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Anionic Chiral Tridentate N-Donor Pincer Ligands in Asymmetric Catalysis

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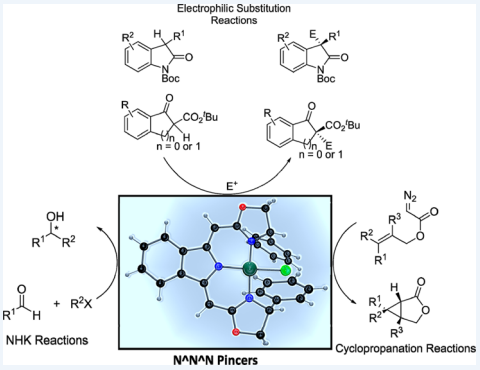
CONSPECTUS: Tridentate monoanionic ligands known as "pincers" have gained a prominent place as ligands for transition metals and, more recently, for main-group metals and lanthanides. They have been widely employed as ancillary ligands for metal complexes studied inter alia in bond activation steps relevant to catalytic processes. The central formally anionic aryl or heteroaryl unit acts as an "anchor" in the coordination to the metal, which kinetically stabilizes the resulting complexes. Their stability, activity, and reactivity can be tuned by subtle modifications of substitution patterns on the pincer ligand or by modifying the donor atoms. The challenges in pincer ligand design for enantioselective catalysis have been met by their assembly from rigid heterocycles and chiral ligating units in the "wingtip" positions, which generally contain the stereochemical information. The resulting well-defined geometry and shape of the reactive sector of the molecular catalyst favor orientational control of the substrates. On the other hand, the kinetic stability allows reduced catalyst loadings.



Recently, a new generation of tridentate anionic N^N^N pincer ligands has been developed which give rise to highly enantioselective transformations. Their applications in asymmetric catalysis have focused primarily on the asymmetric Nozaki–Hiyama–Kishi coupling of aldehydes with halogenated hydrocarbons as well as Lewis acid catalysis involving enantioselective electrophilic attack onto metal-activated β-keto esters, oxindoles, and related substrates. These include highly selective protocols for Friedel–Crafts alkylations with Michael acceptors, electrophilic fluorinations, trifluoromethylations, azidations, and alkylations and subsequent transformations. Increasingly, these stereodirecting ligands are being employed in other types of transformations, including hydrosilylations, cyclopropanations, and epoxidations. The stability and well-defined nature of the molecular catalysts have made them attractive targets for mechanistic studies into a wide range of these transformations, thus providing the type of insight required for a more rational approach to catalyst development. This Account reviews work performed by us and other groups in the field and places it into perspective in relation to general research efforts in enantioselective catalysis.

1. INTRODUCTION

The control of stereoselective catalytic transformations with metal complexes rests upon the development of efficient structural platforms for the ancillary stereodirecting ligands.[1] A classical approach to inhibit ligand exchange reactions is to employ polydentate ligands, which provide a large kinetic energy barrier to ligand loss and additional thermodynamic stability to complexes. Apart from the ubiquitous chiral chelates, monoanionic meridionally coordinating tridentate ligand systems, frequently called "pincers", are expected to enhance catalyst stability while offering a structural platform for the construction of efficient stereodirecting units.

Since the first report in the late 1970s, pincer ligands have been extensively studied in organometallic chemistry and catalysis.[2,3] The resulting complexes have been widely applied inter alia in bond activation studies, which are relevant for catalytic transformations. Nowadays, the term "pincer" is occasionally used for all meridionally coordinating ligands, including neutral tridentate systems. This would include inter alia bis(oxazolinyl)-pyridine (pybox) ligands, which have been used extensively in enantioselective catalysis and have been reviewed comprehensively elsewhere.[4] In a narrower sense, pincers consist of a central (formally) anionic donor atom (usually C or N) coordinated via a covalent σ bond and two pendant arms that donate lone pairs of electrons (e.g., from O, N, S, P) to the central metal atom. The chiral ligating units in the "wingtip" positions of pincers generally contain the stereochemical information and, if identical, confer twofold rotational symmetry upon the ligand–metal unit. The resulting well-defined geometry and shape of the reactive sector in the coordination sphere of the molecular catalyst favor orientational control of the substrates, and the molecular symmetry may simplify catalyst optimization routines.

The phebox ligands were the first to perform as efficient stereodirecting pincer ligands in a variety of applications and have been reviewed previously.[5] However, many of the known chiral systems of the pincer type perform relatively poorly in enantioselective catalysis.[6] This may be due in part to a certain lack of control of substrate orientation arising from the flexibility

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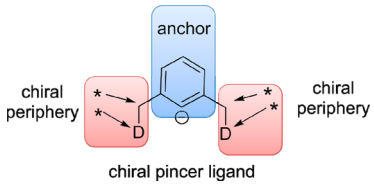
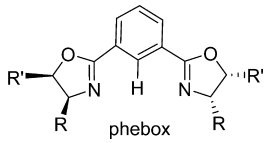


of the ligand backbone. This may be controlled by an assembly from rigid heterocyclic units, as evident in the phebox case.



In this Account of recent developments in the application of N^N^N pincers as efficient stereodirecting ligands in enantioselective catalysis, we focus on five different classes of pincer ligands, Cbzbox (**1**), BOPA (**2**), Boxmi (**3**), BPI (**4**), and PyrrMeBOX (**5**) (Figure 1), which all contain a central anionic

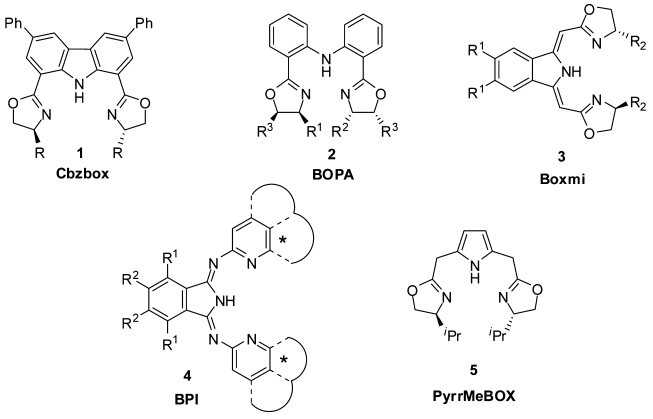


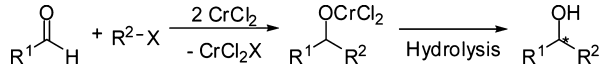
Figure 1. Chiral tridentate N^N^N pincer ligands discussed in this Account.

nitrogen σ donor and two pendant lone-pair donors from nitrogen atoms in oxazoline or pyridine rings. Their applications in asymmetric catalysis have focused initially on the asymmetric Nozaki–Hiyama–Kishi coupling of aldehydes with halogenated hydrocarbons and subsequently as Lewis acid catalysts involving enantioselective electrophilic attack inter alia onto metal-activated β-keto esters and oxindoles. Increasingly, these stereodirecting ligands are being employed in other types of transformations, including hydrosilylations, cyclopropanations, and epoxidations, which will be reviewed in the final section of this Account.

2. APPLICATIONS IN NOZAKI–HIYAMA–KISHI COUPLINGS AND RELATED TRANSFORMATIONS

In the late 1970s, Nozaki and Hiyama employed chromium(II) salts in the "one-pot" coupling reaction of organic halides and carbonyl compounds.[7] Since then, the chromium-catalyzed Nozaki–Hiyama–Kishi (NHK) reaction has become an important tool in carbon–carbon bond-forming reactions (Scheme 1).[8,9] The use of a chiral tridentate pincer ligand at the metal center stabilizes the organochromium species in the catalytic reaction and allows for control of the enantioselectivity. In this section, allylation, methallylation, and crotylation

Scheme 1. NHK Reactions of Organic Halides and Carbonyl Compounds



reactions as well as propargylation and allenylation reactions using chiral-pincer-ligand complexes of chromium are discussed.

The C_2-symmetric tridentate bis(oxazoline)carbazole (Cbzbox) ligand (**1**) was first reported by Nakada in 2003 from the reaction of dicyanodiphenylcarbazole with a chiral alcohol under reflux in the presence of $ZnCl_2$.[10,11] An improved synthesis allowing additional ligand substitution patterns that were inaccessible by the previous route was subsequently reported, involving the direct formation of the chiral amide precursor via a Pd-catalyzed amidation reaction followed by a cyclization reaction using $BF_3{\cdot}Et_2O$ to obtain the ligand **1** (Scheme 2).[12,13]

Nakada demonstrated that the complexes of these Cbzbox ligands (**1b**, R = ^{i}Pr) with $CrCl_2$ were potent catalysts for the asymmetric NHK reactions of aldehydes with allylic halide derivatives.[10] An analysis of the scope of the substrates demonstrated that aryl, alkenyl, and alkyl aldehydes could all be used effectively in this reaction (Scheme 3). The absolute configuration of the products indicated that the reaction preferentially occurred through *Si*-face attack. Importantly, the Cr–Cbzbox ligand complex was found to be water-tolerant and could be recovered and recycled with the ee values being essentially unchanged from those of the initial reaction.[10]

In 2002 and the following years, the tridentate bis(oxazoline)-amido (BOPA, **2**) and isoelectronic bis(thiazoline) pincer ligands were synthesized. In these ligands, an *N*-phenylaniline unit links two oxazoline or thiazoline rings (Figure 2).[14,15] Guiry subsequently reported the application of such tridentate chiral BOPA–chromium complexes in the NHK reaction of aldehydes (Scheme 3).[16,17] It was found that both the extent and sense of the asymmetric induction were highly dependent on the nature and combination of the substituents on the oxazoline rings, with small changes in structure translating into large variations in enantiodiscrimination.[16]

Recently, the NHK reaction of aldehydes using bis-(oxazolinylmethylidene)isoindoline (Boxmi) ligands (**3**) has also been reported.[18] These tridentate N-donor pincer ligands are conveniently prepared from readily available phthalimide starting materials by Wittig coupling with ethyl (triphenylphosphoranylidene)acetate to afford the ligand backbone, which can be subsequently condensed with chiral amino alcohols to give the corresponding ligands (Scheme 4).[18] The substrate scopes for the NHK allylation, methallylation, and crotylation reactions were examined by varying the aldehyde and bromide reactants, which gave the products in high yields with high enantioselectivities (Scheme 3). In the case of methallylation and crotylation, a notable anti/syn ratio of 10/1 was observed.[18]

The enantioselective NHK reaction has also been applied in the total synthesis of natural products. Cbzbox–Cr complexes were employed in the catalytic methallylation of chiral aldehyde **6** to give **7**, an important intermediate in the synthesis of calcitriol lactone, a metabolite of vitamin D_3 (Scheme 5). Cbzbox ligand **1b** gave a −94% dr value, while its enantiomer gave a 97% dr value.[10]

The enantioselective total syntheses of FR901512 (IC_{50} = 0.95 nM) and FR901516 (IC_{50} = 14.0 nM), inhibitors of HMG-CoA

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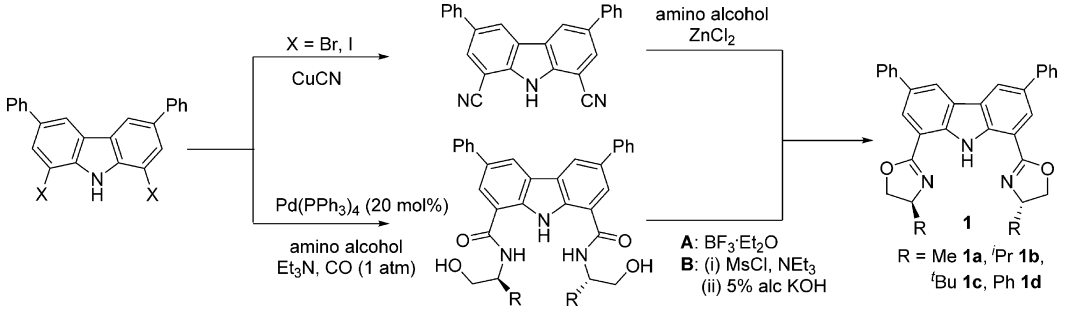
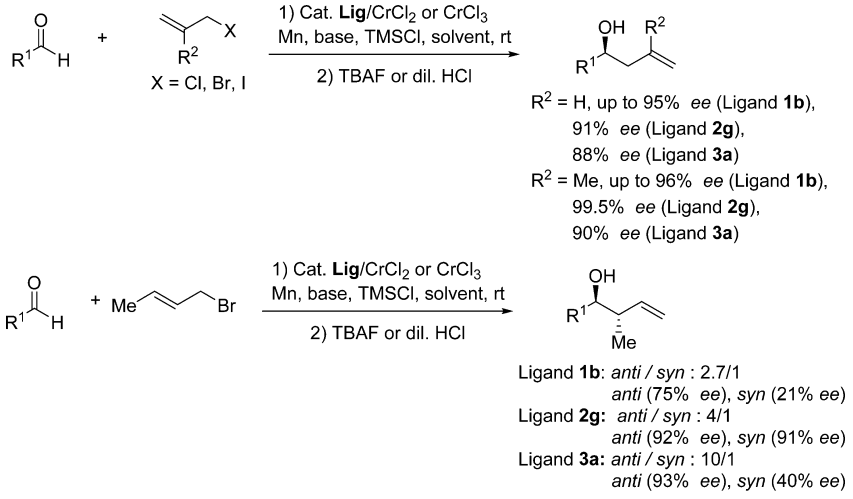
Scheme 2. Synthesis and Structures of Cbzbox Ligands



Scheme 3. Cr-Catalyzed Asymmetric NHK Reactions Using Various Tridentate Pincer Ligands



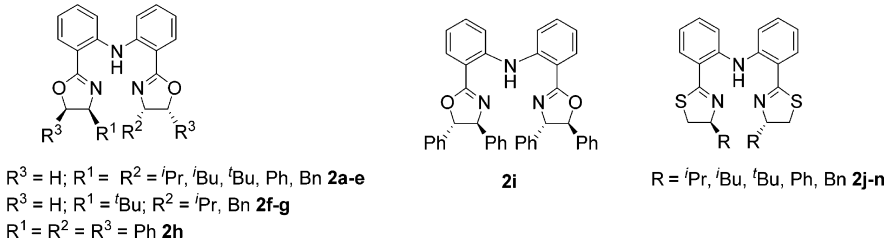


Figure 2. (left) Bis(oxazolinylphenyl)amido (BOPA) and (right) bis(thiazoline) ligands.

reductase (an enzyme controlling cholesterol synthesis), was accomplished by using the asymmetric NHK reaction twice within the synthesis (Scheme 6). Methallyl chloride was coupled with the aldehyde starting material (5-methyl-2-vinylbenzaldehyde) to afford the intermediate alcohol **8**. A subsequent asymmetric NHK allylation of aldehyde **9** using the same catalyst provided the corresponding homoallylic alcohol **10** in excellent yield and stereoselectivity.[19]

Cbzbox ligands **1a–c** have also been employed in the catalytic asymmetric propargylation of aldehydes with good to excellent enantioselectivities,[20] providing an alternative to the previous use of chiral Lewis acids in the addition of allenyltin reagents to aldehydes.[21] The Cr-catalyzed propargylation of a range of aldehydes (Scheme 7, top) was found to depend critically on the substituent pattern on the ligand. When the ligand substituent is small [Me (**1a**), ^{i}Pr (**1b**)], the aldehyde substrate is thought to preferentially coordinate to the metal in the equatorial position (Scheme 7, bottom left), favoring attack at the *Si* face of the carbonyl unit, whereas a bulky substituent [^{t}Bu (**1c**)] favors coordination of the aldehyde in the apical position (Scheme 7, bottom right), and thus, attack of the metal–allene intermediate at the *Re* face of the aldehyde occurs.

The enantioselective NHK allenylation of aldehydes with terminally silylated propargyl halides using Cbzbox ligand **1a** has also been reported.[22] The 2-silylated allenic alcohol products were obtained with up to 82% ee (Scheme 8, top), with bulkier silyl groups resulting in lower enantioselectivities than the smaller dimethylsilyl (DMS) group. These reactions show *Si*-face selectivity, which can be explained by the coordination modes of the propargyl group and aldehyde to the chromium center. The bulky silylated propargyl group prefers to bind to the less sterically encumbered apical position of the metal, leaving the aldehyde to coordinate to the equatorial position, resulting in *Si*-face attack (Scheme 8, bottom).[22] The 2-silylated secondary allenic alcohol products can then be desilylated to the allenic alcohols, which are important as intermediates in synthetic chemistry, as in the synthesis of 2,5-dihydrofurans or amino alcohols.[22]

Connell provided further examples of the use of tridentate Cbzbox ligands in the allenylation of a variety of aldehydes with

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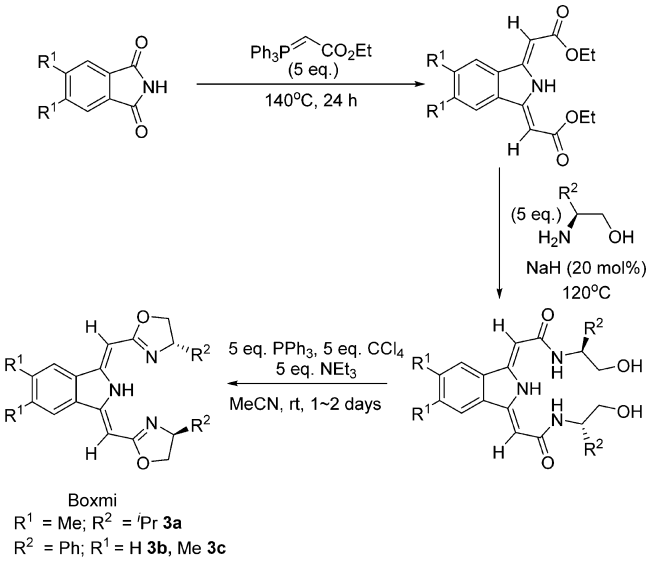
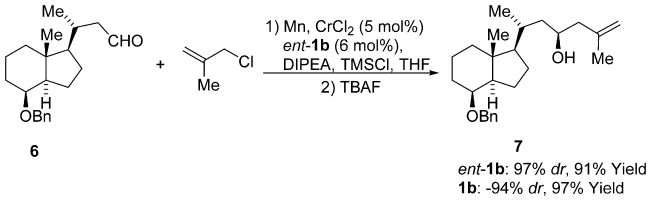
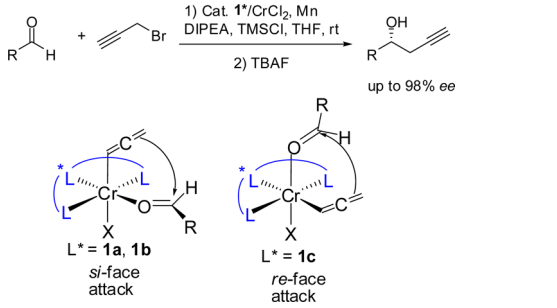
Scheme 4. Synthesis of Boxmi Ligands



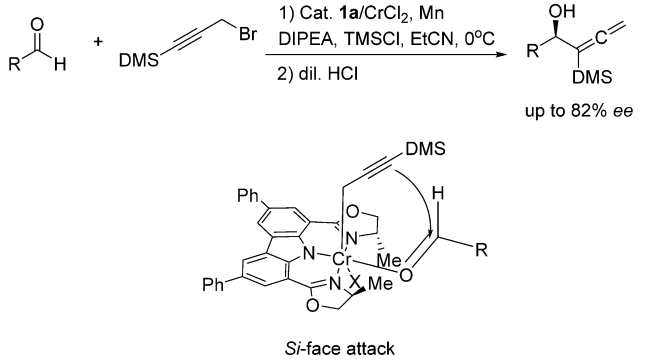
Scheme 5. Applications of Chiral Pincer Ligands in Natural Product Synthesis



Scheme 7. (top) Catalytic Asymmetric Propargylation of Aldehydes; (bottom) Rationale for the Selectivity of the Reaction When the Chiral Ligand Is Changed



Scheme 8. (top) Allenylation Reactions of Aldehydes with Terminally-Silylated Propargyl Halides; (bottom) Explanation of the Selectivity of the Reaction



(4-bromobut-2-ynyl)trimethylsilane.[13,23] The desired [1-(silylmethyl)allenyl]methanols were obtained in reasonable to good yields and enantioselectivities using ligands **1**. The products could be subsequently desilylated and isomerized to afford asymmetric butadienylmethanols with little reduction in the ee value (Scheme 9, top).[23]

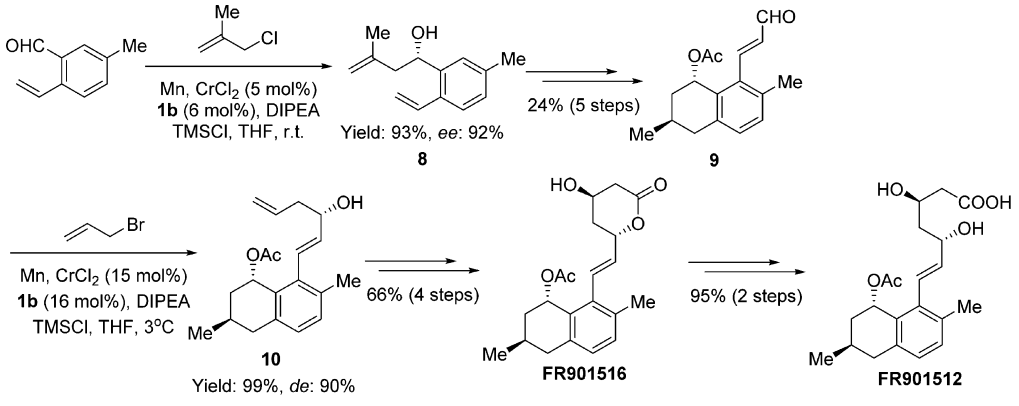
Allenic alcohols are important building blocks in the syntheses of pharmaceuticals and natural products.[24] A great advance in this area was therefore the report of the first regio- and enantioselective Cr-catalyzed homoallenylation of aldehydes with homoallenyl bromide using tridentate BOPA ligands (Scheme 9, bottom).[24] The preferred ligand for this reaction was found to be the non-C_2-symmetric bis(oxazoline) ligand **2f**, which was unusual in this regard as normally C_2-symmetric catalysts generally perform better in this type of reaction.[16,25]

3. ELECTROPHILIC SUBSTITUTIONS

3.1. Friedel–Crafts Alkylations with Michael Acceptors

Carbon–carbon bond formations, such as the Friedel–Crafts reaction, have a paramount place in the construction of the backbones of complex organic molecules.[26] In recent years, the use of nitroalkene substrates in asymmetric Friedel–Craft alkylations of heterocycles has attracted a lot of attention.[27] Nitroalkenes are good Michael acceptors, and the nitro group can be easily converted into other functional groups, allowing further derivatization.[28] In light of this, Du and co-workers reported the catalytic asymmetric Friedel–Crafts alkylation of

Scheme 6. Total Syntheses of FR901512 and FR901516



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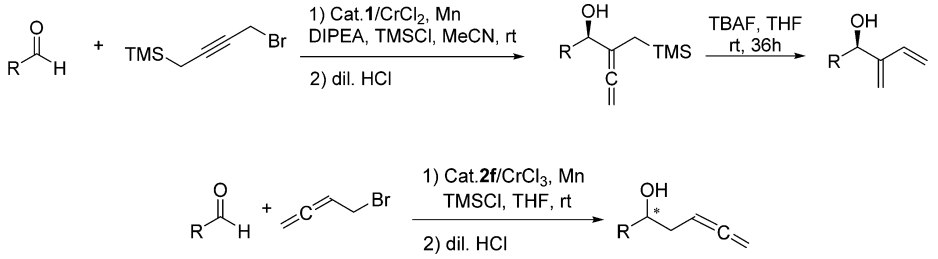
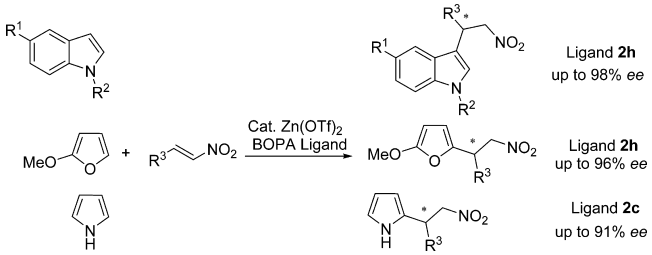
Scheme 9. (top) Cbzbox−Cr-Catalyzed Silylallenylation Reactions and Subsequent Desilylation/Isomerization Reactions To Afford Asymmetric (Butadienyl)methanols and (bottom) BOPA−Chromium-Mediated Homoallenylation Reactions



indoles,[29] 2-methoxyfurans,[30] and pyrroles[31] with nitroalkenes using chiral bis(oxazoline) **2**−$Zn(OTf)_2$ complexes as catalysts to give nitroalkylated products in high yields and enantioselectivities (Scheme 10). The authors also immobilized the diphenylamine-linked bis(oxazoline) ligand onto Fréchet-type dendrimers[32] to catalyze the Friedel−Crafts alkylation of indoles with nitroalkenes. Notably, the enantioselectivity of the products was maintained at 93% ee after in situ recycling of the catalyst four times.[33]

Scheme 10. Asymmetric Friedel−Crafts Alkylations Using Chiral Bis(oxazoline) 2−$Zn(OTf)_2$ Complexes



This methodology was then extended to the Friedel−Crafts alkylation of indoles with other nitroalkene derivatives, including nitrodienes and 2-propargyloxy-β-nitrostyrenes, giving enantioselectivities of up to 89% ee and 93% ee, respectively, using the **2i**−$Zn(OTf)_2$ catalyst (Scheme 11).[34] High reactivity was also observed with 3-nitro-2*H*-chromenes as substrates catalyzed by BOPA− and the corresponding bis(thiazoline)−Zn(II) complexes under mild conditions to give the indolyl(nitro)chroman products (Scheme 11). In these reactions, ligand **2d** outperformed the other bis(oxazoline) and bis(thiazoline) ligands.[35]

The enantioselective tandem Friedel−Crafts alkylation/Michael addition of 1-methylindoles with nitroolefin enoates catalyzed by a bis(oxazoline)−Zn complex has also been reported by Xiao and co-workers using ligand **2h**.[36] This provides an efficient route to highly substituted chromans (Scheme 12).[36]

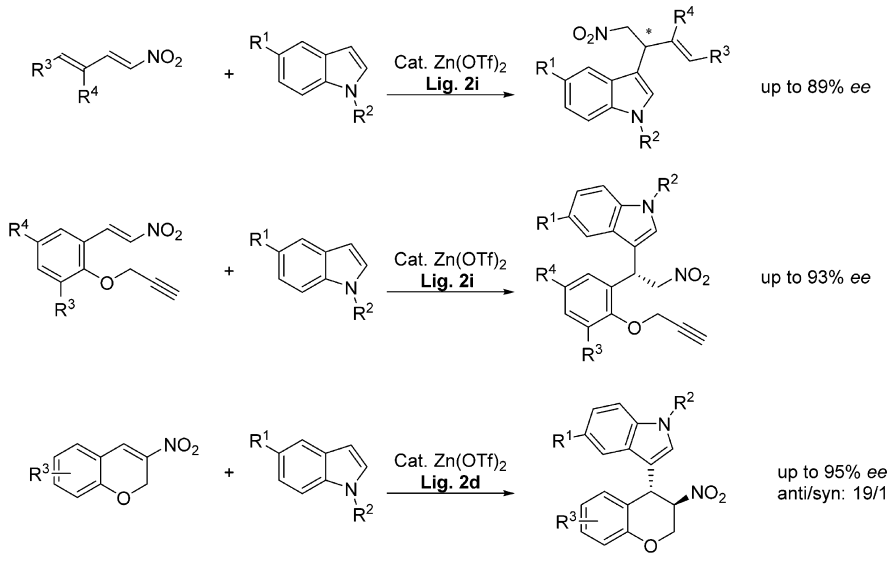
3.2. Fluorinations

The presence of fluorine atoms in pharmaceuticals tends to result in significant changes in their biological activity and physical properties.[37] The Ni-catalyzed asymmetric fluorination of oxindoles and cyclic β-keto esters using Boxmi ligands **3** has been reported, with ligand **3b** affording the fluorinated products with extremely high enantioselectivities (up to >99% ee) (Scheme 13).[18] In particular, the *R* isomer of *N*-Boc-protected MaxiPost, which is an effective opener of maxi-K channels and a potential agent for the prevention or treatment of stroke,[38] was obtained in 90% yield with 99% ee. This is the highest enantioselectivity for a catalytic synthesis of MaxiPost to date.

3.3. Trifluoromethylations

Trifluoromethylated compounds are of current interest since the trifluoromethyl group has been shown to significantly alter the properties of organic molecules. While CF_3 groups are easily incorporated via catalytic nucleophilic trifluoromethylation

Scheme 11. Friedel−Crafts Alkylations Using Bis(oxazoline)−$Zn(OTf)_2$ Catalysts



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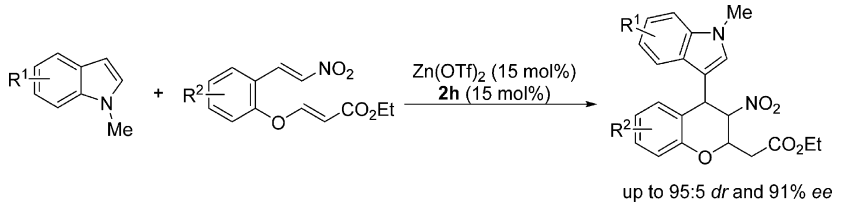
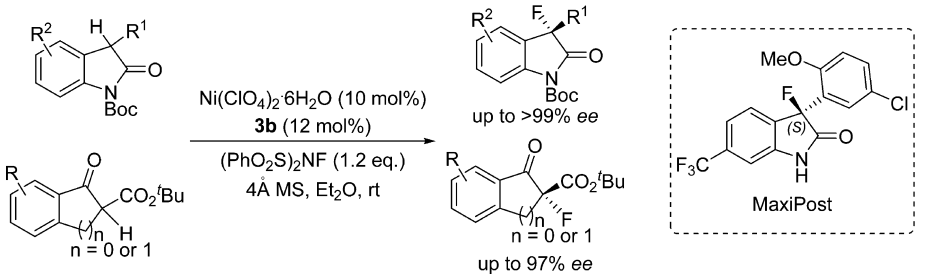
Scheme 12. Tandem Friedel–Crafts Alkylation/Michael Additions Using Bis(Oxazoline)–Zn Complexes

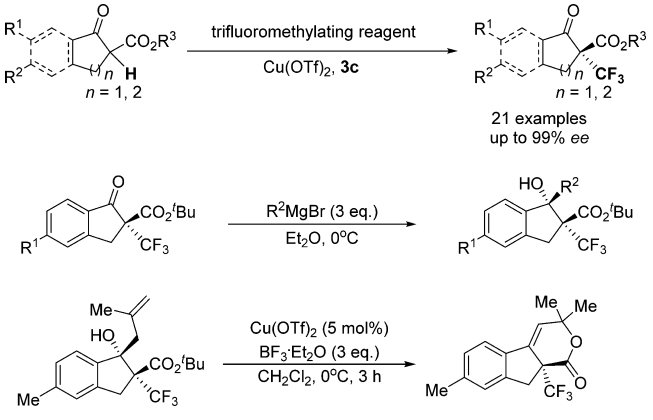


Scheme 13. Ni-Catalyzed Asymmetric Fluorination of Oxindoles and Cyclic β-Keto Esters Using Boxmi Ligands



reactions, electrophilic trifluoromethylations are difficult, and to date only a handful of examples are known.[39,40] In this context, a range of Cu–Boxmi **3c**-catalyzed enantioselective electrophilic trifluoromethylations of five- and six-membered-ring β-keto esters using Togni's and Umemoto's reagents, respectively, were studied. The resulting trifluoromethylated β-keto ester products with quaternary carbon centers were generated in high yields with up to 99% ee under mild conditions (Scheme 14, top).[41]

Scheme 14. (top) Electrophilic Trifluoromethylation Reactions of β-Keto Esters followed by (center) Grignard and (bottom) Lactonization/Dehydration Reactions



Additionally, the subsequent Grignard reaction constructed two adjacent quaternary stereocenters with well-defined absolute configurations to give stereochemically pure α-trifluoromethyl-β-hydroxy esters (Scheme 14, center).[41] Moreover, lactonization and dehydration of the α-trifluoromethyl-β-hydroxy esters readily occurred, yielding the corresponding products (Scheme 14, bottom).[41]

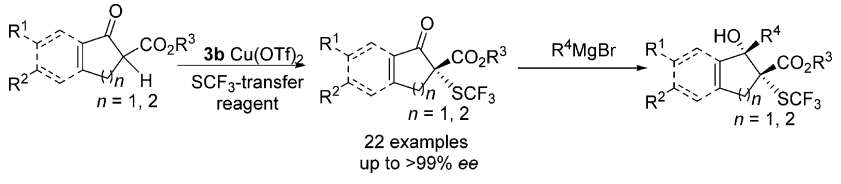
3.4. Trifluoromethylthiolations

Similarly, the role that a trifluoromethylthio (SCF_3) group may play in modifying the physiological activity of pharmaceuticals and agrochemicals has been of increasing interest. This is due to its lipophilicity, which allows the SCF_3-containing drug molecules to cross cell membranes, as well as its high electronegativity, which improves the stability of the drug, particularly in acidic environments.[42,43] Consequently, an efficient protocol for the enantioselective electrophilic functionalization of β-keto esters using a combination of a Boxmi–transition-metal catalyst and a SCF_3-transfer reagent was developed.[44] Under conditions similar to those described above for trifluoromethylations, Lu and Shen's phosphorus-based SCF_3-transfer reagent[43] was employed in the trifluoromethylthiolation of five- and six-membered-ring β-keto esters to give the corresponding products in high yields with up to >99% ee.[44] Subsequent reaction with Grignard reagents gave rise to stereochemically pure α-trifluoromethylthio-β-hydroxy esters containing two adjacent quaternary stereocenters with a well-defined absolute configuration (Scheme 15).[44]

3.5. Azidations

In view of the importance of organic azides as precursors in synthetic chemistry,[45] the enantioselective Boxmi–Fe-catalyzed azidation of cyclic β-keto esters and 3-aryloxindoles using the readily available and stable azidoiodinane as an N_3-transfer reagent was developed (Scheme 16).[46] 3-Azido-3-aryloxindoles were obtained with up to 94% ee using the catalyst prepared from iron(II) propionate and ligand **3b** in situ.[46] The α-azido esters

Scheme 15. Boxmi–Cu-Catalyzed Trifluoromethylthiolation and Subsequent Reactions



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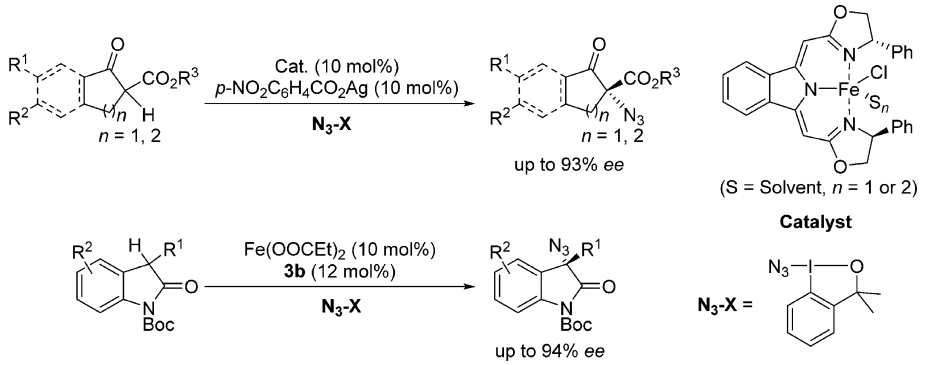
Scheme 16. Boxmi–Fe-Catalyzed Azidations of Cyclic β-Keto Esters and 3-Aryloxindoles

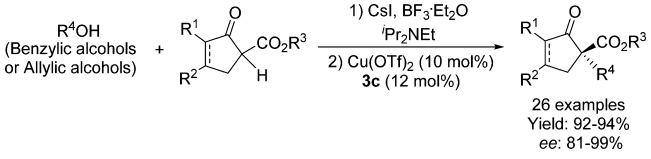


could be converted smoothly into the corresponding α-amino esters by palladium-catalyzed hydrogenolysis or into triazoles via a copper-catalyzed "click" reaction.[46]

3.6. Alkylation and Subsequent Cyclization Processes

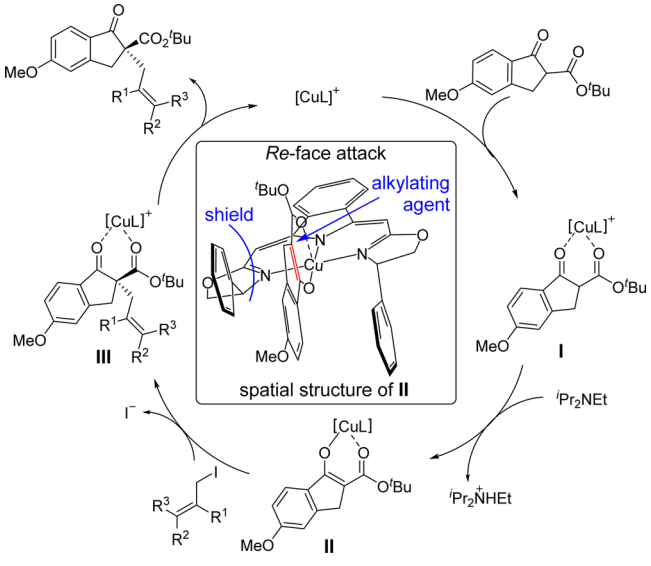
In a manner similar to that described above, it was found that Boxmi **3c**–Cu(II) complexes are also highly efficient for the enantioselective alkylation of cyclic β-keto esters to afford all-carbon quaternary products stereoselectively (Scheme 17).[47] On

Scheme 17. Enantioselective Alkylation of Cyclic β-Keto Esters



the basis of the absolute configuration of the products and X-ray crystal structure analysis of the copper complex, a mechanism for this catalytic reaction explaining the stereochemistry of the reaction was proposed (Scheme 18).[47] Initially, the β-keto ester substrate coordinates to the Cu complex through its two carbonyl oxygen atoms to give intermediate **I**. Subsequent

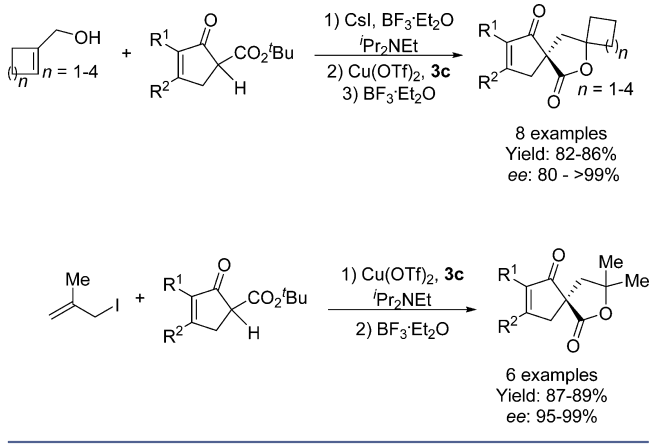
Scheme 18. Proposed Catalytic Cycle for the Enantioselective Alkylation of Cyclic β-Keto Esters



deprotonation of the β-keto ester with $^{i}Pr_2NEt$ leads to the formation of the enolate ester intermediate **II**, which then reacts with the in situ-generated benzyl (or allyl) iodide to afford intermediate **III**. Finally, release of the product from intermediate **III** regenerates the active Cu catalyst. An examination of the molecular structure of intermediate **II** reveals that the *Si* face of the substrate is blocked by the phenyl group in the oxazolinyl unit of the Boxmi ligand, and therefore, the alkylating agents preferentially approach from the *Re* face of the substrate.[47]

The alkylation products derived from 2-substituted allylic alcohols or their corresponding iodides could be converted to spirolactones and bispirolactones in good to excellent yields and enantioselectivities by addition of $BF_3{\cdot}Et_2O$ in a one-pot reaction (Scheme 19). In these transformations, the Cu complex plays a

Scheme 19. Enantioselective Synthesis of Bispirolactones



key role since in its absence only trace amounts of product were formed.[47] Analogous β-keto ester-substituted allylsilanes could also be prepared from β-keto esters using 3-iodo-2-[(trimethylsilyl)methyl]propene and transformed into spirolactones by subsequent treatment of the primary chiral allylation products with $BF_3{\cdot}Et_2O$ in the presence of $Cu(OTf)_2$. On the other hand, the reactions with TBAF afforded the desilylated cyclopentanol cyclization products (Scheme 20).[47]

4. OTHER ENANTIOSELECTIVE TRANSFORMATIONS

4.1. [4 + 2] Cycloadditions

In 2012, Xiao[48] developed a practical and convenient catalytic asymmetric [4 + 2] cycloaddition of 3-nitro-2*H*-chromenes to 1-benzyl-2-vinyl-1*H*-indoles in the presence of a chiral $Zn(OTf)_2$/

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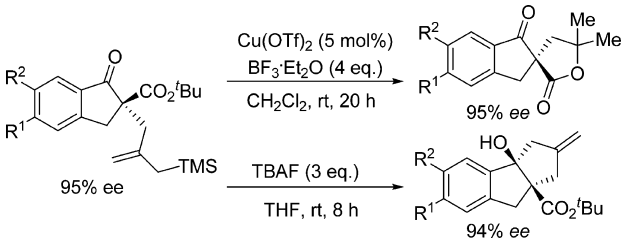
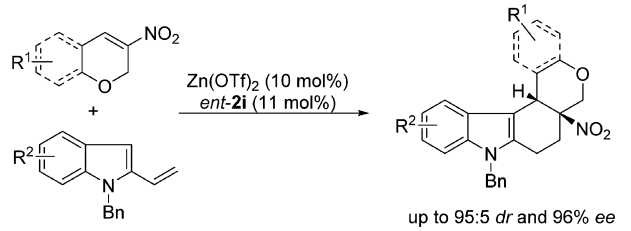
Scheme 20. Subsequent Reactions of β-Keto Ester-Substituted Allylsilanes with (top) $BF_3{\cdot}Et_2O$ and (bottom) TBAF



BOPA **2** complex. High reaction yields and good stereoselectivities were obtained for a variety of biologically important fused heterocycles bearing a quaternary stereocenter (Scheme 21).[48]

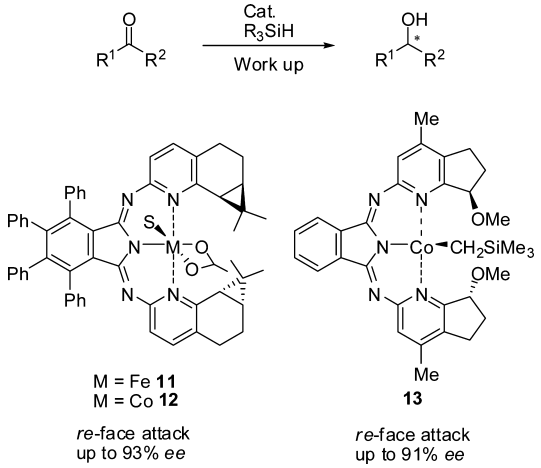
Scheme 21. Synthesis of Fused Heterocycles Using a Chiral $Zn(OTf)_2$/Bis(oxazoline) Ligand Complex



4.2. Hydrosilylations of Ketones

Although bis(pyridylimino)isoindole (BPI) compounds (**4**) have been known for a long time, only very recently have there been reports of chiral pincer derivatives generated from the reaction of phthalonitrile with chiral 2-aminopyridines.[49,50] Fe–BPI complex **11** and Co–BPI complex **13** were subsequently reported to be active in the catalytic asymmetric hydrosilylation of ketones (Scheme 22).[49,50] Nishiyama also reported iron-catalyzed asymmetric hydrosilylations using BOPA ligands.[51−53] The combination of $Fe(OAc)_2$ and BOPA ligand **2e** gave the products as the *R* enantiomers with up to 90% ee from *Si*-face attack, whereas the **2e**–$FeCl_2$ complex in combination with zinc afforded predominantly the (*S*)-alcohols with up to 95% ee via *Re*-face attack. Notably, each enantiomer of the product can be

Scheme 22. Catalytic Asymmetric Hydrosilylation of Ketones Using BPI–Metal Complexes (S = Donor Solvent)

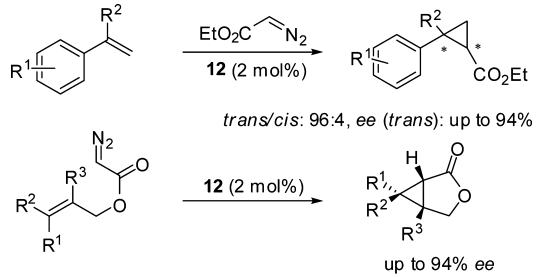


obtained in the BOPA–Fe-catalyzed reaction from a single starting material with either the absence or presence of a small quantity of zinc.[51]

4.2. Cyclopropanations

Catalytic enantioselective cyclopropanations of olefins, first reported in 1966,[54] have gained widespread interest because of their application in the synthesis of chiral cyclopropane derivatives, as found, for example, in several classes of insecticides.[55] Co–BPI-catalyzed asymmetric intermolecular and intramolecular cyclopropanations of diazo compounds gave the desired cyclopropyl derivatives exclusively (Scheme 23) and thus without undesired byproducts generated by

Scheme 23. Intermolecular and Intramolecular Cyclopropanation Reactions

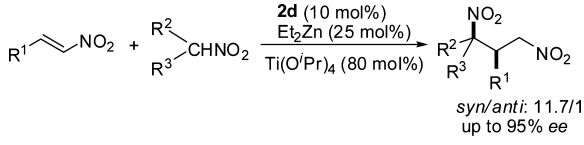


diazoalkane coupling.[49] In the intermolecular reaction with the optimized catalyst [Co(tetraphenyl-carBPI)(OAc)] (**12**), cyclopropanes were obtained from the reaction of styrene derivatives or related substrates with ethyl diazoacetate with excellent diastereoselectivities and enantioselectivities.[49]

4.3. Asymmetric Catalytic Michael Reactions

Du and co-workers reported a Zn-catalyzed stereoselective Michael addition of nitroalkanes to a range of nitroalkenes using BOPA ligands **2** to generate 1,3-dinitroalkanes with high diastereoselectivity and enantioselectivity (up to 95% ee depending upon the substrates/ligand used) (Scheme 24).[56]

Scheme 24. Zn-Catalyzed Stereoselective Michael Addition Reactions of Nitroalkanes to a Range of Nitroalkenes



The resulting 1,3-dinitro compounds are of interest as precursors for heterocycles,[57] 1,3-difunctionalized compounds, and energetic materials,[58] inter alia. For example, hydrogenation of the nitro groups to form 1,3-diamines (which are themselves synthetically versatile) was achieved, and subsequent reaction with CS_2 afforded a chiral cyclic thiourea in 53% yield without loss of enantiomeric excess.[56]

4.4. Henry Reactions

The Henry reaction, which affords β-nitro alcohols through a carbon–carbon bond-forming reaction between a carbonyl compound and a nitroalkane, provides access to important synthetic building blocks.[59] BOPA ligands **2a–e** and bis(thiazoline) ligands **2j–n** were examined in Henry reactions using the Lewis acidic metals copper and zinc to give the products with high enantioselectivities (up to 85% ee) (Scheme

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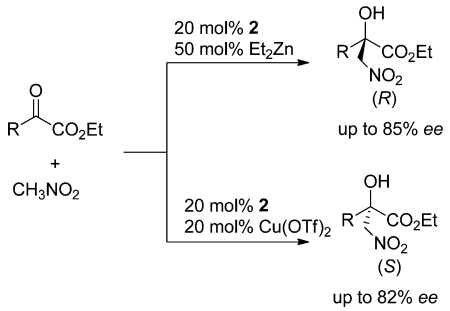
25). Reversal of the enantioselectivity of the reaction can be achieved by changing the Lewis acid center from Zn(II) to Cu(II) using the same ligand, although the origin of this reversal of configuration remains unclear.[60]

Scheme 25. Henry Reactions Using Copper and Zinc Lewis Acid Complexes



4.5. Hydro-dehalogenations of Geminal Dihalides

The first enantioselective hydro-dehalogenation reactions using a chiral molecular catalyst have been reported.[61] The ligand in these systems is the bis(oxazolinylmethylidene)pyrrolido (PyrrMeBOX) ligand (**5**),[62] which undergoes a thermodynamically favorable isomerization to form a planar conjugated 10-π-electron system capable of binding strongly to the metal center. Several PyrrMeBOX–Ni(II) hydride complexes **14** were synthesized from the reaction of the nickel chloride complex with $LiEt_3BH$;[61] complexes **14** then underwent reversible elimination of hydrogen to afford T-shaped Ni(I) complexes **15** (Figure 3).[61] Chiral Ni(II) complexes **14** were found to be active catalysts for the asymmetric hydro-dehalogenation of geminal dihalogenides, with the best results being observed with the phenyl-substituted ligand **14c**, which gave the hydro-dehalogenated product in up to 84% yield and 74% ee. The mechanism of the reaction was proposed to proceed through the initial reaction of the dihalogenide substrate with Ni(I) complex **15** to form halogenido complex **16** and organoradical **17**, which is then reduced enantioselectively by nickel hydride complex **14** to yield the product and regenerate the catalyst (Scheme 26).[61]

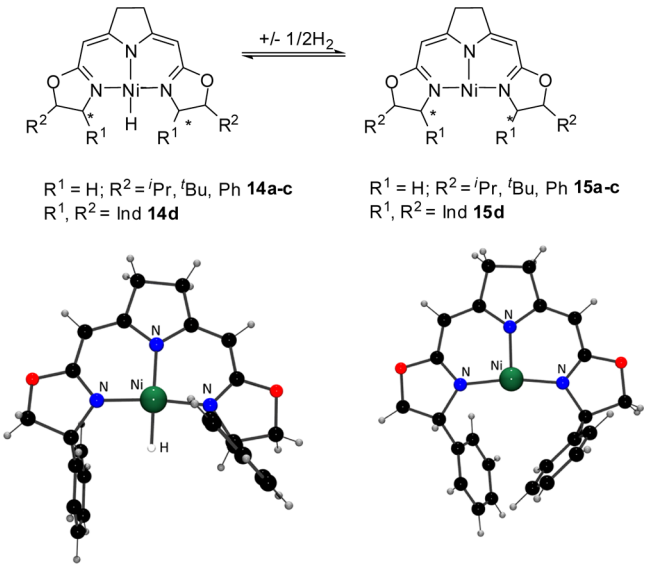
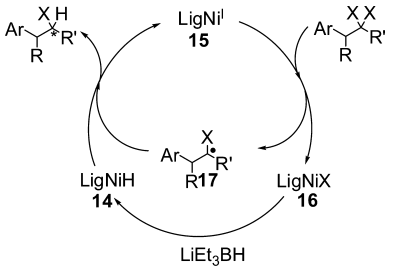


Figure 3. (top) Conversion of **14** to **15** by the addition/removal of H_2. (bottom) Structures of **14c** and **15c**.

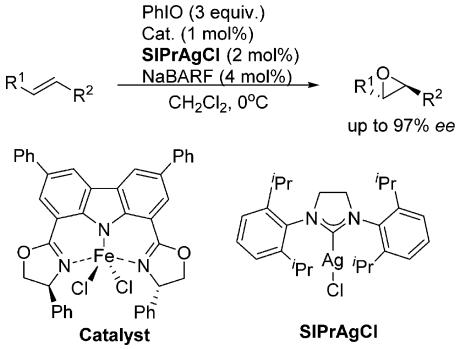
Scheme 26. Mechanism of Hydro-dehalogenation Reactions Using Ni(I)



4.6. Epoxidations of Alkenes

Recently, Nakada reported a non-heme iron(III) complex bearing Cbzbox ligand **1d** that displays porphyrin-like properties in its ability to catalyze the highly enantioselective asymmetric epoxidation of (*E*)-alkenes (Scheme 27).[63] As in heme proteins, the reaction appears to occur via a two-electron oxidation in which the metal and the ligand each undergo a one-electron oxidation. It was observed that the cationic iron(III) complex, when subjected to a two-electron oxidation, generated an iron(IV) radical cation species that has an electronic structure identical to that of iron porphyrins.[63]

Scheme 27. Non-Heme Iron-Catalyzed Epoxidation Reactions



5. CONCLUSIONS

Several types of chiral N^N^N pincer ligands containing two oxazoline rings or pyridine moieties to afford the chiral environments have been developed. They have been found to effectively stabilize molecular catalysts of the 3d transition metals, in particular, but have also shown potential as stereodirecting ligands for group 2 and 3 metals as well as lanthanides.[64] These ligands effectively deliver a C_2-symmetric environment around the active metal center, leading to complexes that show high activities and stereoselectivities for a broad range of asymmetric catalyses, especially for Lewis acid-catalyzed reactions. The ability to tailor the steric and electronic effects within the pincer ligand design augers well for the future exploitation of their complexes in a range of other organic transformations.

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The authors declare no competing financial interest.

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Rebecca L. Melen undertook her undergraduate degrees and Ph.D. (with Prof. Dominic Wright) at the University of Cambridge. She subsequently moved to the University of Toronto (Canada) as a postdoctoral fellow with Prof. Douglas Stephan and was recently awarded a Humboldt Fellowship to study at the University of Heidelberg (Germany). She received the RSC Dalton Young Researcher Award (2013) and the European Young Researcher Award (2014).

Lutz H. Gade obtained his Ph.D. with Jack Lewis at Cambridge University. After completing his Habilitation at the University of Würzburg, he moved to Université Louis Pasteur (Strasbourg, France) to take up a full professorship in inorganic chemistry in 1998. In 2003 he moved to his present position in Heidelberg, where he has acted, inter alia, as chairman of the Collaborative Research Center on Molecular Catalysis (SFB 623) and Dean of the Faculty.

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