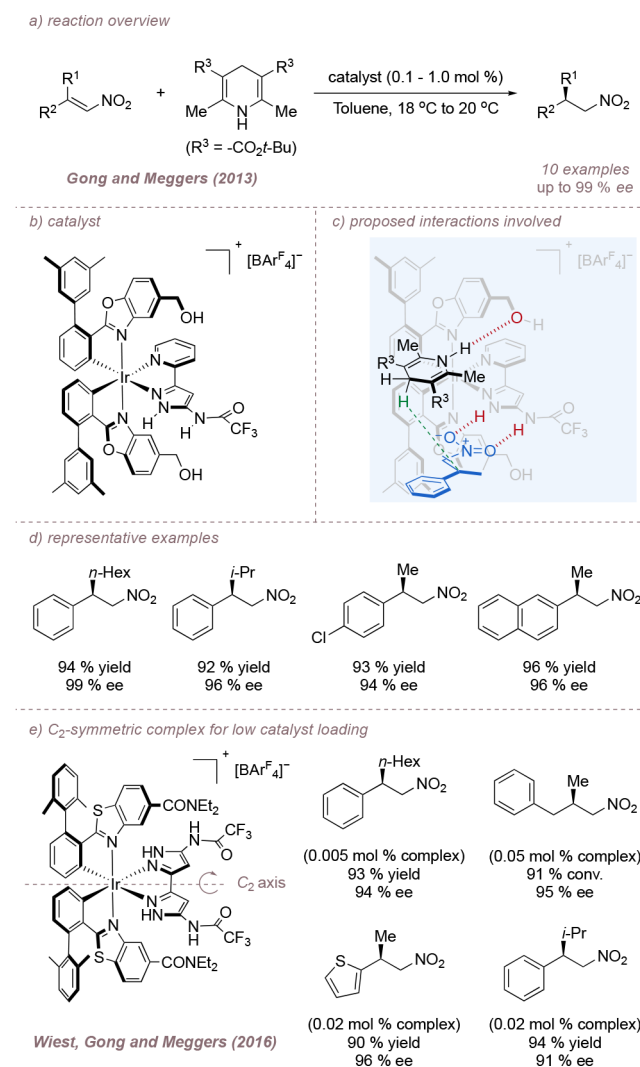
a) reaction overview

Gong and Meggers (2013)

(R³ = -CO₂t-Bu)

10 examples
up to 99 % ee

b) catalyst

c) proposed interactions involved

d) representative examples

94 % yield
99 % ee

92 % yield
96 % ee

93 % yield
94 % ee

96 % yield
96 % ee

e) C₂-symmetric complex for low catalyst loading

Wiest, Gong and Meggers (2016)

(0.005 mol % complex)
93 % yield
94 % ee

(0.05 mol % complex)
91 % conv.
95 % ee

(0.02 mol % complex)
90 % yield
96 % ee

(0.02 mol % complex)
94 % yield
91 % ee

Figure 48. Chiral-at-metal iridium complex for the conjugate reduction of nitroalkenes.

a) reaction overview

Meggers and Gong (2016)

precatalyst (0.2 - 1.0 mol %)
ligand (10 mol %)
HCO₂NH₄ (9 equiv.)
THF:H₂O (1:1)
40 °C or 60 °C

24 examples
up to 99 % ee

b) precatalyst and ligand

c) proposed interactions involved

ligand

(simplified ligand)

d) representative examples

91 % yield
90 % ee

98 % yield
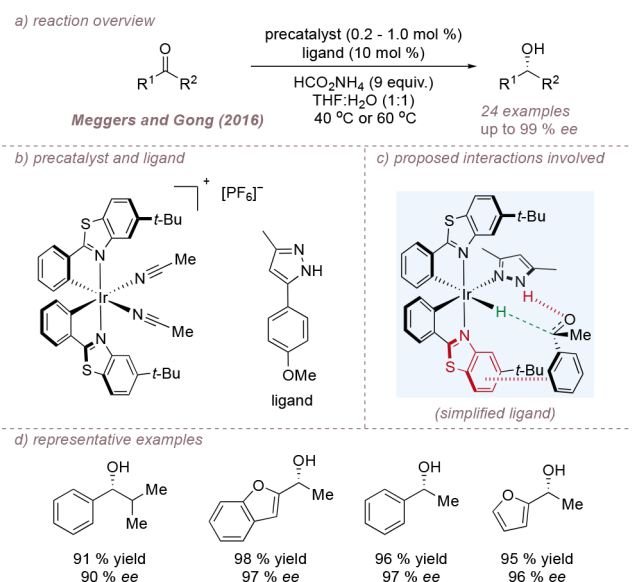97 % ee

96 % yield
97 % ee

95 % yield
96 % ee

Figure 49. Chiral-at-metal iridium-catalyst for transfer hydrogenation of ketones.

substituted pyrazole ligand (Figure 49b), which undergoes a fast ligand exchange with the metal-bound acetonitrile molecules. Addition of formate generates an iridium-hydride complex, which then acts as catalyst for transfer hydrogenation. The pyrazole ligand bearing a free N−H group was necessary for high reactivity. An X-ray crystal structure of the pyrazole-coordinated iridium complex revealed that the N−H unit lies in the optimum orientation to act as a bifunctional transfer hydrogenation catalyst and in the proposed transition state, the interaction between the ketone oxygen and the pyrazole N−H is crucial. A further attractive π−π interaction between one of the cyclometalated ligands and the aromatic group of the substrate was also proposed (Figure 49c). Alcohol products were obtained with excellent enantioselectivity (Figure 49d), and later, Gong found that ammonia could also be used as a bifunctional ligand in the related catalytic system for the hydrogenation of N-sulfonylimines.[191]

The Zhang research group has developed several new Josiphos-type ligands for the rhodium-catalyzed asymmetric hydrogenation of nitroalkenes (Figure 50a).[192,193] While complexes based on the standard Josiphos ligands (such as L20) are effective for these reactions, it was hypothesized that a thiourea group appropriately built into the ligand scaffold (such as in L21) might engage in dual hydrogen bonding interactions with the substrate, increasing reactivity, and possibly leading to higher enantioselectivities (Figure 50b,c).[192,193] ZhaoPhos (L21), incorporating a thiourea tethered to the ferrocene ring indeed achieved these goals (Figure 50d), although L20 was still typically excellent in most cases.[193] In further developments, a monomethylated version of L21 (ent-L21-Me) gave excellent results for the hydrogenation of β-cyanocinnamic esters (Figure 50e),[194] although L21 provided similar outcomes. In this case, the ester group in the substrate is thought to act as a hydrogen bond acceptor to interact with the thiourea. This catalyst family has been very general for the asymmetric hydrogenation of a variety substrates bearing a hydrogen bond acceptor.[195−201]

Later, the remit of ZhaoPhos (L21) was expanded as the authors hypothesized that the thiourea functionality could act as an anion-binding motif through interaction with the halide

donor, similar to a thiourea. It is proposed that this activates the nitroalkene substrate via dual hydrogen bond interactions, while a hydroxyl group on one of the remaining benzoxazole ligands acts as a hydrogen bond acceptor, interacting with the hydride source in a highly organized ternary transition state (Figure 48c). The efficient transformation of a range of substituted nitroalkenes bearing aromatic rings was reported (Figure 48d). Subsequently, Meggers, Gong, Wiest, and co-workers developed a new iridium complex incorporating a bis-pyrazole ligand (Figure 48e). This contained two catalytic sites per C₂-symmetric complex and was found to be highly reactive for the hydrogenation of nitroalkenes.[186] Remarkably, the reaction proceeded efficiently with catalyst loadings as low as 40 ppm. Detailed experiments and calculations suggested that the outstanding catalytic activity is driven by careful orientation of the substrate and catalyst via a combination of hydrogen bonding and van der Waals interactions. In addition, this general approach also proved to be successful for the asymmetric addition of indoles to nitroalkenes (see Section 2.1, Figure 10).[187,188]

The chiral-at-metal approach was also applied to the asymmetric hydrogenation of ketones (Figure 49a).[189,190] In this system, the iridium complex is used together with a

a) reaction overview

[Rh] (cat)
ligand **L20** or **L21**
CH$_2$Cl$_2$ or i-PrOH, 35 °C

Zhang (2012, 2013)

22 examples up to 96 % *ee* (**L20**)
13 examples, up to 99 % *ee* (**L21**)

b) ligands

(Ar = 4-CF$_3$C$_6$H$_4$)
L20
(Josiphos)

L21
(Zhaophos)

Conditions
- H$_2$ 50 atm.
- [Rh(NBD)$_2$]SbF$_6$
1.5 mol %

Conditions
- H$_2$ 5 atm.
- [Rh(COD)Cl]$_2$
1.0 mol %

c) proposed interactions involved

d) representative examples

L20: 85 % conv.
94 % *ee*
L21: 99 % yield
99 % *ee*

L20: > 99 % conv.
92 % *ee*
L21: 99 % yield
99 % *ee*

e) methylated ligand and representative examples

ent-L21-Me

98 % yield
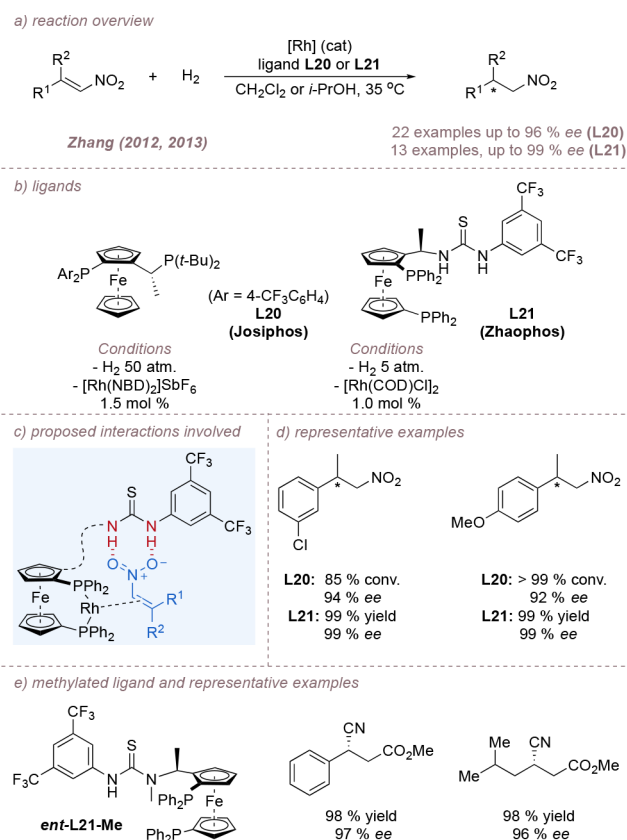97 % *ee*

98 % yield
96 % *ee*

Figure 50. Zhang's bisphosphine-thiourea ligands for enantioselective hydrogenation.

counteranion of prochiral iminium salts (Figure 51a).[202] Various control experiments demonstrated that the thiourea

a) reaction overview

[Rh(COD)Cl]$_2$ (1.0 - 4.0 mol %)
ent-L21 (1.1 - 4.4 mol %)
i-PrOH, 25 °C

Wang, Anslyn and Zhang (2014)

15 examples
up to 95 % *ee*

b) proposed interactions involved

c) representative examples

84 % yield
90 % *ee*

97 % yield
82 % *ee*

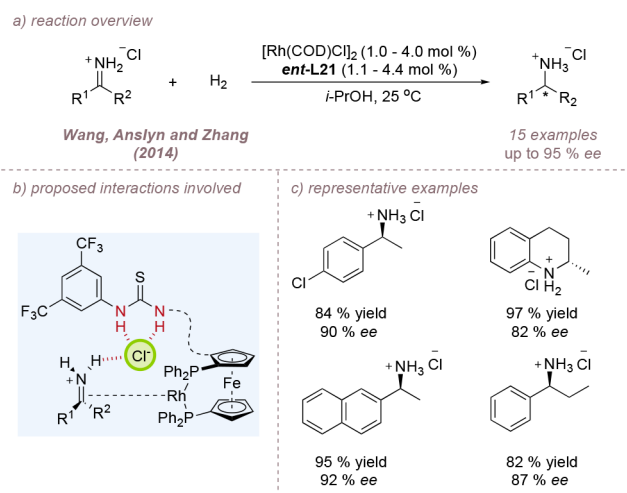95 % yield
92 % *ee*

82 % yield
87 % *ee*

Figure 51. Enantioselective hydrogenation of iminium salts through anion binding.

plays a crucial role and NMR studies confirmed the importance of dual hydrogen bonding between the two N−H units and a chloride anion for reaction success (Figure 51b). This resulted in the hydrogenation of ketimines with excellent yields and enantioselectivity to afford the ammonium salt products (Figure 51c). This strategy has since proven to be successful for enantioselective hydrogenation of a wide range of imine-type substrates.[203−206]

In 2007, Chen, McCormack, and co-workers reported a new ferrocene-based C_2-symmetric diphosphine ligand (TriFer) containing three ferrocene units for the highly enantioselective hydrogenation of α-substituted cinnamic acids (Figure 52a,b).[207] The effectiveness of this ligand was proposed to

a) reaction overview

Rh-**ChenPhos** (0.1 mol %)
CF$_3$CH$_2$OH, r.t.

Chen (2013)
Chen, Zhang and Zhang (2016)

18 examples
up to 99 % *ee*

b) ligands

Trifer   **ChenPhos**

c) proposed interactions involved

d) representative examples

99 % yield
95 % *ee*

97 % yield
94 % *ee*
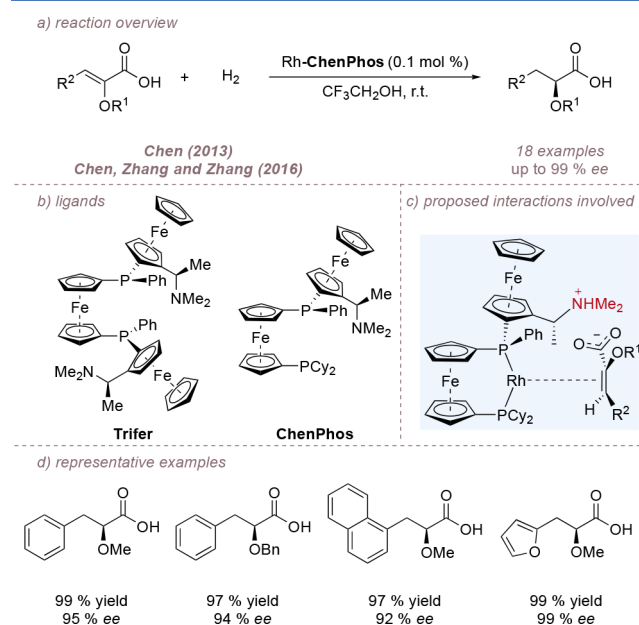
97 % yield
92 % *ee*

99 % yield
99 % *ee*

Figure 52. Chenphos ligand for enantioselective hydrogenation of α,β-unsaturated acids.

hinge on the ability of the dimethyl amino group to deprotonate the substrate carboxylic acid, resulting in a key electrostatic interaction during the hydrogenation step. In 2013, Chen and co-workers envisioned that one dimethyl amino group should be sufficient to interact with the substrate and that the substituents on the second phosphine could be used productively to tune steric and electronic control.[208] Ligand screening led to the new ChenPhos ligand, which was found to be significantly more reactive than the original TriFer, and was applicable to the asymmetric hydrogenation of various α,β-unsaturated acids (Figure 52b). The putative substrate–ligand electrostatic interaction (Figure 52c) was critical to achieving high selectivity (Figure 52d). Removal of either the dimethyl amino group on the ligand or the acid group on the substrate compromised both ee and reactivity. ChenPhos has been similarly applied to the hydrogenation of α-oxy functionalized α,β-unsaturated acids as well as conjugated α-substituted dienoic acids.[209,210] A hydrogen bond between the substrate hydroxyl group and the catalyst amino group is proposed to be crucial in the asymmetric hydrogenation of 2-substituted-2-alkenol substrates, which possess no carboxylic acid.[211]

In 2016, Zhang, Dong, and co-workers reported a modified family of chiral bisphosphine ligands which incorporate a single ferrocenyl unit and a basic tertiary amine, which can deprotonate and form an ion pair with unsaturated acids during hydrogenation (Figure 53a).[212] The Wudaphos ligand, proposed to possess three-hindered-quadrants, was demonstrated to be efficient for enantioselective hydrogenation of 2-aryl and 2-alkyl acrylic acids (Figure 53b). In the proposed stereochemical model, the high product enantioselectivity arises from the bulky substrate substituent projecting into the
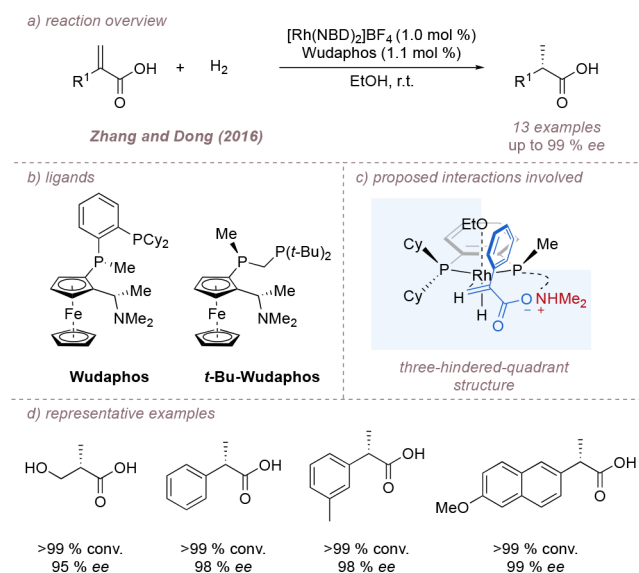
Figure 53. Zhang and Dong's Wudaphos ligands for enantioselective hydrogenation of unsaturated acids.

lone "open" quadrant of the catalyst (Figure 53c,d). Alkenyl sulfonates were also capable substrates for this reaction.[213] Recently, a *t*-Bu-WudaPhos variant (Figure 53b) was developed and proved to be an efficient ligand for the asymmetric hydrogenation of 4-keto-acrylic acids[214] and vinyl benzoic acids.[215]

In the next development, the phosphine group in Wudaphos that is attached to the ferrocene was replaced with a secondary phosphine oxide (SPO) group for the hydrogenation of 4-keto-acrylic acids (Figure 54a).[216] The authors hypothesized that the SPO functionality could simultaneously ligate the metal as well as interact with the substrate ketone group through hydrogen-bonding interactions from the hydroxyl moiety
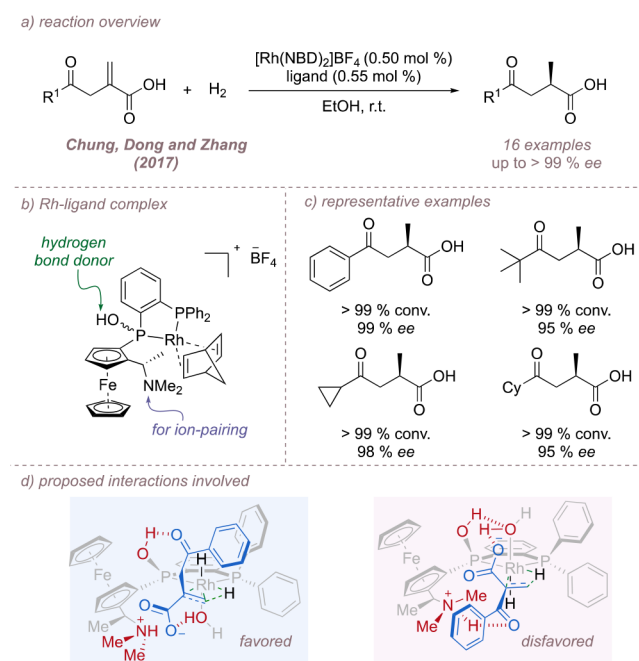

Figure 54. Zhang and Dong's SPO-Wudaphos ligand for enantioselective hydrogenation of carboxylic acids.

(Figure 54b). The SPO-Wudaphos ligand delivered the hydrogenated acids with excellent enantioselectivity (Figure 54c) and was also found to be capable for the reduction of alkenyl phosphonic acids.[217] Control experiments and DFT calculations suggested that a hydrogen bonding interaction with the substrate ketone oxygen was present in addition to the ion-pairing interaction between the protonated amine of the ligand and the carboxylate of the substrate (Figure 54d).

Chikkali and co-workers have developed interesting rhodium catalysts formed from the dimerization of *P*-chiral phosphines by way of hydrogen bonding between urea units on the ligands.[218] These have shown potential for enantioselective hydrogenation, although few examples have been reported to date (Figure 55a,b).[219] Detailed NMR studies led the authors to propose the interactions depicted (Figure 55c).[218]
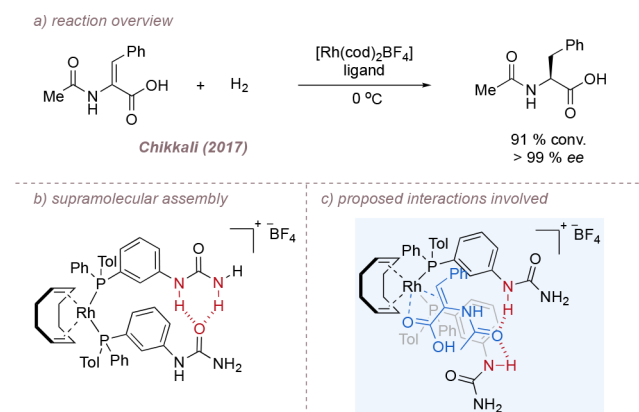

Figure 55. Enantioselective hydrogenation reaction developed by Chikkali.

In 2018, Chen, Xiao, and co-workers explored half-sandwich iridium complexes for transfer hydrogenation reactions (Figure 56a).[220] The *N*,*C*-chelated iridium catalyst (**C1**) was originally designed to hold an ester group adjacent to a chiral center, which was anticipated to act as a hydrogen bond acceptor
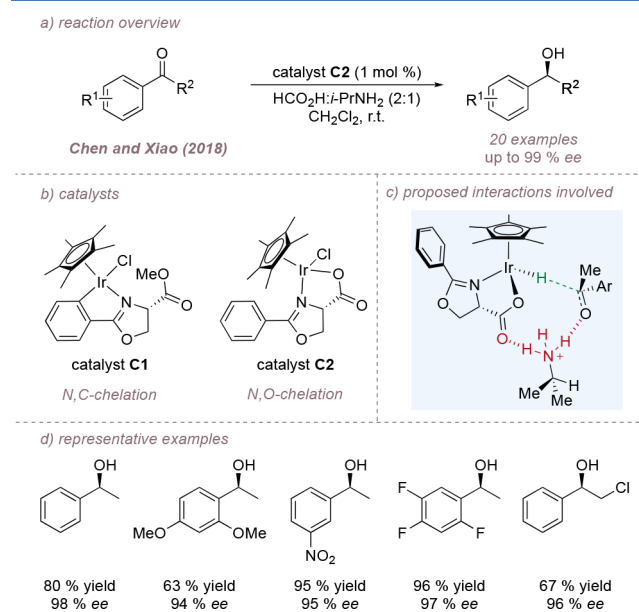

Figure 56. Transfer hydrogenation of ketones catalyzed by Chen's *N*,*O*-chelated iridium complex.

(Figure 56b). During the synthesis of this iridium complex, the *N,O*-chelated catalyst (**C2**) was also obtained. In reactions using this complex, the nature of the amine additive and the ratio of formate:*iso*-propylamine greatly affect the selectivity, and DFT calculations suggested that a protonated *iso*-propylamine molecule bridges between the ligand and substrate via multiple hydrogen bonding interactions (Figure 56c). Interestingly, the *N,O*-chelated iridium catalyst (**C2**) greatly outperformed the *N,C*-chelated iridium catalyst (**C1**) for asymmetric transfer hydrogenation of acetophenones (Figure 56d). For example, the *N,O*-chelated iridium catalyst (**C2**) gave 98% ee for hydrogenation of acetophenone, and the *N,C*-chelated iridium catalyst (**C1**) gave only 4% ee. This constitutes an interesting example where a more extended network of hydrogen bonding interactions is thought to be involved.

4. CARBON−HETEROATOM BOND-FORMING REACTIONS

In terms of historical context, the Sharpless asymmetric dihydroxylation reaction exemplifies the remarkable control that can be achieved through the use of attractive noncovalent interactions in transition metal-catalyzed carbon-heteroatom bond formation.[221] Remarkably broad in scope, the transformation has found use in countless synthetic applications. There has been much debate over both the reaction mechanism and the precise origin of enantioselectivity, yet meticulous studies from the Sharpless laboratory among others have provided convincing evidence as to the importance of NCIs in determining the stereochemical outcome. Typical asymmetric dihydroxylation conditions for a terminal alkene are shown (Figure 57a) along with the structure of an exemplary ligand (Figure 57b). Systematic ligand variation has led to the synthesis of over 300 cinchona alkaloid-derived ligands in the Sharpless laboratory alone, from which important relationships between ligand structure and product enantiomeric excesses have been deduced.[222] Most importantly, the nature of the O(9) substituent is critical to the

stereochemical outcome, more so than any other component of the alkaloid scaffold. Other detailed studies have confirmed that the origin of the high enantioselectivities and rates lies in a transition state stabilization effect as opposed to a destabilizing ground state steric effect.[222] These separate pieces of information suggest that several subtle, attractive noncovalent interactions are operating in the favored transition state.[222]

These proposed key interactions are shown in Sharpless and co-workers' model of a styrene-derived osmaoxetane intermediate (Figure 57b).[221] There are four features that are of note in this complex. The first (Figure 57c (i)) is that the quinuclidine nitrogen on the active alkaloid moiety coordinates the osmium. The second (Figure 57c (ii)) is the four-membered osmaoxetane ring, which is proposed to arise from a [2 + 2] reaction and which subsequently rearranges to the glycolate product. For the styrene substrate, the aromatic ring is perfectly placed to interact with the phthalazine linking the two halves of the ligand through offset, attractive π−π interactions (Figure 57c (iii)). A further edge-to-face attractive interaction (Figure 57c (iv)) is proposed between the substrate aromatic ring and the quinoline portion of the "bystander" ligand (Figure 57c (v)). These attractive interactions precisely orient the substrate within what seems to be a tailor-made pocket and provide a convincing explanation for the high enantioselectivities observed, especially with substrates possessing aromatic groups (Figure 57d). Evidence supporting this proposal has been obtained from substrate and solvent variation studies along with NMR experiments.[222]

4.1. Carbon−Boron Bonds. The formation of carbon−boron bonds is a process of fundamental synthetic importance as the resulting boronic acid or ester products serve as hugely versatile intermediates. The Ito laboratory has developed numerous copper-catalyzed enantioselective carbon−boron bond forming reactions. Two recent examples in which attractive NCIs are implicated are described below. The first is the enantioselective borylation of aliphatic ketones through 1,2-nucleophilic attack to afford chiral tertiary alcohol products (Figure 58a).[223] Critical to success was the use of an NHC
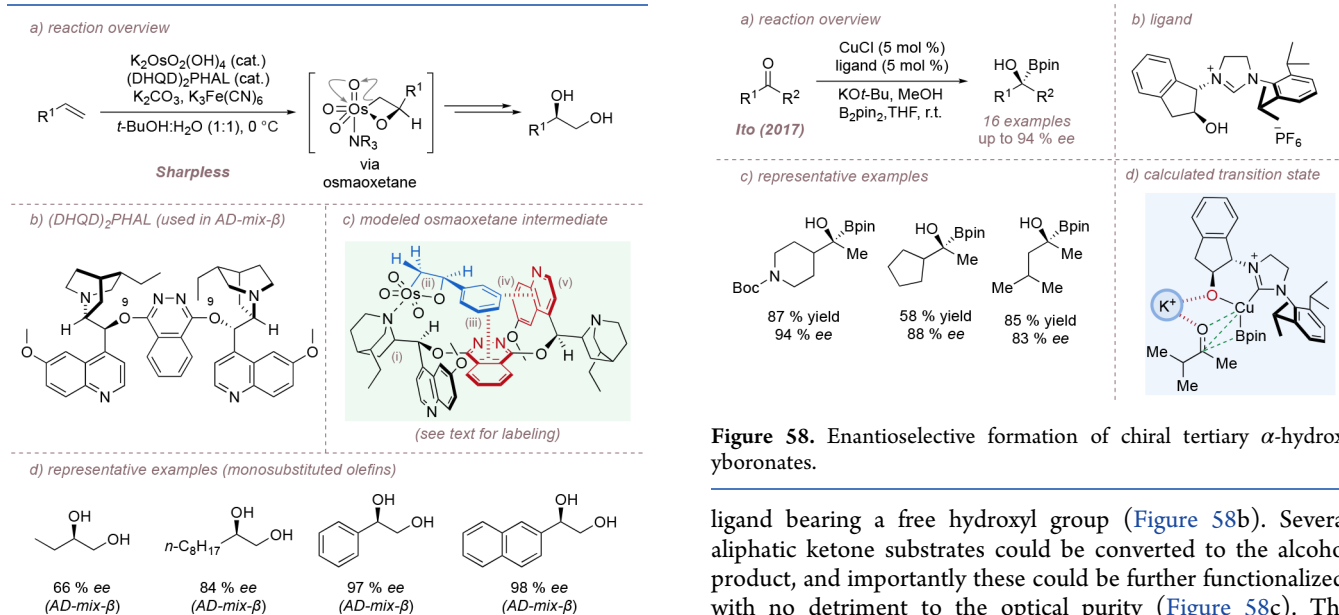
Figure 57. Involvement of attractive NCIs in the Sharpless asymmetric dihydroxylation.

Figure 58. Enantioselective formation of chiral tertiary α-hydroxyboronates.

ligand bearing a free hydroxyl group (Figure 58b). Several aliphatic ketone substrates could be converted to the alcohol product, and importantly these could be further functionalized, with no detriment to the optical purity (Figure 58c). The mode of enantioinduction, as deduced from DFT calculations, is particularly intriguing (Figure 58d). Under the basic reaction conditions, the ligand hydroxyl group is deprotonated and

forms a potassium alkoxide. The potassium cation can then act as a bridge to associate the borylcopper(I) complex and the ketone oxygen atom. In the favored transition state, this rigidifying interaction orients the bulkier ketone substituent away from the bulky 2,6-di-*iso*-propylphenyl ring of the NHC. *O*-methylation of the ligand resulted in poor enantioselectivities, as did the use of alkoxide bases possessing lithium or sodium counterions, supporting the crucial role of the potassium cation and highlighting the noninnocent role that associated cations can exert.

In the second example, Ito and co-workers reported an enantioconvergent borylation reaction of racemic benzyl chlorides thought to proceed via a radical mechanism (Figure 59a).[224] Central to the success of the strategy was the use of a
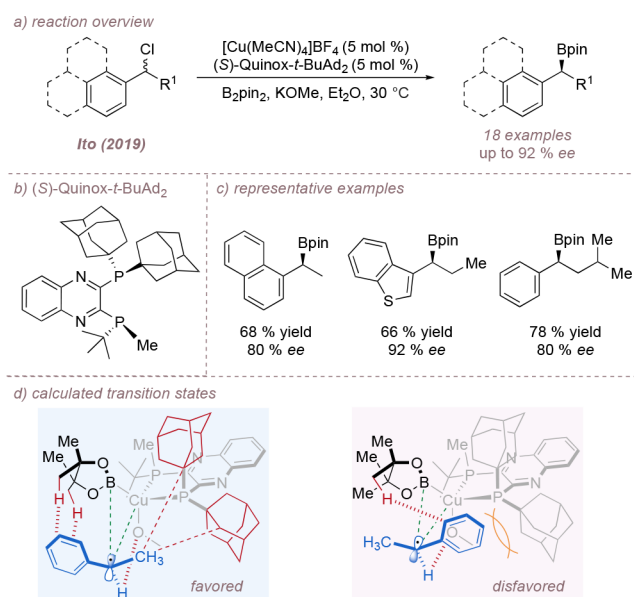

Figure 59. Enantioconvergent borylation of racemic benzyl chlorides.

copper complex bearing a ligand belonging to the QuinoxP* family of bisphosphines (Figure 59b). These rigid bidentate phosphines are easily assembled and the nature of the substituents in each of the four ligand quadrants can be systematically varied. Using this ligand, a range of benzyl chlorides possessing differing aromatic and aliphatic substituents were converted to the valuable boronic ester building blocks in good yield and in good to excellent ee (Figure 59c). Various experiments suggested that the reaction proceeds through a common, planar radical intermediate, and a mechanism was proposed in which the enantiodetermining step is the combination of this radical with a Bpin ligand delivered from the chiral copper(II) complex. DFT calculations showed that in the favored transition state, the methyl groups of the Bpin moiety were found to engage in attractive C−H⋯π interactions with the aromatic group on the substrate (Figure 59d). For substrates possessing extended aromatic systems, these interactions are stronger and result in higher enantioselectivities. In the disfavored transition state, the strength of these C−H⋯π interactions is much reduced as a result of poorer spatial overlap. In both cases there is also a nonclassical hydrogen bond between the hydrogen atom adjacent to the radical and the methoxide coordinated to the copper. Attractive dispersive interactions between the substrate alkyl group and the ligand adamantyl groups were found to

play a small role in addition, which correlated with the observation that substrates bearing bulkier alkyl groups afforded products with higher enantioselectivities.

In the area of C−H borylation, Maeda, Sawamura, and co-workers recently studied the iridium-catalyzed asymmetric borylation of unactivated methylene C(sp³)−H bonds (Figure 60a).[225] Fundamental to achieving the challenging differ-
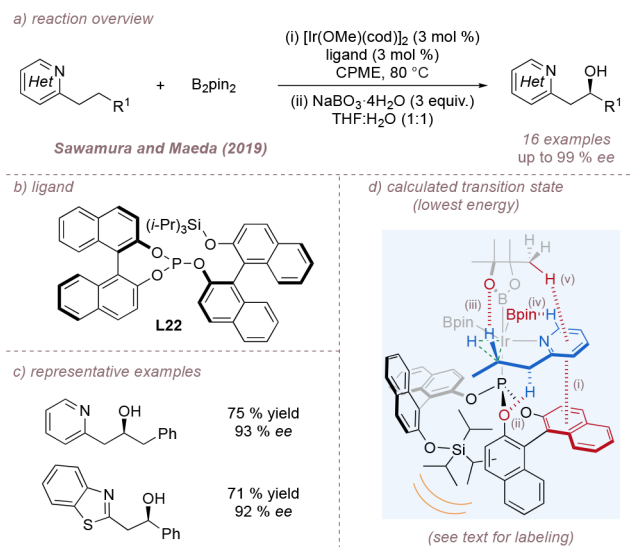

Figure 60. Discrimination of unactivated enantiotopic C(sp³)−H bonds in an enantioselective borylation reaction.

entiation between the enantiotopic β-hydrogens of the substrate was the use of chiral phosphite ligand **L22** (Figure 60b). Under the optimized conditions, a variety of heterocycles containing basic nitrogens could be converted to the corresponding chiral β-alcohols with high enantioselectivity following oxidative workup (Figure 60c). Calculations using the artificial force induced reaction (AFIR) method suggested that in the lowest-energy transition state for iridium insertion into the C(sp³)−H bond, multiple attractive NCIs operate in the narrow chiral reaction pocket formed by the metal−ligand complex (Figure 60d). First, the substrate heteroarene is proposed to engage in attractive π−π interactions with one of the BINOL-derived naphthalenes (Figure 60d, (i)). Second, an attractive C−H⋯π interaction between a C−H on one of the pinacol methyls and the aromatic ring of the substrate (Figure 60d, (v)) stabilizes the lower-energy transition state and is notably diminished in the transition state leading to the opposite enantiomer. Finally, three nonclassical hydrogen bonds are also suggested by the calculations (Figure 60d, (ii), (iii), (iv)).

In a later publication, Sawamura and co-workers investigated ligand **L22** further, this time in the context of enantioselective rhodium-catalyzed synthesis of α-aminoboronates.[226] With an appropriate heterocycle present in the substrate, enantioselective functionalization of N-adjacent sp³ C−H bonds was observed with excellent enantioselectivity. Importantly, however, under the new conditions, the substrate scope could be extended to amides (Figure 61a), and the resulting optically enriched α-aminoboronate products (Figure 61b) are of interest in the context of medicinal chemistry as amino acid analogues. In order to achieve high enantioselectivities, amides possessing aromatic moieties were required, and this was rationalized in terms of key attractive π−π interactions likely
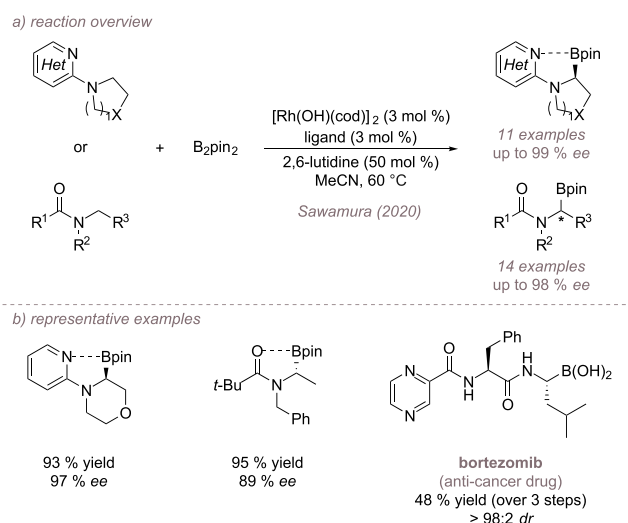
Figure 61. Rhodium-catalyzed enantioselective C(sp^3)−H borylation of heterocycles and amides.

operating between the hydrophobic pocket of the catalyst active site and the substrates.

In general, the employment of chiral cations in strategies involving transition metal catalysis is rare, partly because it is relatively uncommon to encounter anionic metal complexes, with which to pair a chiral cation, in catalytic cycles. There are notable exceptions, however, including association of achiral anionic transition metal complexes (such as permanganates, tungstates, and molybdates) with chiral cations to catalyze enantioselective oxidations.[227,228] Further examples have been documented in a recent review.[229] In 2020, Phipps and co-workers utilized a chiral cation to control enantioselectivity in a challenging, remote iridium-catalyzed arene borylation (Figure 62a).[230] Structurally distinct, prochiral benzhydrylamide and phosphinamide substrates could be desymmetrized through borylation to give the *meta*-borylated products in good yields and excellent enantioselectivities. The transformation was achieved through the use of an ion-paired chiral ligand consisting of an achiral sulfonated bipyridine moiety and a chiral cation based on the quaternized quinine scaffold (Figure 62b). On the basis of previous studies, it was envisaged that a hydrogen bonding interaction would occur between the hydrogen bond donor of the substrate and the sulfonate of the ligand which would allow a controlled assembly of substrate and catalyst.[231] The chiral cation, possessing a very bulky quaternizing group as well as various points which may engage attractive noncovalent interactions, is thought to provide an appropriate environment under which the enantiodetermining C−H activation step can occur with high stereochemical control (Figure 62c). Various control experiments were carried out to probe the nature of the catalyst−substrate interactions, which broadly supported the scenario depicted. In previous studies, a variant of ligand **L23** bearing a tetrabutylammonium cation in place of the chiral cation had been shown to control the regioselectivity of borylation in 1,2-disubstituted aromatic systems where NCIs between ligand and substrate were plausible.[231−234] There existed the possibility that as well as controlling enantioselectivity, chiral ligand **L23** might in addition, be able to control regioselectivity in substrates that possess a choice. This was indeed the case and for certain benzhydrylamide starting materials, *meta*-borylated products could be obtained with both excellent
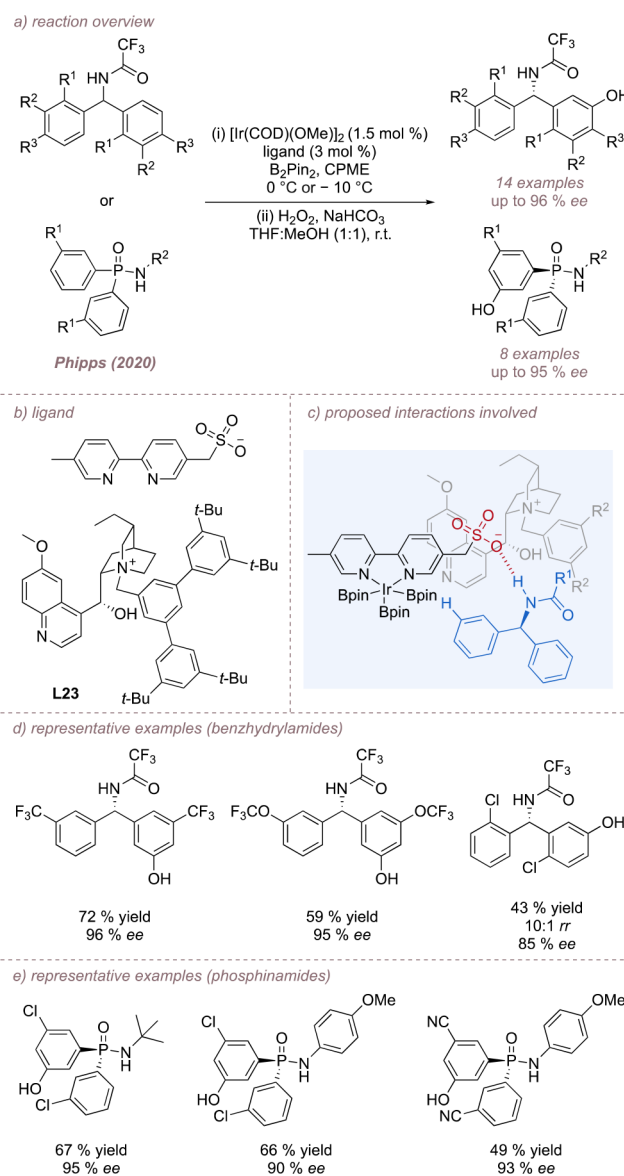

Figure 62. Enantioselective, desymmetrizing arene borylation directed by a chiral cation.

regioselectivity and enantioselectivity (Figure 62d). In the case of the phosphinamide substrates, the control of regioselectivity proved more challenging, potentially as a result of conformational effects. However, for substrates posing no regioselectivity challenge in the borylation, very high enantioselectivities could be achieved (Figure 62, e).

4.2. Carbon−Oxygen Bonds. The group of Thorsten Bach has pioneered the use of chiral lactam recognition elements for enantioselective catalysis in a strategy that has been successfully applied to a remarkably broad range of synthetic transformations, including those catalyzed by transition metals.[235] Typically, a rigid, chiral recognition element is appended to a privileged achiral transition metal ligand scaffold and is sufficiently remote from the reactive site so as not to interfere with the reactivity. The most commonly used motif is an amide capable of two-point hydrogen bonding that is uniquely effective in recognizing and engaging cyclic amides in hydrogen bonding interactions which precisely position the substrate over the reactive metal center. In certain

cases, the strategy can exert control over the site-selectivity of the reaction as well as enantioselectivity.

Within the context of carbon−oxygen bond formation, Bach first investigated the enantioselective epoxidation of vinyl-quinolones (Figure 63a).[236] This was achieved using a
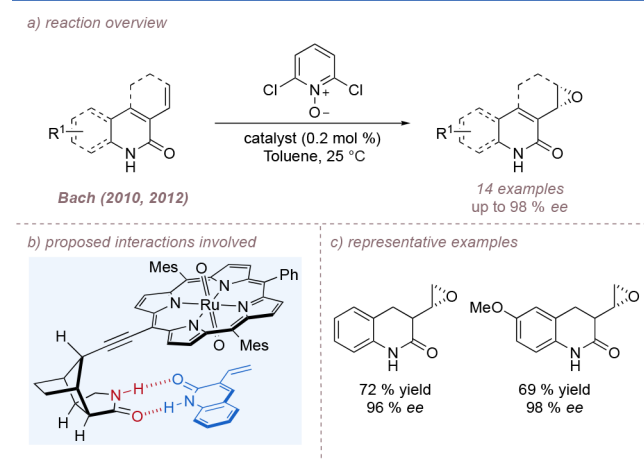

Figure 63. Enantioselective epoxidation enabled by a remotely functionalized porphyrin ligand.

ruthenium porphyrin complex functionalized with a "V"-shaped hydrogen bonding motif, joined to the scaffold via an alkyne linker (Figure 63b). The "V"-shaped motif is based on a chiral, tricyclic octahydro-1*H*-4,7-methanoisoindol-1-one structure and is the recognition element of choice for the transition metal ligand modifications. The epoxide products were typically obtained with good yields and enantioselectiv-ities (Figure 63c). Control experiments showed that both of the hydrogen bonds proposed are critical to achieving high enantioselectivities. Notably, control of site-selectivity was also possible in a competition substrate bearing two alkenes. Subsequent in-depth studies expanded the scope of the transformation to other substituted 3-vinylquinolones, alke-nylpyridones, and primary alkenoic amides. The origin of selectivity was also explored using DFT.[237]

Next, this catalyst system was used to tackle the challenge of enantioselective oxygenation of aliphatic C−H bonds, mimicking the action of cytochrome P450 enzymes. A particular challenge in this case is the tendency for the desired secondary alcohol product to be further oxidized, eradicating the newly installed stereocenter. As an initial solution, Bach and co-workers desymmetrized a spirocyclic oxindole to test their system (Figure 64a).[238] Following reaction completion, the crude mixture was exhaustively oxidized to convert any residual alcohol to the ketone. A slightly modified porphyrin catalyst was optimal and a representation of the proposed interactions involved in the transformation is shown below (Figure 64b). Structurally intriguing ketones could be obtained in moderate to good yield and with good enantioselectivities, proving the viability of this scaffold for enantioselective C−H oxidation (Figure 64c). A change in the catalytic metal, which largely suppressed deleterious overoxidation enabled the hitherto elusive chiral secondary alcohols to be obtained (Figure 64d).[239] By using manganese in place of ruthenium and reoptimizing, formation of the ketone byproducts was minimized, and an analogous mode of stereocontrol was invoked (Figure 64e). In a reaction truly reminiscent of one catalyzed by a cytochrome P450 enzyme, mono-oxygenated
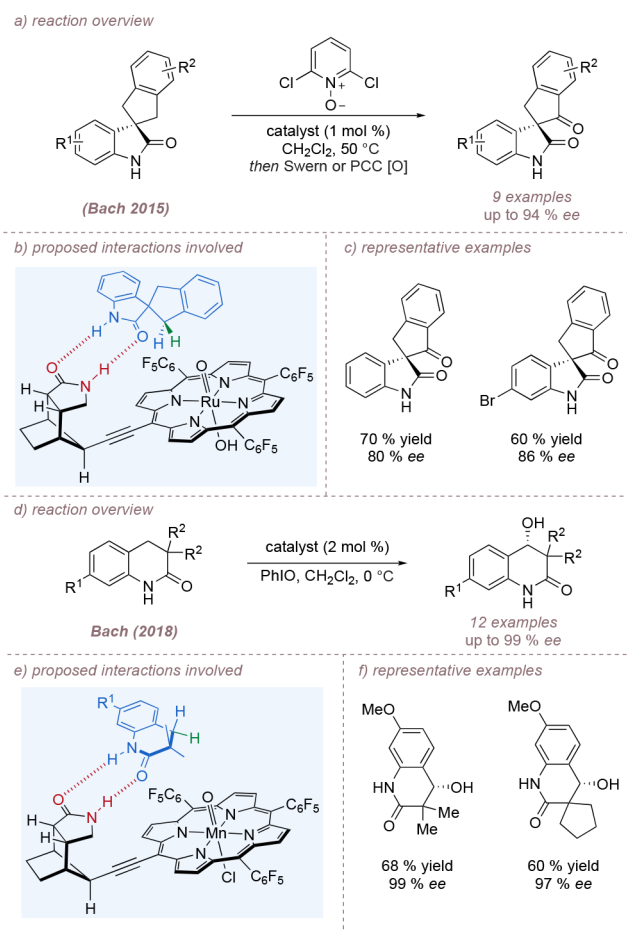

Figure 64. Examples of enantioselective oxygenation reactions using bifunctional porphyrins.

products could be obtained with good to outstanding enantioselectivity (Figure 64f).[240] In a more recent update to the methodology, the selective mono-oxygenation of con-formationally more flexible substrates possessing exocyclic methylene groups was achieved.[241] In this later example, the catalyst controlled site-selectivity in addition to enantioselec-tivity, with preferential functionalization at the exocyclic methylene groups.

In 2017, Zhang, Zanoni, and co-workers chose to use the cyclization of allenols as a testing ground to validate a new chiral bifunctional ligand design for gold(I) catalysis (Figure 65a).[242] The researchers developed a ligand in which a basic amide is incorporated into the lower aryl ring of a chiral BINOL-derived phosphine scaffold (Figure 65b). It was proposed that in the transition state, the substrate orients itself such that the free alcohol is placed near to the amide carbonyl group, a good hydrogen bond acceptor, which can subsequently act as a general base and increase the nucleophilicity of the alcohol (Figure 65c). In the transition state leading to the minor product, this interaction would not be possible. An analogous chiral ligand possessing a similar scaffold but lacking the amide resulted in large decreases in both rate and enantioselectivity. Achiral starting materials could be converted to the products with outstanding enantioselectivities and yields but arguably more important were the results obtained when racemic starting materials were employed (Figure 65d). The selectivity for *Re*-face attack of the allene was extremely high for both starting material
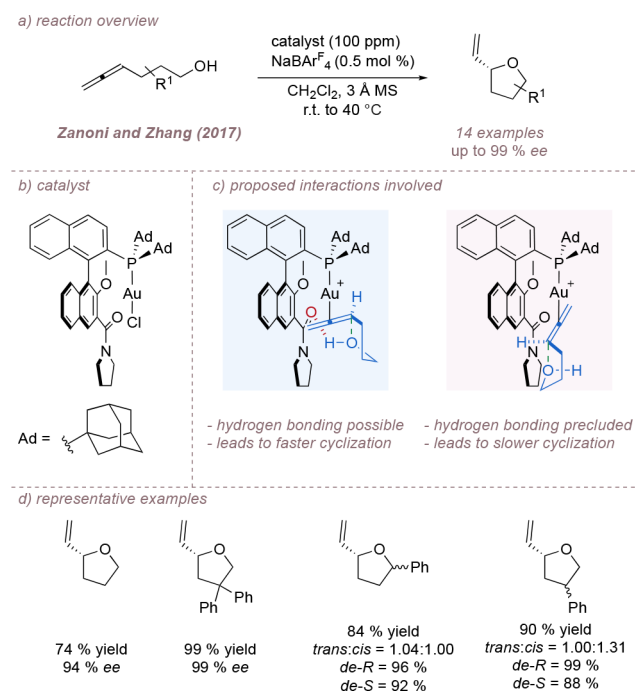
Figure 65. Enantioselective gold(I)-catalyzed cyclization of allenols.

Figure 66. Tethered counterion-directed enantioselective gold catalysis.

enantiomers, demonstrating that any pre-existing stereo-chemical information on the substrate did not affect the facial selectivity of nucleophilic attack. This was also reflected in the low *cis/trans* selectivity observed for these cyclization precursors. Since both enantiomers of the ligand can be readily accessed, when enantioenriched starting materials were used, single stereoisomers could be obtained with very high dr and de values. Of note is that catalyst loadings as low as 100 ppm were used.

Guinchard, Marinetti, and co-workers in 2020 recognized that one possible hazard of the chiral anion approach lies in the potential flexibility of the key ion pair, if additional interactions are not present. The authors suggested that a covalent tether between a chiral phosphoric acid and an achiral phosphine ligand might rigidify certain systems and potentially lead to better organization of the reaction components. To test this, the gold(I)-catalyzed cycloisomerization/nucleophilic addition of 2-alkynylenones was studied using a novel chiral catalyst (Figure 66a,b).[243] This transformation using indole nucleophiles had been achieved previously by Toste and co-workers through a combination of chiral phosphates with copper catalysis.[244] The reaction mechanism starts with a halide abstraction to form the cationic gold(I) active catalyst which coordinates the substrate alkyne, activating it toward a 5-*endo*-*dig* cyclization (Figure 66c). Gold remains bound to the substrate and it is postulated that the planar, stabilized carbocation can engage the pendant chiral phosphate in a tight ion-pairing interaction which ensures that only one face of the prochiral cation is sterically accessible to the external nucleophile upon attack. A wide substrate scope demonstrated that both the nucleophilic and alkynyl enone components could be varied while maintaining good to excellent levels of enantioselectivity (Figure 66d). Notably, *N*-Me indole gave no loss in enantioselectivity, suggesting that a hydrogen bond between the nucleophile and the catalyst is not important. Two further advantages of the protocol include the remarkably low catalyst loading (0.2 mol %) and the fact that in some cases,
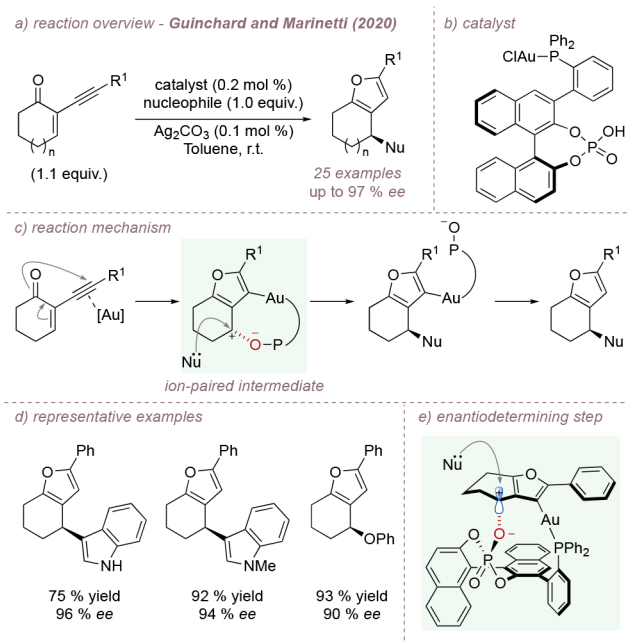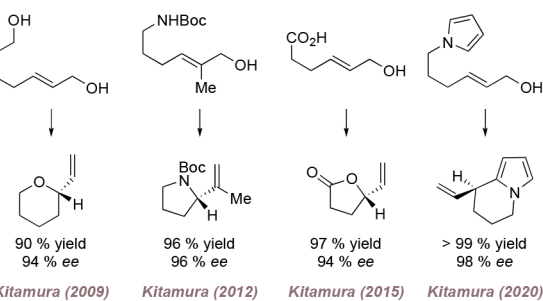
the use of a silver salt to perform the halide abstraction was not required. Control experiments demonstrated that both components of the ligand, connected in the proper orientation, are essential. DFT modeling of the putative cationic intermediate suggested that the chiral phosphate is well positioned to the ion pair with the cation from the bottom face of the substrate as drawn above, forcing nucleophilic attack to occur from the top face (Figure 66e). This *tethered* counterion-directed catalysis strategy is an interesting extension of the chiral anion concept, and it will be intriguing to see how it may be applied to other transition metals beyond gold.

Over the past 10 years, the Kitamura group has reported a series of enantioselective intramolecular allylation reactions of various tethered nucleophiles to form valuable cyclic products. Effective nucleophilic groups include −OH, −NHBoc, −CO$_2$H, and pyrrole and a notable feature is that an activated leaving group in the allylic system is not required—a free hydroxyl is sufficient (Figure 67a).[245−248] In these processes, a ruthenium catalyst is used in combination with a novel atropisomeric, pyridine-2-carboxylic acid-derived ligand that incorporates a 2-chloronaphthalene component (Figure 67b). The active catalyst is formed by combination of this ligand with a ruthenium(II) source. A key component of this catalyst is the Brønsted acidic carboxylic acid group which is able to hydrogen bond to the allylic hydroxyl to promote oxidative addition. Furthermore, the authors propose that the nucleophilicity of the intramolecular, protic nucleophile can be enhanced by the formation of a hydrogen bond with the basic carboxylate oxygen atom of the ligand after oxidative addition (Figure 67b). A deuterium labeling experiment was used to provide insight into the reaction mechanism by monitoring the stereorelationship between geometric isomers and enantiomers.[247] More recently the authors have intriguingly proposed a second NCI that may promote catalytic activity: the formation of a halogen bond between the chlorine of the ligand and the intramolecular nucleophile. This was considered after modifying the ligand to contain stronger halogen bond
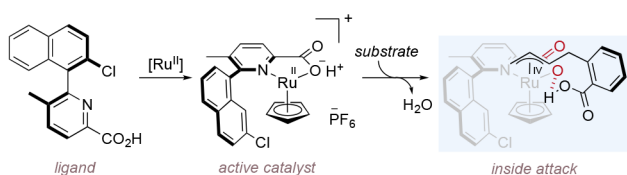
Figure 67. Asymmetric, intramolecular cyclization of allyl alcohols developed by Kitamura.

Figure 68. Enantioselective phosphorus−carbon cross coupling enabled by a bifunctional Xiao-Phos ligand.

donors (from Cl to Br and I) resulted in a significant acceleration in reactivity when using an intramolecular pyrrole nucleophile.[248] This would be a very rare case of halogen bonding being implicated in catalysis, but investigation of this class of NCIs is certainly on the increase.[249]

4.3. Carbon−Phosphorous Bonds. The members of the sulfinamide-phosphine (Sadphos) ligand family have been successfully employed as ligands in various transition metal-catalyzed reactions, some of which implicate NCIs. In a recent notable example, Zhang and co-workers reported an asymmetric arylation of secondary phosphine oxides using palladium catalysis.[250] While PC-Phos (see Figure 39) gave racemic product, the new ligand Xiao-Phos was found to give excellent results (Figure 68a,b). Control experiments underlined the importance of the sulfinamide moiety: N-methylation prevented reaction as did the removal of the sulfinyl group. The authors used DFT to model the possible intermediates preceding the reductive elimination step. In these, the ligand engages the approximately planar palladium complex in two-point binding via the phosphine and the sulfinyl oxygen group. In the two relevant intermediates invoked to explain the enantioselectivity, hydrogen bonding occurs between the palladium-ligated phosphine oxide and the sulfinamide N−H (Figure 68c). In the lower-energy intermediate, the phosphine oxide alkyl substituent points toward the aryl bromide-derived aromatic ring. By contrast, in the higher-energy intermediate, the aryl rings of both the phosphine oxide and aryl ligand on palladium are adjacent, leading to unfavorable steric interactions. Good variation of both the alkyl group on the racemic starting material as well as on the aryl bromide coupling partner was achieved (Figure 68d). In an elegant demonstration, the authors devised a flexible and scalable route for the synthesis of privileged DiPAMP-type bisphosphine ligands in outstanding ee.
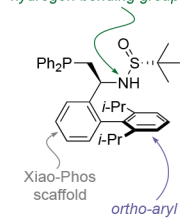
4.4. Carbon−Nitrogen Bonds. Complementary to direct, enantioselective C−H oxygenation reactions are corresponding aminations which insert a nitrogen atom into aliphatic C−H bonds, with the formation of a stereocenter. Both transformations are of unparalleled synthetic importance, yet within
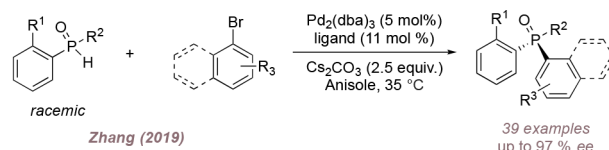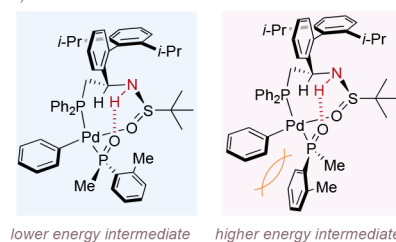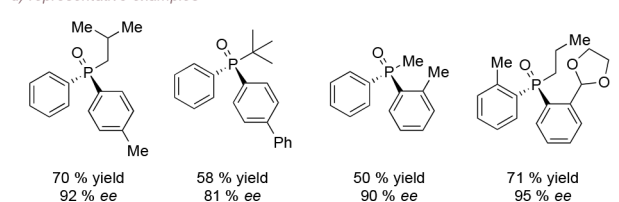
the field of enantioselective $C(sp^3)$−H amination, much further work is needed in order to attain the generality of the well-established achiral variants, particularly in the context of intermolecular reactions.[251]

Dirhodium tetracarboxylates are arguably the catalysts of choice for intermolecular, aliphatic C−H amination, and pioneering work from the Du Bois laboratory in particular has done much to develop these.[252] Du Bois' $Rh_2(esp)_2$ catalyst is extremely robust and its unique performance has enabled the expansion of the methodology from *intra*molecular to *inter*molecular reactions.[253] Bach and co-workers recognized that the $Rh_2(esp)_2$ scaffold would be well-suited to modification with a chiral recognition element to target enantioselective amination, according to the same principles outlined at the start of section 4.2 (Figure 69a). Accordingly, the chiral lactam motif was attached to the *meta* position of each bridging aromatic ring belonging to the strapped
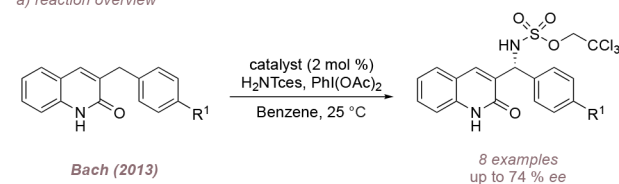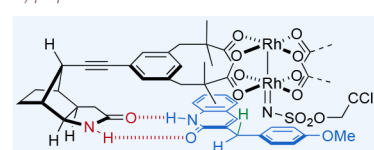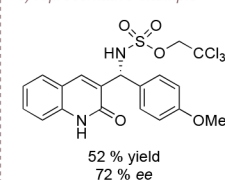
Figure 69. Bach's modified version of the Du Bois catalyst $Rh_2(esp)_2$ used for enantioselective amination.

dicarboxylate groups of the dirhodium catalyst (Figure 69b).[254] Using this catalyst, the authors found that the electron-rich methylene group in 3-benzylquinolone substrates could be aminated in up to 74% ee (Figure 69c). The same catalyst could also be used for the enantioselective aziridination of quinolones bearing exocyclic alkenes, to afford dihydrobenzo[2,3-*b*]quinolines in up to 95% ee following an intramolecular ring opening of the newly formed aziridine.[255]

Other metals in addition to rhodium have also proven effective catalysts for intermolecular aliphatic C−H amination, and silver has been extensively studied by the groups of Che, Pérez, and Schomaker for this purpose.[256] In a very recent publication, Bach reported an enantioselective intermolecular amination using silver catalysis (Figure 70a).[257] This was

a) reaction overview

Bach (2020)

13 examples
up to 97 % ee

b) ligand

c) proposed interactions involved

d) representative examples

70 % yield
94 % ee

51 % yield
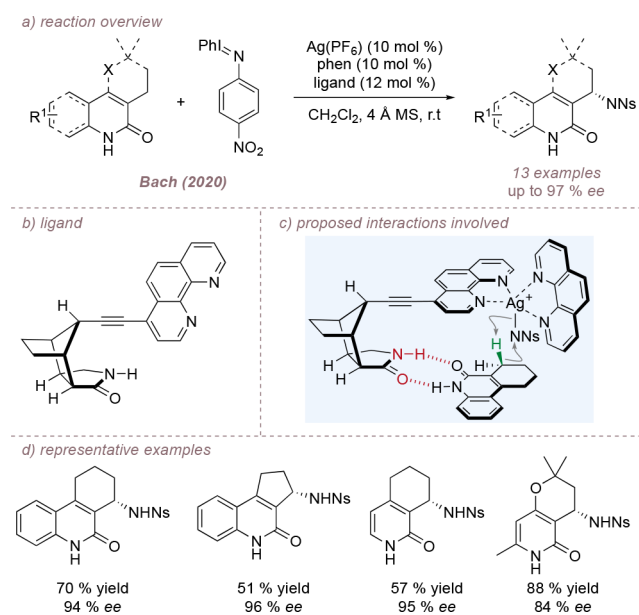96 % ee

57 % yield
95 % ee

88 % yield
84 % ee

Figure 70. Enantioselective intermolecular C−H amination proceeding via a silver nitrenoid.

achieved through the use of a phenanthroline ligand functionalized with the recognition unit at the C-4 position (Figure 70b). An achiral 1,10-phenanthroline coligand was used alongside to assist formation of a heteroleptic silver complex. As previously, two-point hydrogen bonding between the substrates and the ligand for the silver nitrenoid ensured that only one of the enantiotopic C−H bonds was correctly oriented to undergo the reaction and efficient amination of 2-quinolone and 2-pyridone substrates in high yields with excellent enantioselectivities was achieved (Figure 70c,d). The reaction is an exemplar of ligand accelerated catalysis. So much so, that in certain cases, racemic HPLC comparison traces had to be obtained using a racemic version of the chiral hydrogen bonding ligand because the activity of the achiral phenanthroline-ligated control catalyst was so low. As an aside, attractive noncovalent interactions have also been invoked in silver-catalyzed nitrene transfer reactions to control aspects of site-selectivity.[258] Given the ubiquity of phenanthroline ligands in transition metal catalysis and the ongoing efforts dedicated to the development of chiral variants, it is anticipated that this novel chiral scaffold may impart enantioselectivity to other important reaction classes.[259]

The application by the Zhang research group of D_2-symmetric cobalt-porphyrin catalysts to enantioselective

carbene chemistry has been discussed previously in section 2.5. Parallel to their investigations in this area, the group has also studied the analogous aziridination and amination reactions which can be mediated by these catalysts. In these transformations, hydrogen bonding between the side arms of the porphyrin ring and the highly reactive postulated intermediates is once again suggested to be a crucial factor in obtaining high reaction efficiencies.

Within the context of aziridination, early studies by Zhang and co-workers in 2008 focused on the development of an efficient racemic aziridination protocol for aromatic olefins using arylsulfonyl azides.[260] In order to achieve this, the authors designed a cobalt porphyrin catalyst in which appropriately placed achiral hydrogen-bond-donating amide groups on the ligand backbone could interact through hydrogen bonding with the $-SO_2$ group of the assumed metal nitrene intermediate.[260] Such interactions were anticipated to both stabilize the formation of the reactive intermediate and enhance its electrophilicity. Notably, catalysts which lacked these hydrogen bond-donating groups performed poorly in the same reaction. Subsequent computational work supported the hydrogen bonding hypothesis and provided evidence to show that this interaction accelerated the formation of the cobalt(III) nitrene radical species.[261]

Incorporation of these hydrogen bond-donating groups within a chiral environment subsequently enabled the development of enantioselective aziridination reactions. In an example from 2013, Zhang and co-workers reported the enantioselective aziridination of alkenes with fluoroaryl azides (Figure 71a).[262] In this particular case, stabilizing NH···F

a) reaction overview

catalyst (1 mol %)

Fluorobenzene,
4 Å MS, r.t.

Zhang (2013)

28 examples
up to 98 % ee

b) proposed interactions involved

c) representative examples

99 % yield
92 % ee

80 % yield
96 % ee

95 % yield
94 % ee

R^1 = 3,5-*t*-Bu-C_6H_3, R^2 = ß-Naphth
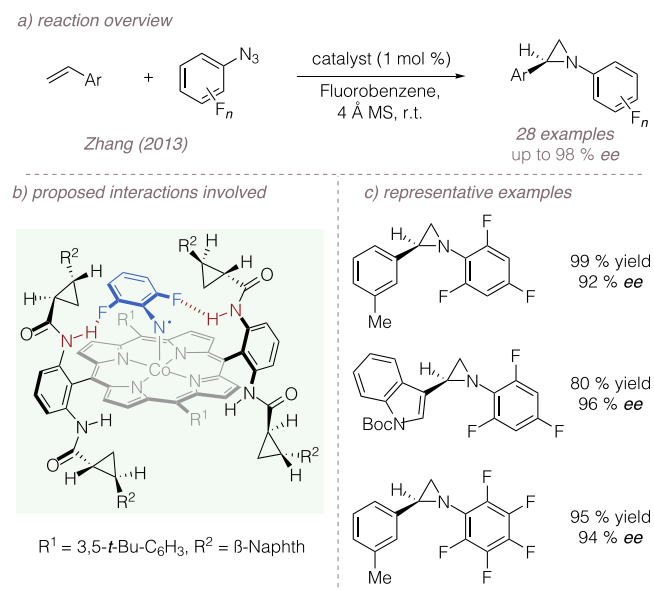
Figure 71. An enantioselective cobalt-mediated aziridination reaction.

hydrogen bonds between the cobalt(III)-nitrene radical intermediate and the chiral side arms of the porphyrin (Figure 71b) were invoked and the transformation resulted in product formation with excellent yields and enantioselectivities (Figure 71c).

Subsequent to this publication, the group has reported further examples of asymmetric aziridination and amination processes invoking the same ligand acceleration effect through hydrogen bonding. These include intermolecular aziridination

reactions using phosphoryl azide[263] and the intramolecular radical aziridination of allylic sulfamoylazides[264] together with an enantioselective radical construction of cyclic sulfonamides.[265] More recently the group has developed a series of structurally intriguing second generation D_2-symmetric chiral porphyrin ligands in which alkyl bridges link the two chiral amide units on either side of the porphyrin ring. The hydrogen bond-donating ability of the amide groups in these new catalysts is improved, and the catalysts themselves show enhanced activity.[266,267]

The Chang group has made seminal contributions to C−H amination chemistry and two selected examples of intramolecular enantioselective aminations in which NCIs are implicated will be presented. These reactions generate versatile γ-lactams and while the products of both reactions are structurally very similar, the NCIs through which stereochemical control is exerted in each one are thought to be entirely different. Together, these cases provide a powerful demonstration of how separate catalytic systems employing distinct NCIs can offer highly creative yet contrasting solutions to a common synthetic challenge.

In the first example, 1,4,2-dioxazol-5-ones, easily accessed from the parent carboxylic acid, are utilized as stable precursors to the active iridium nitrenoid species (Figure 72a).[268,269]
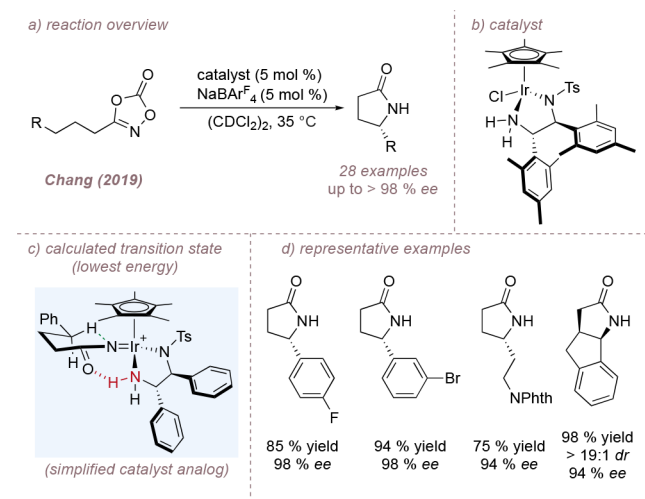

Figure 72. Enantioselective iridium-catalyzed intramolecular C−H amination.

Following chloride abstraction from the iridium precatalyst (Figure 72b), complexation of the heterocycle with the cationic iridium triggers decarboxylation to afford the singlet iridium−carbonylnitrenoid. This highly reactive species can then insert into a C(sp^3)−H bond along the chain to give the five-membered product, and the chiral catalyst bearing a diamine ligand with mesityl groups on the backbone gave the best stereoselectivities. DFT was used to rationalize the outcome, and in the lowest-energy transition state for the insertion of the iridium nitrene, there is a stabilizing hydrogen bond between the protons of the metal-coordinated diamine and the carbonyl oxygen of the nitrenoid (Figure 72c). A half-chair geometry is adopted in which the substrate phenyl group lies pseudoequatorially. A variety of careful control and mechanistic experiments were carried out which supported this picture. The methodology could be used for the intramolecular functionalization of benzylic positions, less-

reactive aliphatic positions and also in a desymmetrization mode (Figure 72d). In work published simultaneously, an identical transformation was reported by the Yu group using ruthenium(II) catalysis with a similar proposal as to the importance of hydrogen bonding.[270]

In the second example, published almost immediately after, Chang, He, Chen, and co-workers achieved the same transformation with an entirely different catalyst system, again with NCIs proposed to be fundamental to enantiocontrol (Figure 73a).[271] This system also employs iridium-catalyzed
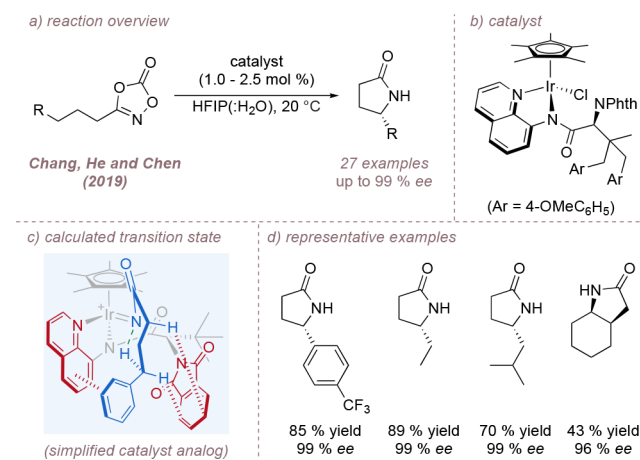

Figure 73. Enantioselective iridium-catalyzed intramolecular C−H amination using an alternative catalyst system.

decomposition of 1,4,2-dioxazol-5-ones, but here the ligand comprises a bidentate 8-aminoquinoline linked to a phthalimide-protected *tert*-butylglycine-derived amino acid (Figure 73b). The use of a highly polar solvent system is intriguing and is in marked contrast to the apolar medium of the previous transformation. The origin of enantioselectivity, as deduced from DFT calculations performed with a simplified ligand, is striking (Figure 73c). The arrangement of the Cp*, aminoquinoline, and Phth groups around the iridium center results in the formation of a hydrophobic chiral pocket which extends around the deeply embedded metal center. In the highly polar reaction medium, the lipophilic aliphatic substrates readily enter the chiral pocket and bind to the cationic iridium center, as a consequence of the hydrophobic effect. This enables the efficient formation of the nitrenoid following decarboxylation. Subsequently, an intramolecular nitrene insertion occurs through a chairlike transition state. Several key NCIs are thought to be operative in the favored transition state. First, a π−π stacking interaction between the aromatic ring of the substrate and the aminoquinoline and, second, the phthalimide group on the opposite side of the pocket can engage hydrogens at the α- and γ- positions of the chain in attractive C−H···π interactions. The enantioselectivities obtained using this elegant enzyme-like system are extremely high and consistent across a range of substrates, from those that are purely aliphatic to those bearing aromatic groups (Figure 73d). It is also worth noting that attractive noncovalent interactions have been exploited in iridium-catalyzed nitrene insertion processes to exert control over the reaction regioselectivity also.[272]

Overall, the two examples discussed above have enabled the synthesis of valuable chiral lactam products. A direct comparison of the two approaches shows that the application of attractive noncovalent interactions in catalysis offers creative

chemists endless and varied possibilities to solve given synthetic problems.

5. CONCLUSIONS AND OUTLOOK

The breadth of transformations highlighted in this Review demonstrate how widespread it is now for attractive non-covalent interactions to be involved in enantioselective transition metal catalysis. In some of these cases, the initial system design was for these interactions to be at the forefront. In other cases, these interactions were subsequently found to be important either through mechanistic experiments or, increasingly commonly, after computational analysis of the reaction pathway using DFT calculations. What is becoming ever more apparent is that for many systems in which control was quite reasonably presumed to occur by purely steric interactions, closer analysis points toward a more nuanced picture in which multiple weak attractive NCIs operate in tandem alongside the expected repulsive interactions. While such, at times complex, rationales do not necessary translate in a direct manner to the design of novel systems, they are extremely valuable and over time will allow synthetic chemists to adopt a more complete understanding of all factors to take into account. From the venerable Diels−Alder reaction to contemporary C−H activation, this approach has proven to be very generally applicable and while there are undoubtedly numerous unpublished studies in which success was not achieved, this does not necessarily mean a fundamental incompatibility with any particular reaction type. More likely it is just that the proper system to accomplish it has not yet been developed.

It is also apparent from this survey that the rational design of systems which possess what are typically the strongest NCIs, such as hydrogen bonds or ion pairs, does produce excellent and tangible outcomes and there are many examples of this detailed in this Review. The majority of common and useful functional groups used in synthetic chemistry are capable of engaging in NCIs of some form. As a result, most substrates intrinsically possess some functional handle with which they might engage in an interaction with a suitable ligand. These interactions not only help to draw the substrate to the catalyst, with the associated increase in rate, but also importantly provide an extra level of organization as the enantiodetermining transition state is approached.

This survey covers selected literature from the last 10 years so does not aim to be comprehensive, but it can hopefully give the reader an impression of the rapid advances which have taken place during this time. We believe that there has been a shift in mindset whereby NCIs are being considered as a more mainstream control element by synthetic chemists when designing processes involving transition metals. This is perhaps due to the widespread adoption of noncovalent strategies for organocatalysis. Combining these insights with the ever-increasing diversity of transition metal reactivity and the established principles of chiral ligand design should make for exciting developments in the future, and we hope that the compilation of this survey may help in some way to facilitate these.

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