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Chiral *N,N′*-Dioxides: New Ligands and Organocatalysts for Catalytic Asymmetric Reactions

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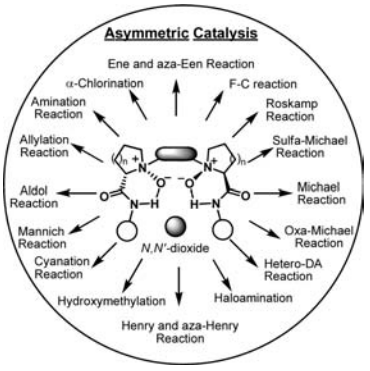
CONSPECTUS

Homochiral catalysts that can effect asymmetric transformations are invaluable in the production of optically active molecules. Researchers are actively pursuing the design of new ligands and organocatalysts by exploiting concepts derived from the application of bifunctional and C_2-symmetric catalysts. Many homochiral catalysts containing amines, ethers, alcohols, and phosphines as electron-pair donors have been successfully developed.



Amine *N*-oxides are highly polar substances. Despite their pronounced capacity as electron-pair donors, *N*-oxides have been underutilized in asymmetric reactions; they have only made a visible impact on the field in the preceding decade. Systematic studies have instead largely focused on pyridine- or quinoline-based scaffolds in organosilicon and coordination chemistry. The application of chiral tertiary amine *N*-oxides has not been widely pursued because of the difficulty of controlling the chirality at the tetrahedral nitrogen of the *N*-oxide moiety. In this Account, we outline the design of a new family of C_2-symmetric *N,N′*-dioxides from readily available chiral amino acids. We then discuss the application of these chiral amine *N*-oxides as useful metal ligands and organocatalysts for asymmetric reactions.

The high nucleophilicity of the oxygen in *N*-oxides is ideal for organocatalytic reactions that rely on nucleophilic activation of organosilicon reagents. These catalysts have been successfully applied in the asymmetric addition of trimethylsilylcyanide to aldehydes, ketones, aldimines, and ketimines, with good yields and excellent enantioselectivities. Asymmetric organocatalytic chlorination of β-ketoesters with *N*-chlorosuccinimide has also been achieved through hydrogen bond activation.

The molecular framework of these *N,N′*-dioxides, with their multiple O-donors, also serves as a new tetradentate ligand that can coordinate a range of metal ions, including Cu(I), Cu(II), Ni(II), Mg(II), Fe(II), Co(II), In(III), Sc(III), La(III), Y(III), Nd(III), and others. These versatile metal complexes are efficient catalysts for a variety of asymmetric reactions. Asymmetric cycloadditions have been achieved with these chiral Lewis acid catalysts. We have also found success with asymmetric nucleophilic additions to C═O or C═N bonds; substrates include 3-substituted 2-oxindoles, alkenes, enamides, enecarbamates, diazoacetate esters, nitroalkanes, glycine Schiff bases, and phosphate. Notably, the first catalytic asymmetric Roskamp reaction was realized, which was successful because of the high efficiency of the catalyst. Asymmetric conjugate additions between α,β-unsaturated compounds and nucleophiles such as nitroalkane, malonate, thioglycolate, and indoles have been accomplished. The first asymmetric haloamination of chalcones was discovered, and the reaction proceeded with high regio- and enantioselectivity. In some cases, we were able to reduce the catalyst loading to just 0.01−0.05 mol % while maintaining excellent outcomes.

Some particularly interesting phenomena were observed over the course of the research. These include a remarkable amplification of the asymmetry in a sulfa-Michael reaction, as well as the reversal of enantioselectivity after alteration of the central metal or the subunits of the ligand in two other reactions. These unusual results have facilitated a deeper understanding of the catalytic mechanism.

Introduction

The ongoing quest for chiral compounds has stimulated intensive research into the development of new catalysts for asymmetric reactions. The ideal catalyst, in principle, should be inexpensive, convenient to manipulate, amenable to structural modification, and stable, and have high

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activity and selectivity. Many homochiral controllers having heteroatom-containing groups such as amines, ethers, alcohols, and phosphines as electron-pair donors have been developed. Impressive progress has been achieved using a unique set of privileged chiral catalysts[1] and the concepts drawn from uses of bifunctional catalysis[2] and C_2-symmetry.[3] However, there is no universal chiral activator that satisfies all of the demands of asymmetric transformations. The rational design of chiral ligand–metal complexes and organocatalysts presents a formidable challenge.

Amine *N*-oxides are highly polar substances that can be easily prepared by *N*-oxidation of *N*-heteroaromatic compounds or tertiary amines with H_2O_2 or peroxoic acid. The generated oxygen atom in the *N*-oxide has a stronger dipole than the oxygen atoms of other common oxo-donors such as alcohols, ethers, and amides. In *N*-heteroaromatic *N*-oxides, such as pyridine *N*-oxide, the oxygen 2pπ electrons are conjugated with the *N*-heteroaromatic ring, whereas an amine-oxide is approximately tetrahedral. Therefore, if the parent tertiary amine contains three different groups, the corresponding *N*-oxide will include a stable chiral center on nitrogen.

Tertiary amine *N*-oxides can undergo synthetically useful reactions and serve as selective oxidants or protective groups. Importantly, the unique properties of the electron-pairs of *N*-oxides offer opportunities to form molecular adducts with protons or alcohols or for complexation with various Lewis acids. The coordination chemistry of *N*-heteroaromatic *N*-oxides was thoroughly investigated four decades ago.[4] After a period of waning interest, the use of chiral pyridine or quinoline-type *N*-oxides as activators of silicon reagents in asymmetric allylation and aldol condensation has attracted attention.[5,6] However, the design and application of chiral tertiary amine *N*-oxide catalysts has been reported rarely, possibly owing to the difficulty in synthesizing optically pure compounds.

Homochiral proline *N*-oxides were incorporated into peptide-like molecules as conformational restraints early in 1993.[7] Oxidation of *N*-alkylated prolinamide proceeded diastereoselectively to give a stable chiral *N*-oxide where the amine oxide is *syn* to the adjacent carboxyamide through intramolecular hydrogen bonding. This modular structure enables the formation of an easily fine-tuned catalyst library. In this Account, we highlight our efforts to develop C_2-symmetric chiral *N,N′*-dioxide amides and to apply them in asymmetric reactions.

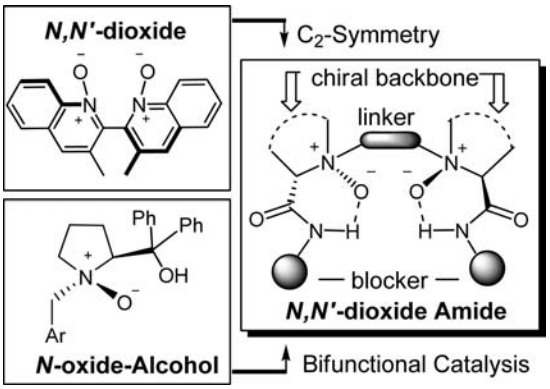
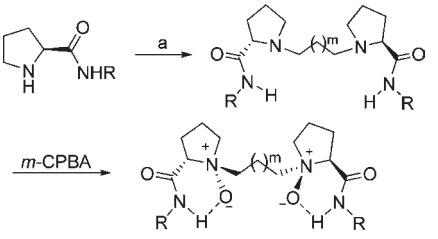


FIGURE 1. Design of C_2-symmetric *N,N′*-dioxide amides.

SCHEME 1. General Synthetic Route for *N,N′*-Dioxides

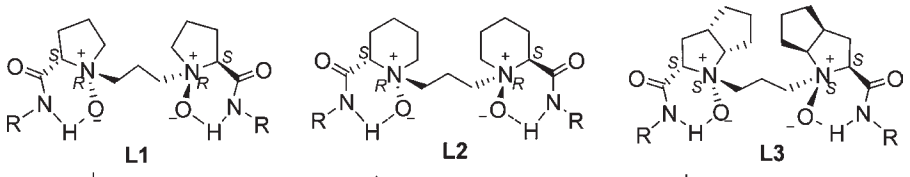


Design and Synthesis of C_2-Symmetric Chiral *N,N′*-Dioxides

Our interest in *N*-oxides was stimulated by investigations of the role of these substances as activators in asymmetric silylcyanation reactions. A biquinoline *N,N′*-dioxide organocatalyst[8] and a titanium complex of mono *N*-oxide from *L*-prolinol[9] were employed with modest results. The unsatisfying outcomes were attributed to the poor activating group and an unfavorable chiral environment. Subsequent efforts were directed at combining the key characteristics of the catalysts for multidentate bifunctional catalysis.[2] C_2-Symmetric[3] *N,N′*-dioxides that can be formed by the connection of the two *N*-oxide amide subunits via a linker were chosen for this purpose (Figure 1).

C_2-Symmetric *N,N′*-dioxides were prepared from commercially available chiral amino acids and amines. The linkage unit could be either a conformationally flexible straight alkyl chain or a rigid aryl chain; the former will be discussed in this Account. Optically pure *N,N′*-dioxides were obtained without resolution (Scheme 1). Representative structures are shown in Figure 2.

The stereoselective oxidation and formation of six-membered hydrogen bonded rings were confirmed by



L1

L1	R
L1a	cyclohexyl
L1b	cyclopentyl
L1c	Ph
L1d	4-BrC_6H_4
L1e	2,6-$Me_2C_6H_3$
L1f	2,6-$iPr_2C_6H_3$

L2

L2	R
L2a	cyclopentyl
L2b	1-adamantyl
L2c	$C_6H_5CH_2$
L2d	$C_6H_5(CH_2)_2$
L2e	2-BrC_6H_4
L2f	2,6-$iPr_2C_6H_3$
L2g	Ph
L2h	2,4,6-trimethylphenyl

L3

L3	R
L3a	$C_6H_5CH_2$
L3b	Ph_2CH
L3c	cyclopentyl
L3d	Ph
L3e	2,6-$Me_2C_6H_3$
L3f	2,6-$iPr_2C_6H_3$
L3g	3-anthracenylmethyl

FIGURE 2. Representative chiral *N,N′*-dioxides.

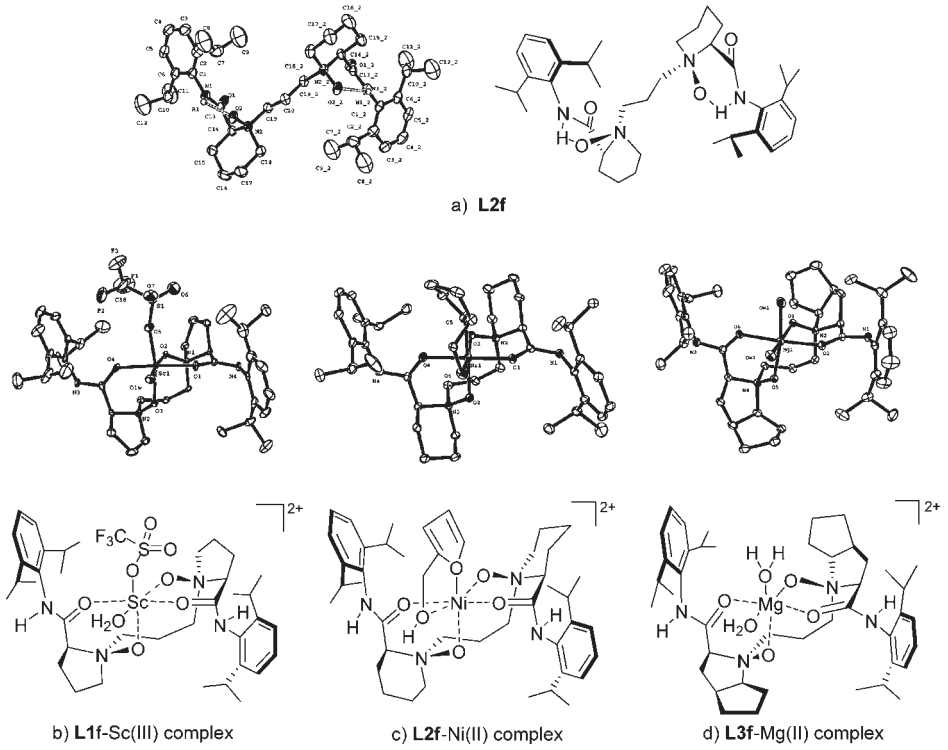


FIGURE 3. Crystal structures and stereoviews of *N,N′*-dioxide and the metal complexes.

^{1}H NMR and X-ray analysis of *N,N′*-dioxides. However, free **L2f** exhibits a conformation in which the two *N*-oxide amide moieties are located away from each other (Figure 3a),[10] casting doubt as to whether this soft backbone would promote good stereoinduction for asymmetric reactions.[1] As a result of the chelate effect, the structure of the *N,N′*-dioxides becomes compacted in the presence of a Lewis acid, which serves to attract the four oxygen atoms together. The chirality-at-nitrogen is maintained in the formed complex, even though the original intramolecular hydrogen bonds are disrupted. X-ray analysis of the **L1f**–Sc(OTf)$_3$,[10,11] **L2f**–Ni(BF$_4$)$_2$,[10,12] and **L3f**–Mg(OTf)$_2$[10] complexes (Figure 3b–d) reveals that the spatial arrangement of *N,N′*-dioxide varies, especially that of the amide moieties. The *N,N′*-dioxide behaves as a neutral tetradentate ligand that both oxygens of *N*-oxide as well as both carbonyl oxygens coordinate to the metal center, and the two amide groups on the opposite sides are disposed in a bibrachial manner. The structure also features a metal-centered spirocycle that the two (C=O)–metal–(O–N) six-membered rings lie in perpendicular planes. A cycle generated from the alkyl linkage breaks the C_2-symmetry of the complex and effectively shields one quadrant. Two unoccupied positions in the quadrilateral bipyramid offer opportunities for the

coordination of the substrate in what is hereafter termed a proper chiral environment. Additionally, the central metal can also fine-tune the spatial arrangement of the ligand, as evidenced by the disparity in bond lengths and bond angles of the various metal complexes.

Based on the aforementioned considerations, the chiral *N*,*N*′-dioxide appears to be a suitable choice as an organocatalyst or as a metal ligand in asymmetric catalysis.

N,*N*′-Dioxides as Chiral Organocatalysts

A number of groundbreaking studies on chiral *N*-oxides toward asymmetric metal-free transformations have been reported over the last 10 years.[5,6] Stemming from the formation of hypervalent silicate intermediates, chiral pyridine-type *N*-oxides have been extensively used in asymmetric addition reactions of allylchlorosilane.

Silylcyanation of Aldehydes, Ketones, and Imines. The cyanation of carbonyl compounds and imines is one of the most prevalent strategies for producing homochiral cyanohydrins and amino nitriles. Trimethylsilylcyanide (TMSCN) is a potential nucleophile, accelerated by anionic or neutral Lewis bases. However, few studies have attempted to activate TMSCN with *N*-oxides. We explored the potential of *N*,*N*′-dioxide amide to catalyze silylcyanation reactions, considering that it should facilitate the activation of TMSCN and the electrophile at the fixed positions defined by the dual activation centers composed of the Lewis base and hydrogen bond.

Systematic variation of the subunits of the amide, amino acid, and linker of the *N*,*N*′-dioxides showed that optimal silylcyanation of aldehydes was achieved with the L-proline-based *N*,*N*′-dioxide **L1a** (Scheme 2).[13] *N*,*N*′-Dioxide **L1b** was most effective in the asymmetric silylcyanation of α,α-dialkoxy ketones. Interestingly, **L1b** could be prepared in situ from *m*-chloroperoxybenzoic acid (*m*-CPBA) and the precursor, bisamide **L4a**.[14] A similar methodology was successfully employed in the asymmetric Strecker reaction of phosphinoyl ketimines with L-piperidinamide **L4b** and *m*-CPBA.[15] Chiral *N*,*N*′-dioxide was quantitatively recovered and was able to be reused at least five times without loss of efficiency.

Comparative experiments using a mono *N*-oxide amide or bisamide yielded poor results.[14,15] A possible bifunctional catalytic model of *N*,*N*′-dioxide organocatalysis is shown in Figure 4. The hypervalent silicon intermediate generated from the bidentate *N*,*N*′-dioxide which enhanced both the nucleophilicity of the cyano group and the rigidity of the reaction environment. The cyano group therefore

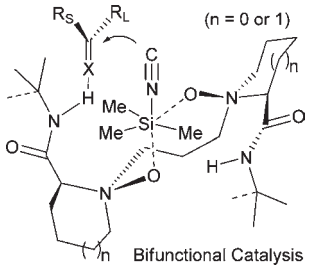
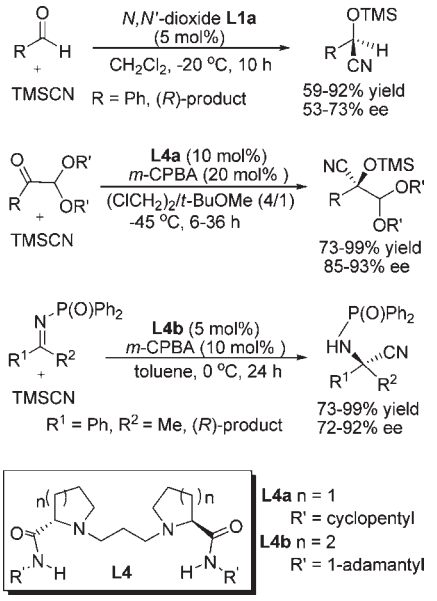


FIGURE 4. Possible catalytic model.

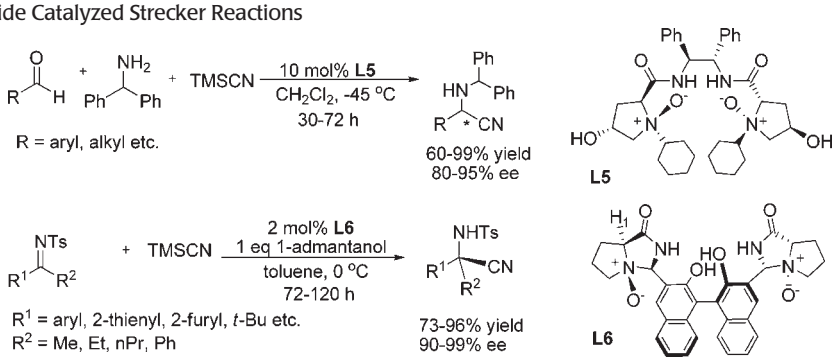
SCHEME 2. Asymmetric Silylcyanation Reactions



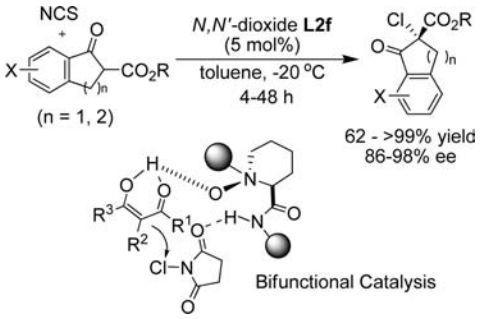
stereoselectively attacked the substrate, which was activated by the hydrogen bond of a nearby amide. In these cases, aliphatic-amine-derived *N*,*N*′-dioxides achieved better enantioselectivities owing to the steric hindrance effect of the amide subunit. Contemporaneously, a mono *N*-oxide amide was developed by Hoveyda et al., which was employed in the organocatalytic allylation of aldehydes.[16] This represents the only other example of the use of an amine *N*-oxide in asymmetric reactions, so far.

In order to improve the stereoselectivity of the asymmetric reactions, we also designed other types of chiral *N*,*N*′-dioxides (Scheme 3). The connection of amides via (1*S*,2*S*)-1,2-diphenylethane-1,2-diamine produced the *N*,*N*′-dioxide **L5** which exhibited improved performance in the three-component Strecker reaction.[17] A concentration of 2 mol % of catalyst **L6**, which incorporates the BINOL structure, efficiently catalyzed the Strecker reaction of various aryl and alkyl *N*-tosyl ketimines in 90−99% enantiometric excess (ee),[18] indicating that organocatalysts with more rigid backbones could enhance the stereoselectivity of the reaction.

SCHEME 3. Other *N,N′*-Dioxide Catalyzed Strecker Reactions



SCHEME 4. α-Chlorination of Cyclic β-Ketoesters



α-Chlorination of β-Ketoesters. Asymmetric halogenation is a useful strategy for producing halogen-containing chiral compounds. The *N,N′*-dioxide **L2f** was effective for the asymmetric α-chlorination of cyclic β-ketoesters with *N*-chlorosuccinimide (NCS). It represents a departure from the conventional role of *N*-oxide as an activator for silicon reagents.[19] A series of α-chloro-β-ketoesters were obtained in 86−98% ee. The bifunctional character of the organocatalyst enables simultaneous activation of NCS with amide-NH and of the β-ketoester with the *N*-oxide moiety as a hydrogen acceptor (Scheme 4).

N,N′-Dioxides as Chiral Ligands in Metal Complexes Catalysis

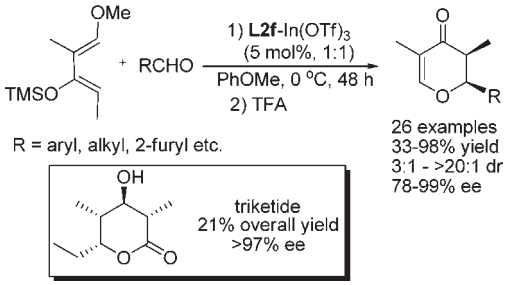
The utilization of *N*-heteroaromatic *N*-oxides in metal complexes can be traced back to the 1970s,[4] but their application to asymmetric catalysis lay dormant for decades. Chiral pyridine−*N*-oxide−metal complexes were sporadically used in a negligible number of asymmetric reactions with less than satisfactory results, which eclipsed their roles in asymmetric transformations. A major breakthrough came in the form of our study on the *N,N′*-dioxide−In(III) complex catalyzed enantioselective allylation reaction,[20] following which the use of *N,N′*-dioxides as versatile ligands in asymmetric reactions was expanded.

Cycloaddition Reaction. The catalytic asymmetric [4 + 2] cycloaddition reaction is effective for the construction of six-membered ring compounds. Chiral dihydropyranones, dihydropyridinones, and tetrahydroquinolines were obtained using chiral *N,N′*-dioxide−metal complexes.

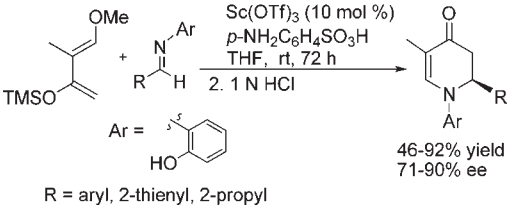
Chiral 2,5-disubstituted dihydropyrones have been prepared via asymmetric hetero-Diels−Alder (HDA) reaction of Danishefsky's diene derivatives using a Schiff base−Cr(III) complex or BINOL−Ti(IV) complex. However, control of the stereochemistry of the reaction of 2,5-dimethyl substituted Danishefsky-type diene to produce 2,3,5-trisubstituted dihydropyrone with two chiral centers is more difficult. We attempted to realize this reaction by the use of chiral *N,N′*-dioxide as a ligand.[21] Indium(III), an element that is about three times as abundant as silver, was found to be amenable to coordination with *N,N′*-dioxide and activating carbonyl groups. The subunits of the *N,N′*-dioxide moiety exerted significant effects on both the yield and the stereoselectivity of the reaction. Interestingly, aromatic- and aliphatic-amide-based *N,N′*-dioxides exhibited enantioswitching and the former produced better results. The stable catalyst **L2f**−In(OTf)$_3$ mixed with 4 Å molecular sieves showed excellent activity and chiral control in the formation of 3,5-dimethyldihydropyranones from a variety of aromatic, aliphatic, and cyclic aldehydes (Scheme 5). Subgram quantities of propionaldehyde could be used for the transformation to the triketide. The cycloaddition of 2-methyl-substituted Danishefsky-type diene also performed well with 80−98% ee.

Chiral Lewis acids including binaphthol−Zr(O*t*-Bu)$_4$, binaphthol−boron, and ferrocene−Cu(I) were developed for the aza-Diels−Alder reaction of Danishefsky's diene to synthesize chiral 2,5-disubstituted dihydropyridinones. We have utilized an *N,N′*-dioxide−scandium(III) complex to catalyze the asymmetric cycloaddition of *N*-arylimines generated from aldehydes and 2-aminophenol.[22] Sc(OTf)$_3$, which has the advantages of strong Lewis acidity and stability even

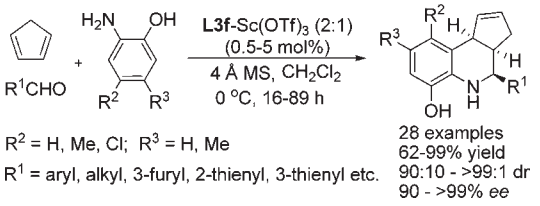
SCHEME 5. Asymmetric Synthesis of 2,3,5-Trisubstituted Dihydropyrones



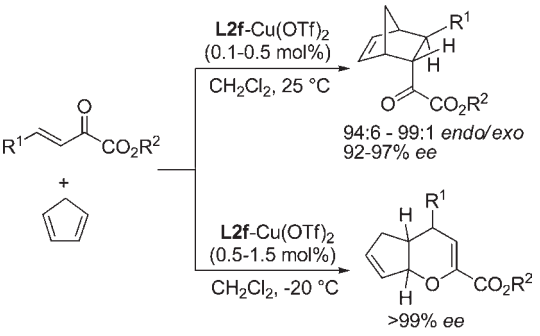
SCHEME 6. Asymmetric Synthesis of Dihydropyridinones



SCHEME 7. Asymmetric Synthesis of Tetrahydroquinolines



SCHEME 8. Asymmetric DA and IEDDA Reactions



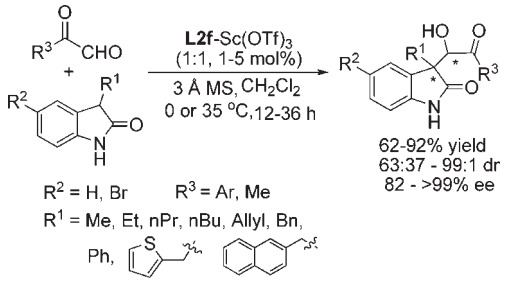
in aqueous media, was most suitable for the asymmetric cycloaddition of *N*-arylimines. Moderate to good enantioselectivities were achieved at a 2:1 molar ratio of **L1f** to $Sc(OTf)_3$ (Scheme 6). A strong positive nonlinear relationship[23] between the enantiomeric excess of the product and **L1f** was observed which might be due to the reservoir effect.

N-Arylimines are also able to serve as dienes in the inverse electron-demand aza-Diels–Alder reaction (IEDDA), using electron-rich alkenes as dienophiles to produce tetrahydroquinolines. Previous efforts using cyclopentadiene as the dienophile failed to produce the mutual benefits of high yield and enantioselectivity. Lewis acids such as $La(OTf)_3$, $Y(OTf)_3$, and $Yb(OTf)_3$ produced only trace amounts of the product. Catalyst **L3f**–$Sc(OTf)_3$, derived from L-ramipril acid, exhibited excellent stereofacial discrimination in the reaction (Scheme 7).[24] Chiral cyclopenta[3,2,*c*]quinolines were obtained from various aldehydes in a one-pot synthesis. The products may undergo transformations to potentially pharmaceutically active tetrahydroquinoline derivatives.

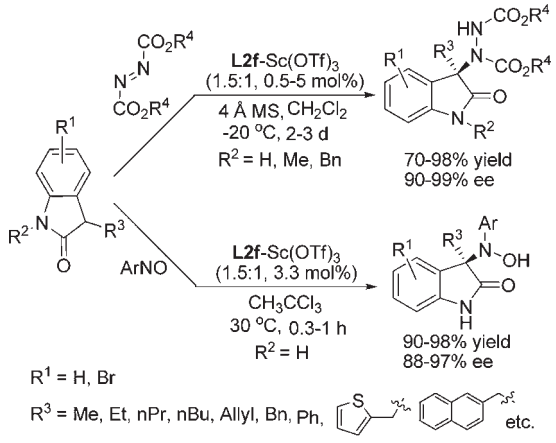
The **L2f**–$Cu(OTf)_2$ complex was used in asymmetric cycloadditions of β,γ-unsaturated α-ketoesters with cyclopentadiene as diene or dienophile, respectively (Scheme 8).[25] Brideged bicyclic compounds were the main product of the Diels–Alder (DA) process at room temperature, whereas ring-fused pyran derivatives were the dominant product of the IEDDA process at −20 °C. The improved chemoselectivity and milder reaction conditions compared with those of the oxazoline–scandium complex provide an insight into the potential of the synthetic avenues of *N*,*N*′-dioxides.

Aldol Type Reaction. The asymmetric aldol reaction remains the focus of extensive studies, and the development of the useful nucleophiles for such reactions is of great importance, especially for the construction of quaternary stereogenic centers. Biologically active oxindole-containing compounds could be conventionally produced from oxindoles or isatins. We first focused our attention on the aldol reaction of 3-substituted oxindoles.[26] Neither $Sc(OTf)_3$ nor *N*,*N*′-dioxide by itself could initiate the reaction between 3-methyl-2-oxindole and glyoxal derivatives. However, it was found that, in a ligand-accelerated process, *N*,*N*′-dioxide–$Sc(OTf)_3$ complex could promote the reaction efficiently. The yield and stereoselectivity were affected by the amide moiety of the ligand. 2,6-Diisopropylbenzenamine-derived ligands exhibited better yields than others, with **L2f** producing the best results. The addition of 3 Å molecular sieves shortened the reaction time. Various glyoxals or trifluoropyruvates and 3-substituted-2-oxindoles could be used to produce 3-(α-hydroxy-β-carbonyl)oxindoles with quaternary stereocenters (Scheme 9). Although the ratio of ligand to $Sc(OTf)_3$ was 1:1, a (+)-NLE was observed for both diastereomers, which was a consequence of the formation of oligomeric species.[23] The same catalyst could also successfully be employed in the enantioselective α-amination using

SCHEME 9. Asymmetric Synthesis of α-Hydroxyoxindole Derivatives



SCHEME 10. Asymmetric Amination Reactions of 2-Oxindole Derivatives



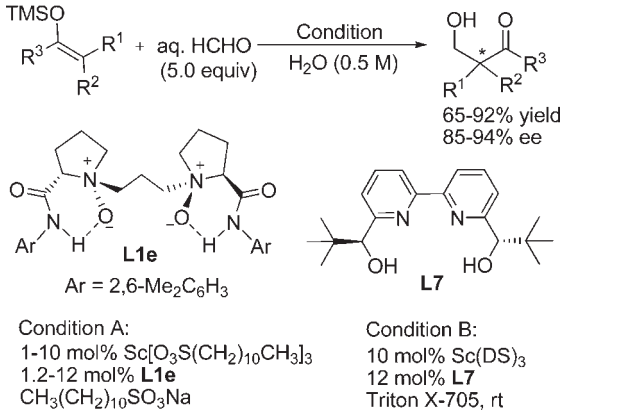
azodicarboxylates and hydroxyamination using nitrosoarenes[27] to generate 3-amino-2-oxindole derivatives (Scheme 10).

By exploiting the water-tolerant nature of the scandium complexes, Kobayashi's group developed an asymmetric hydroxymethylation reaction between aqueous HCHO and silicon enolate in water.[28] Both **L7**−$Sc(DS)_3$ in the presence of Triton X-705 and *N,N′*-dioxide **L1e**−$Sc[O_3S(CH_2)_{10}CH_3]_3$ with $CH_3(CH_2)_{10}SO_3Na$ were able to afford the desired products with excellent results, and the loading of the latter catalyst could be reduced to 1−2 mol % without sacrificing the reaction efficiency (Scheme 11).

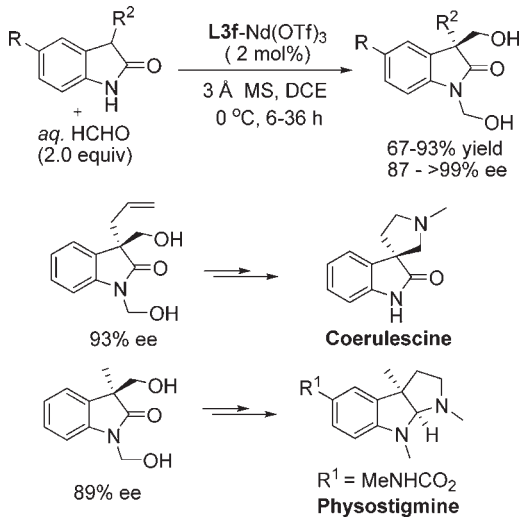
It was found that the **L3f**−$Nd(OTf)_3$ complex was water-tolerant in the enantioselective hydroxymethylation reaction of unprotected 3-substituted-2-oxindoles and formalin.[29] An unexpected tandem C- and N-addition process was found to give 1,3-bis(hydroxymethyl)-2-oxindole derivatives (Scheme 12). This method reduces the synthetic process to enantioenriched linchpins such as physostigmine and coerulescine. $Nd(OTf)_3$ and the ligand could be recovered and reused with loss of neither activity nor enantioselectivity.

Roskamp Reaction. α-Diazoesters can function as nucleophiles, and the decomposition of diazo functionality can

SCHEME 11. Asymmetric Hydroxymethylation Reaction

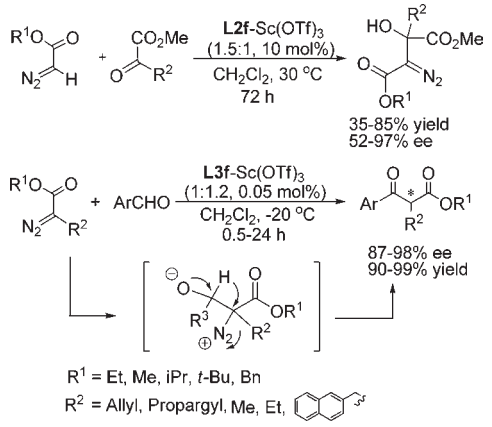


SCHEME 12. Asymmetric Synthesis of 1,3-Bis(hydroxymethyl)-2-oxindole Derivatives

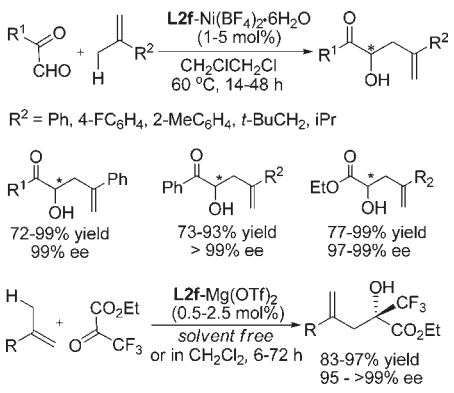


afford a variety of transformations. Asymmetric aldol reaction of α-diazoacetate and α-ketoesters using the **L2f**−$Sc(OTf)_3$ complex was realized to yield tertiary alcohols with the reservation of the diazo group (Scheme 13). However, when the catalyst was employed in the reaction between aldehydes and α-alkyl-α-diazoacetates, the Roskamp reaction occurred to produce α-alkyl-β-ketoesters through the addition of α-diazoacetate with concomitant 1,2-H-migration and extrusion of diazo (Scheme 13). There are relatively few reports of the catalytic asymmetric Roskamp reaction, due to the difficultly controlling the chemoselectivity and racemization of α-alkyl-β-ketoesters. These issues were addressed, for the first time, by using the highly efficient *N,N′*-dioxide **L3f**−$Sc(OTf)_3$ catalyst.[30] The catalyst loading could be reduced to 0.05 mol %, which allowed for convenient separation of the catalyst and the product by flash filtration

SCHEME 13. Asymmetric Reactions of α-Diazoacetates



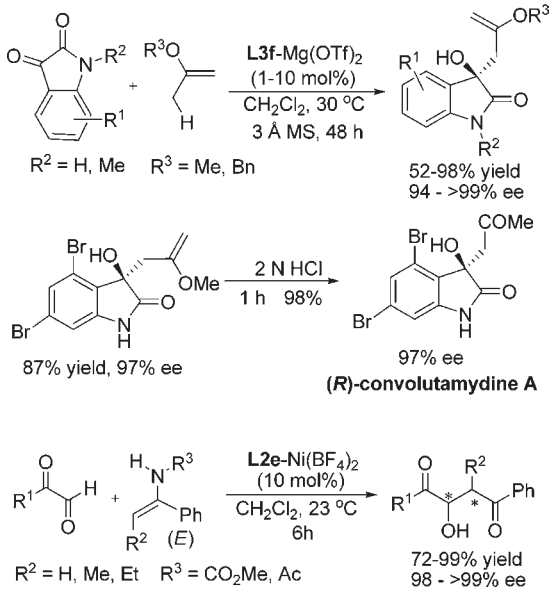
SCHEME 14. Asymmetric Carbonyl–Ene Reactions



and simultaneously prevented racemization of the product. A series of α-alkyl-α-diazoesters with aromatic aldehydes could be used to give the chiral α-alkyl-β-ketoesters chemoselectively in 87–98% ee. Poor results were obtained for aliphatic and α,β-unsaturated aldehydes.

Ene and Aza–Ene Reactions. The ene reaction, which involves the nucleophilic addition of an active allylic C–H bond followed by allylic transposition, can be used to construct multifunctionalized compounds. Significant effort has been devoted to the asymmetric ene-type reaction of glyoxylate using chiral ligands such as BINOL, salen, bis(oxazoline), and diamine derivatives. The *N,N′*-dioxide–metal complexes catalyzed asymmetric reactions employing glyoxal, ketones, or isatins as enophiles, and alkenes, enamides or enecarbamates, or alkyl enol ethers as nucleophiles; those reactions were undertaken with remarkable results (Scheme 14). γ,δ-Unsaturated α-hydroxy carbonyl compounds with 97% to >99% ee were obtained from **L2f**–$Ni(BF_4)_2$ catalyzed carbonyl-ene reaction of glyoxal derivatives and glyoxylate.[31] The chiral magnesium(II) complex of **L2f** was developed and used in the ketone-ene reaction to produce enantioenriched trifluoromethyl-substituted compounds, due to the abundance and low toxicity of this type of alkaline earth metal. The reaction could also be conducted under solvent-free conditions with extremely high enantioselectivity (Scheme 14). Hetero-ene reaction between isatins and alkyl enol ethers gave 3-substituted 3-hydroxyoxindoles with up to 99% ee using **L3f**–$Mg(OTf)_2$ catalyst (Scheme 15).[32] Asymmetric synthesis of (*R*)-convolutamydine A was realized conveniently in 97% ee. The activity of $Ni(BF_4)_2$–**L2e** derived from 2-bromobenzenamine was superior to that of **L2f** from 2,6-isopropylaniline in the aza-ene-type reaction of enamides or enecarbamates.[12] 2-Hydroxy-1,4-dicarbonyl compounds with up to 99% ee were obtained (Scheme 15).

SCHEME 15. Asymmetric Hetero–Ene and Aza–Ene Reactions



Conjugate Addition of α,β-Unsaturated Compounds. Michael addition can be used to introduce functionalized C–C, C–N, C–O, or C–S bonds at the β-position of α,β-unsaturated compounds. The efforts encompass numbers of variants in the terms of the donor and acceptor. Chiral biquinoline *N,N′*-dioxide–$Sc(OTf)_3$ has been used in the Michael addition of β-ketoesters to α,β-unsaturated carbonyl compounds in 73–98% yields and 38–84% ee by the Nakajima group.[6]

The efficacy of *N,N′*-dioxide–metal complexes is also demonstrated in asymmetric conjugate additions, using malonates, nitroalkanes, and the thioglycolate as nucleophiles. Satisfactory results were achieved using **L3f**–$Sc(OTf)_3$ and DMAP as additive in the addition of nitroalkanes to

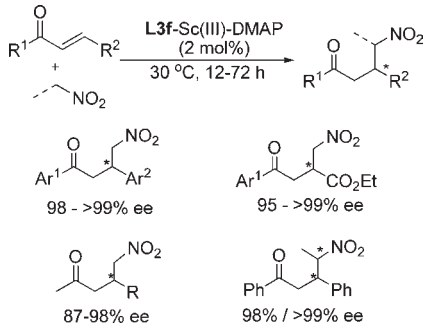


FIGURE 5. Asymmetric conjugate additions of nitroalkanes.

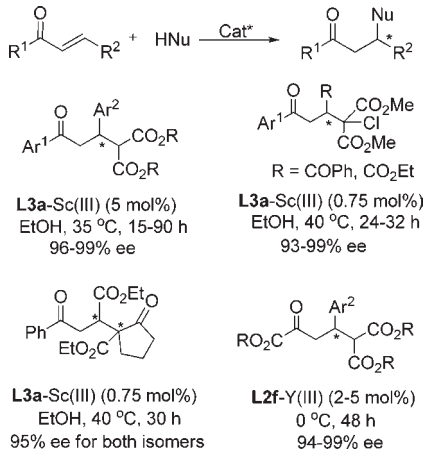
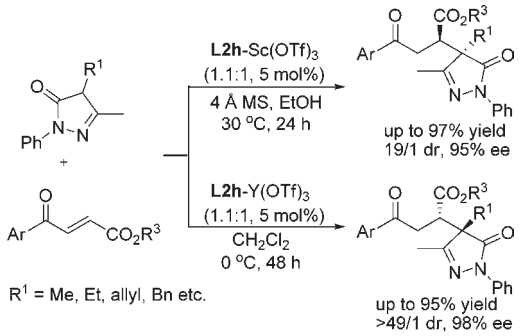


FIGURE 6. Asymmetric conjugate additions of malonates.

enones including (*E*)-4-oxo-4-arylbutenoates, chalcones, and cinnamones (Figure 5).[33] Benzylamine-derived **L3a**–$Sc(OTf)_3$ showed superior performance versus **L3f**–$Sc(OTf)_3$ in the Michael reaction of malonates or α-chloromalonate with a wide range of chalcone derivatives or (*E*)-4-oxo-4-arylbutenoates (Figure 6).[34] In the case of β,γ-unsaturated α-ketoesters and malonates, **L2f**–$Y(OTf)_3$ instead promoted

SCHEME 16. Asymmetric Michael Reaction of 4-Substitituted 5-Pyrazolones



the reaction without extra solvent, whereas *N,N′*-dioxide–$Sc(OTf)_3$ only produced trace amounts of products.

Central metal promoted reversal of enantioselectivity in the asymmetric Michael addition between 4-substitituted-5-pyrazolones and 1,4-dicarbonylbut-2-enes was discovered. Using **L2h** as the ligand, both the $Sc(OTf)_3$ complex and the $Y(OTf)_3$ complex were able to provide the products but with reversed enantioselectivity (Scheme 16).[35] The influence of the solvent was carefully studied, as it may be a key factor in the stereoswitching.

Following C-nucleophiles in the conjugate additions, we examined the sulfa-Michael reaction between thioglycolate and chalcones. Again, the screening of catalysts highlights the influence of the nature of the ligand on the activity and enantioselectivity of the reaction. Ligands bearing 2,6-diisopropylphenylamine were crucial to the enantioselectivity, and **L1f**–$La(OTf)_3$ conferred extremely high inducement (up to 99% ee) at 1 mol % or even 0.01 mol % catalyst loading.[36] The reaction also exhibited an intriguing asymmetric amplification phenomenon in which high enantioselectivity (98% ee) was achieved by using $La(OTf)_3$ and 2% ee ligand **L1f** at

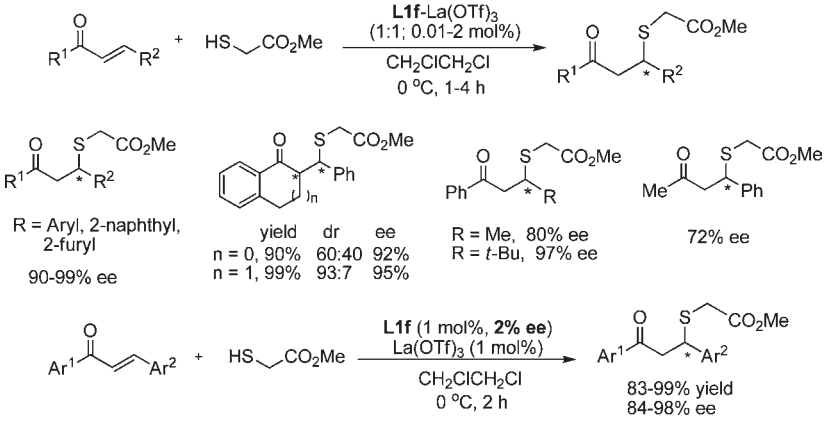


FIGURE 7. Asymmetric sulfa-Michael reaction.

1 mol % catalyst loading (Figure 7). The autocatalytic process was excluded, and a strong positive nonlinear effect implied the presence of polymeric lanthanum species. Further studies on the active intermediates are still ongoing. Michael addition of nitroalkanes to nitroolefins to form the optically active 1,3-dinitroalkanes was effectively mediated by La(OTf)$_3$–**L1c** with high outcomes using mild procedure (Figure 8).[37]

The bidentate chelating nature of the dicarbonyl compounds with nickel complex was utilized for the intramolecular oxa-Michael addition of *tert*-butylester activated α,β-unsaturated ketones to synthesize pharmaceutically active chromanone derivatives (Scheme 17).[38] It was found that the counterion of the Ni(II) complex greatly affected the activity, and the substituent on the amide subunits as well as the amino acid backbone of the ligand had a notable impact on the enantioselectivity of the reaction. The association of *N,N′*-dioxide **L3d**–Ni(Tfacac)$_2$ yielded chromanones in 84–99% ee.

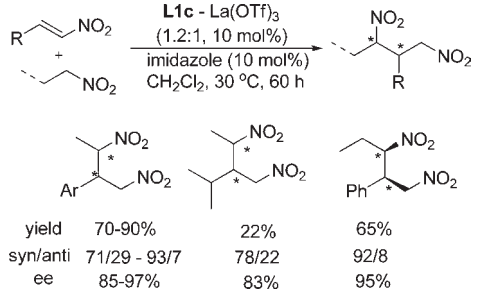
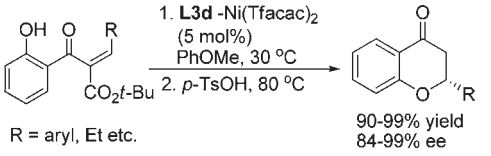
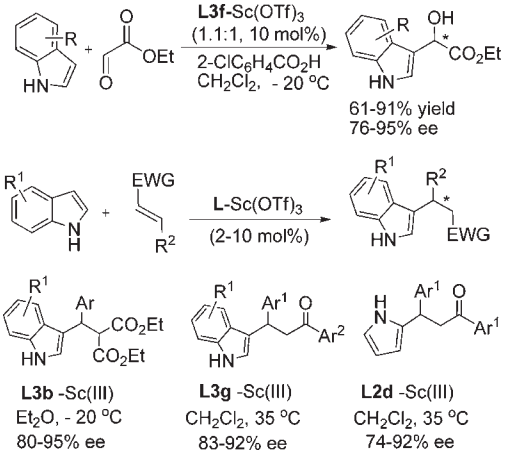


FIGURE 8. Asymmetric synthesis of 1,3-dinitroalkanes.

SCHEME 17. Asymmetric Intramolecular Oxa-Michael Reaction



SCHEME 18. Asymmetric Friedel–Crafts Reaction



Haloamination Reaction. The asymmetric electrophilic haloamination reaction has the potential to generate key synthetic intermediates, vicinal halo-amine compounds. However, the asymmetric methods face the difficulties of control over the regioselectivity and enantioselectivity. The first asymmetric bromoamination reaction of chalcones

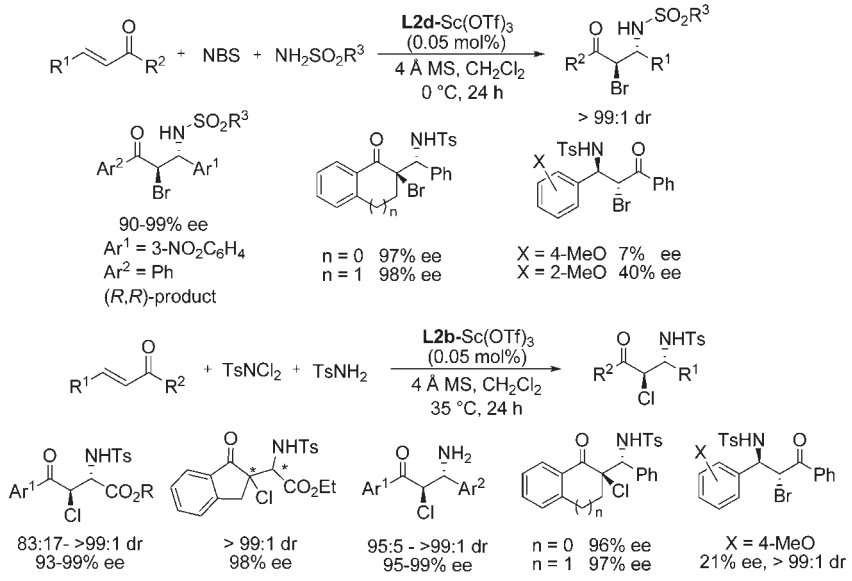


FIGURE 9. Asymmetric haloamination reactions.

was achieved with chiral *N,N′*-dioxide–$Sc(OTf)_3$ through a bromonium-based mechanism (Figure 9).[39] Chiral α-bromo-β-amino ketones with up to 99% ee and 99:1 diastereomeric ratio (dr) were obtained using 0.05 mol % **L2d**–$Sc(OTf)_3$ in the presence of 4 Å molecular sieves. Most of the chalcone derivatives were tolerant, but chalcones with 2-methoxy and 4-methoxy substituents at the β-phenyl group were exceptions with poor enantioselectivity, probably due to the facile racemization of the electron-rich bromonium intermediate through the bimolecular olefin-to-olefin transfer path. Later, we harnessed $TsNCl_2$/$TsNH_2$ as a new effective system of reagents to perform the catalytic asymmetric chloroamination reaction of α,β-unsaturated γ-ketoesters and chalcones. Excellent results were achieved with 0.05–0.5 mol % of the **L2b**–$Sc(OTf)_3$ complex (Figure 9).[40]

Friedel–Crafts Alkylation Reaction. Asymmetric nucleophilic addition of indoles to prochiral electrophiles provides a useful strategy for accessing chiral indole frameworks that represent a privileged class of biologically interesting compounds (Scheme 18). α-Indoly(hydroxyl)acetates were obtained using the **L3f**–$Sc(OTf)_3$ catalyst with good outcomes and to the exclusion of the bisindole byproduct. The reactions between indoles and alkylidene malonates[11] or chalcones were performed smoothly to yield the indole derivatives in moderate to good results. Pyrrole was also tolerable in **L2d**–$Sc(OTf)_3$ catalyzed asymmetric transformation of chalcones.[41]

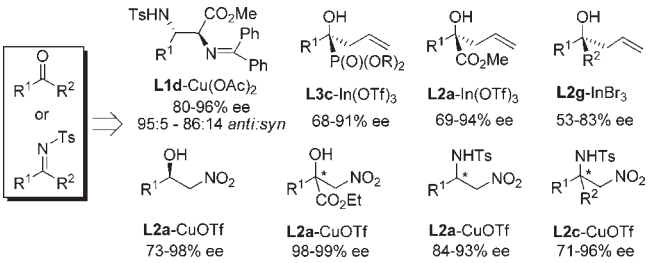
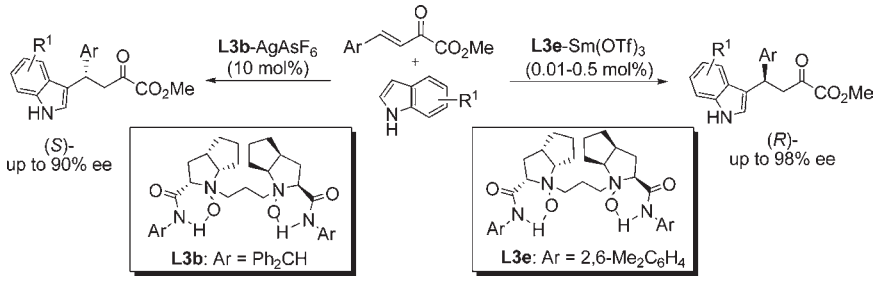


FIGURE 10. Miscellaneous nucleophilic addition reactions.

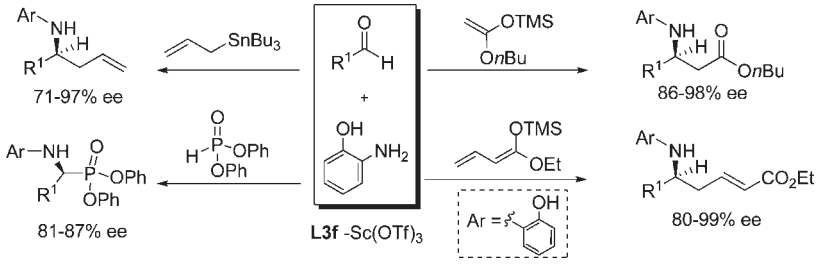
Controlled reversal of enantioselectivity using $Sm(OTf)_3$/$AgAsF_6$ and *N,N′*-dioxides from the same chiral source were observed in the reaction of indole to β,γ-unsaturated α-ketoesters (Scheme 19).[42] This phenomenon was explained by the different coordination capability between Ag(I) and Sm(III).

Miscellaneous Reactions. Systematic studies were also carried out with the complexes of Cu(I), Cu(II), and In(III) as shown in Figure 10. The addition of nitromethane to aldehydes, α-ketoesters, aldimines, and ketimines (for the first time) was achieved using *N,N′*-dioxide–CuOTf catalysts.[43] The Mannich-type reaction of a glycine Schiff base with aldimines was catalyzed by **L1d**–$Cu(OAc)_2$ to afford a wide range of *anti*-α,β-diamino acid esters.[44] The chiral indium complex was useful for asymmetric allylation of ketone derivatives.[20] Catalyst **L3f**-$Sc(OTf)_3$ was found to be effective for use with 2-aminophenol-derived aldimines in the addi-

SCHEME 19. Reversal of the Enantioselectivity in Friedel–Crafts Reaction



SCHEME 20. Nucleophilic Additions of *N*-Arylimine



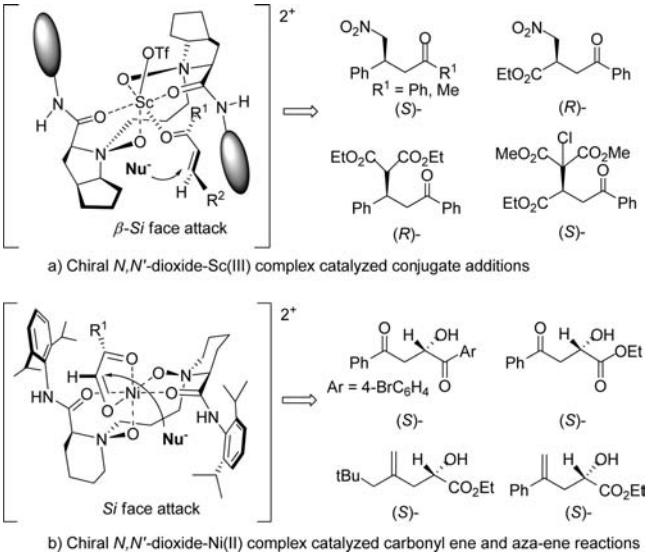


FIGURE 11. Possible stereorecognition model.

tions of allyltributyltin,[45] diphenylphosphite, silyl dienolester, and ketene silylacetal (Scheme 20). Asymmetric reactions arising from other intriguing metal complexes of *N*,*N*′-dioxide are still under way.

Mechanism Consideration. The examples of cycloadditions, nucleophilic additions, conjugate additions, and other reactions illustrated above[46] are important processes that respond strongly to Lewis acid activation. Although the demands of each reaction vary in terms of reactivity and stereoselectivity employing different central metal ion, counterion, chiral backbone, or amide substituent of the ligand, and the ratio of metal to ligand, the sense of asymmetric induction in some respects follows a similar trend. The metal complex of the precursor bisamide proved comparatively inefficient. X-ray crystallography of the chiral complexes[10] revealed a propensity for the coordination of the incoming substrate (Figure 3). For example, in the conjugate additions catalyzed by chiral scandium complexes, the nucleophilic attack of nitromethane or malonate was initiated from the *β-Si* face of the enones because the amide moiety in the rear tightly shielded the *Re* face (Figure 11a).[33,34] In the carbonyl-ene and aza-ene reactions using the chiral nickel complex, the glyoxal derivatives tended to coordinate to the central metal ion in a bidentate fashion in which the *Re* face was blocked by the neighboring amide group (Figure 11b).[12,31] The nucleophile preferred to approach from the *Si* face to give the target products.

The results of these studies highlight the attractive attributes of a family of chiral Lewis acids in bonding and activating substrates for asymmetric reactions. The question of how the chirality transfer proceeds with *N*,*N*′-dioxide−metal catalysts is at the moment hard to rationalize; however, some parameters appear to be important. First, the basicity of the *N*-oxide contributes greatly to its acting as a neutral ligand forming a wide range of metal complexes. Its good stability and solubility in both aprotic and protic solvents ensure resistance under various reaction conditions. Importantly, the use of a C_2-symmetric scaffold favors the geometrical factor which reduces the conformational obscurity of the catalytic intermediate. A comparison of the complexes of privileged ligands such as pybox and salen with that of *N*,*N*′-dioxide indicates that a metal-centered spirocycle could create a chiral environment in which the specific coordination of the substrate occurs to favor the attack of the reagent on a preponderant face. Additionally, the effects of variation of the subunits of *N*,*N*′-dioxide confirm the importance of flexiblility of an ideal ligand. Further studies on the structure−activity relationship, kinetics experiments, and semiempirical calculations should prove valuable for understanding the features that account for the broad applicability of this class of catalysts and for developing new catalysts.

Summmary

It has been demonstrated that C_2-symmetric *N*,*N*′-dioxide amide compounds could participate in a wide range of chiral ligand−metal-catalyzed or organocatalyzed asymmetric reactions under mild reaction conditions. The extensive versatility of this catalyst library in promoting both traditional reactions and new asymmetric reactions is rather gratifying after our long-standing endeavors. The practical benefits of these reactions include excellent enantioselectivity and activity, cheap and available materials, mild reaction temperature, relative insensitivity to moisture, operational simplicity, and facile preparative-scale applications. The future of the *N*-oxide family of catalysts in asymmetric transformation and discrimination is promising.

BIOGRAPHICAL INFORMATION

Xiaohua Liu received her B.S. degree from Hubei Normal University in 2000, and M.S. degree and Ph.D. from Sichuan University in 2003 and 2006 sequentially. She was appointed as an associate professor and joined Prof. Feng's group. Her current research interests cover the asymmetric catalysis and organic synthesis.

Lili Lin received her B.S. degree and Ph.D. from Sichuan University in 2003 and 2008 sequentially. She currently works at Sichuan University. Her interests include the development of new methodologies in asymmetric catalysis.

Xiaoming Feng was born in 1964. He received his B.S. degree in 1985 and M.S. degree in 1988 from Lanzhou University. Then he worked at Southwest Normal University (1988−1993) and became an associate professor in 1991. In 1996, he received his

Ph.D. from the Chinese Academy of Sciences under the supervision of Professors Zhitang Huang and Yaozhong Jiang. He went to the Chengdu Institute of Organic Chemistry, Chinese Academy of Sciences (1996−2000) and was appointed as a professor in 1997. He did postdoctoral research at Colorado State University (1998−1999) with Professor Yian Shi. In 2000, he moved to Sichuan University as a professor, focusing on the design of chiral catalysts, development of new synthetic methods, and synthesis of bioactive compounds.

We are sincerely indebted to a highly talented group of co-workers whose names are listed in the relevant references. We also thank the National Natural Science Foundation of China (Nos. 20732003 and 21021001), the Major Basic Research Development Program (973 program: No. 2010CB833300), and Sichuan University for financial support.

FOOTNOTES

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46 Many asymmetric catalytic reactions noted in the text have also been accomplished by other excellent catalysts. We do apologize in advance for any omission of citing and discussion of these works due to the word limit.