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DEAR READER:

By most measures, China's transformation over the past half-century has been nothing short of spectacular, with its economy now ranked second in the world, an annual GDP north of USD 13 trillion, and 119 Chinese companies making it into Fortune magazine's Global 500 list.

Noteworthy also are China's commitment to, and remarkable advances in, basic and applied research in the natural sciences. Factors such as increased funding for scientific research, workforce qualification and size, and research output, quality, and innovation have propelled China to the #1 spot worldwide in terms of chemistry papers published,[1] and Chinese Universities to occupy 5 of the top 10 spots in chemistry research quality worldwide.[2]

At Merck KGaA, Darmstadt, Germany, we laud China's vigorous research efforts in chemistry and the life sciences, which we believe hold great promise for improving the quality of life for millions of people throughout the world. Moreover, we look forward to establishing strong collaborations with Chinese researchers to make their inventions more accessible worldwide to advance human health for all.

[1] *Nature* Index Country/Territory Outputs – Chemistry (https://www.natureindex.com/country-outputs/generate/Chemistry/global/All/n_article)

[2] *Nature* Index 2019 Tables: Institutions – Chemistry (https://www.natureindex.com/annual-tables/2019/institution/all/chemistry)

Sincerely yours,

Klaus-Reinhard Bischoff
Executive Vice President, MilliporeSigma
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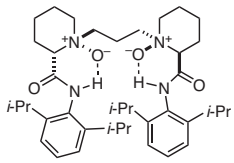
"PLEASE BOTHER US."

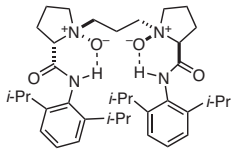
Dear Fellow Chemists,

Professor Xiaoming Feng of the College of Chemistry at Sichuan University kindly suggested that we offer Feng L_3-$PiPr_2$ (**904988**) and Feng L_3-$PrPr_2$ (**904961**) as chiral, *N*,*N*′-dioxide ligands for metals such as nickel(II), indium(III), scandium(III), cobalt(II), yttrium(III), and magnesium(II). The resulting stable complexes act as efficient catalysts for a number of important asymmetric transformations such as ring opening–cycloaddition, Michael addition–alkylation, 1,3-dipolar cycloaddition, and homologation of α-keto esters—leading to the desirable products in high yields and very high diastereo- and enantioselectivities.

(1) Zhang, H. et al. *Org. Lett.* **2019**, *21*, 2388. (2) Kuang, Y. et al. *Chem. Sci.* **2018**, *9*, 688. (3) Zhang, D. et al. *Chem. Commun.* **2017**, *53*, 7925. (4) Li, W. et al. *Angew. Chem., Int. Ed.* **2013**, *52*, 10883.



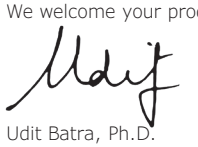
904988
Feng L_3-$PiPr_2$
(1*R*,1′*R*,2*S*,2′*S*)



904961
Feng L_3-$PrPr_2$
(1*R*,1′*R*,2*S*,2′*S*)

904988	Feng L_3-$PiPr_2$, ≥95%	100 mg
904961	Feng L_3-$PrPr_2$, ≥95%	100 mg

We welcome your product ideas. Email your suggestion to **techserv@sial.com**.



Udit Batra, Ph.D.
CEO, Life Science

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ABOUT OUR COVER

How did we in the West end up calling Zhōngguó (中国), China? Several theories exist, but what is making the "Central State" a critical player on the world stage today is not fine china, silk, or tea; rather, it is the breathtaking advances it has made in the past few decades, particularly in science and technology. We, of course, are mostly interested in the life science and physical science advances there. What better to illustrate these advances than the small selection of world-class chemical research that we are featuring in this issue—research that is being carried out at some of the most prestigious Chinese institutions. We hope this gets you as excited about the promise of chemistry research in China and its benefit to mankind as it does us.

Detail from ***One Hundred Flowers***. Photo courtesy The Metropolitan Museum of Art, New York, NY.

One Hundred Flowers (ink and color on silk, 41.9 x 649 cm) is an unattributed, fine handscroll composed during the Qing Dynasty after the style of the well-known Chinese artist Yun Shouping (1633–1690). It depicts a recurring theme in earlier Chinese paintings—flowers in bloom in a seemingly natural setting. This, however, is clearly a composite scene of blooming peonies* with other blossoming flowers, not unlike the still-life-with-flowers genre in western paintings.

This painting is a bequest of John M. Crawford Jr. to the Metropolitan Museum of Art, New York, NY.

** Peonies appear in many Chinese paintings of the past. What could the reason be? To find out, visit* ***SigmaAldrich.com/Acta***

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Asymmetric Catalysis Enabled by Chiral *N,N'*-Dioxide–Nickel(II) Complexes


Prof. Z. Wang


Prof. X. H. Liu


Prof. X. M. Feng

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Keywords. asymmetric catalysis; chiral *N,N'*-dioxide ligand; nickel(II) complex; rearrangements; ene-type reactions; Friedel–Crafts reaction; allylboration; Mannich reaction; Michael reaction; bioactive compounds.

Abstract. The development of efficient catalysts and ligands bearing novel chiral backbones plays a crucial role in asymmetric catalysis. Our group has developed conformationally flexible, C_2-symmetric *N,N'*-dioxide amide compounds as a new class of privileged ligands, which form complexes with a number of metal salts leading to efficient catalysts for a number of asymmetric reactions. In this review, we highlight important asymmetric reactions that are promoted by chiral *N,N'*-dioxide–Ni(II) complexes, and shed some light on their mode of action.

Outline

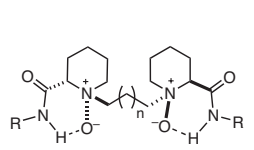
1. Introduction

Catalytic asymmetric reactions have been recognized as fundamental synthetic methods for the construction of optically active compounds.[1–5] Impressive progress has been achieved by using sets of privileged synthetic chiral catalysts that include ligand–metal complexes and organocatalysts.[3,5] In enantioselective coordination catalysis and organometallic catalysis, ligand–metal interactions play a key role in almost every event.[6] An important property of the metal species is their ability to bind the substrate molecules via redistribution of electron density or cleavage in a specific array that is beneficial to high regio- and/or stereoselectivity. Meanwhile, the nature of the chiral ligands plays a crucial role in constructing the three-dimensional structures of the complexes and determining their catalytic activity and specificity.

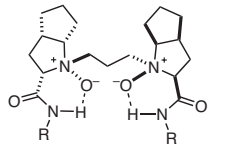
Over the past two decades, our group has developed a class of C_2-symmetric amine oxide ligands, which are easily prepared from optically active amino acids and amines (aliphatic or aromatic) (**Figure 1**). The two *N*-oxide amide units are linked in such a way that conformation-flexible, straight-chain alkanes [–$(CH_2)_{2,3,4,5...}$–] are used. The structure is similar to nunchucks, pronounced "*Shuangjie Gun*" in Chinese, a weapon in Kungfu fighting. There are four oxygen donor groups in *N,N'*-dioxide ligands, all of which can simultaneously bond to the metal center, resulting in very stable complexes. The metal cations derive from main-group metals, transition metals, and rare-earth metals. Our extensive investigations have shown that the resulting chiral *N,N'*-dioxide–metal complexes exhibit excellent reactivity and enantiocontrol in more than 50 types of reactions with wide substrate scopes under mild reaction conditions. Their discovery, structure information, and some applications have been described in several accounts,[7] and will not be discussed in details herein. This mini-review focuses on the catalytic aspects of the chiral *N,N'*-dioxide–nickel(II) complexes in asymmetric reactions.

Nickel(II) forms a large number of complexes with complicated stereochemistry, encompassing coordination numbers 4, 5, and 6, and belonging to all the main structural types. On the other hand,

nickel(II)–*N,N'*-dioxide complexes have a relatively simple distorted octahedral 20-electron arrangement.[8] The powders of such nickel(II) complexes—formed from $Ni(BF_4)_2$ or $Ni(ClO_4)_2$—are characteristically green, and their X-ray crystal structures show that the chelating tetradentate ligands of the chiral *N,N'*-dioxides provide increased stability and a higher degree of control over the chiral coordination environment around the nickel center. The data related to the bite angles generated by coordination of the two carbonyl and the two amine oxide groups to nickel (i.e., the O^c-Ni-O^c angle and the O^N-Ni-O^N angle) indicates that the fine conformation of the catalysts could be tuned by varying the length of the linker between the two amine oxide units (e.g., L_2-PiPr$_2$ vs L_3-PiPr$_2$ vs L_4-PiPr$_2$), the amino acid backbone (L_3-PiPr$_2$ vs L_3-RaPr$_2$), and/or the substituent on the amide nitrogen (L_3-PiPr$_2$ vs L_3-PiCHPh$_2$, or L_3-RaPr$_2$ vs L_3-Ra*m*Bu$_2$).

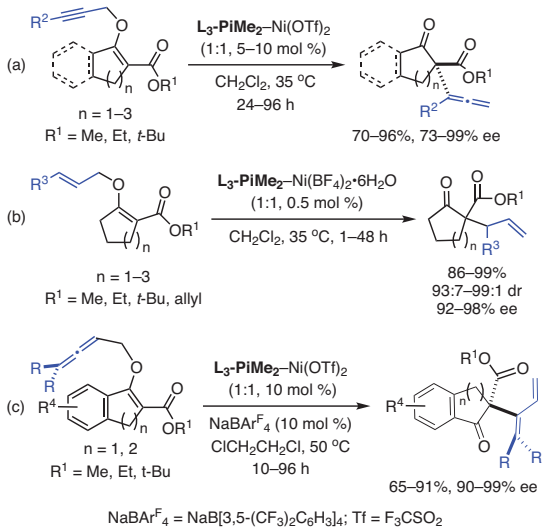


Label	R	n
L_2-PiPr$_2$	2,6-*i*-Pr$_2$C$_6$H$_3$	0
L_3-PiMe$_2$	2,6-Me$_2$C$_6$H$_3$	1
L_3-PiEt$_2$	2,6-Et$_2$C$_6$H$_3$	1
L_3-PiPr$_2$	2,6-*i*-Pr$_2$C$_6$H$_3$	1
L_3-Pi*o*Br	2-BrC$_6$H$_4$	1
L_3-Pi*s*EPh	(*S*)-2-PhEt	1
L_3-PiCHPh$_2$	CHPh$_2$	1
L_4-PiPr$_2$	2,6-*i*-Pr$_2$C$_6$H$_3$	2



Label	R
L_3-RaEt$_2$	2,6-Et$_2$C$_6$H$_3$
L_3-RaPr$_2$	2,6-*i*-Pr$_2$C$_6$H$_3$
L_3-Ra*m*Bu$_2$	3,5-*t*-Bu$_2$C$_6$H$_3$
L_3-RaPr$_3$	2,4,6-*i*-Pr$_3$C$_6$H$_2$
L_3-RaPh	Ph

Figure 1. A Selection of C_2-Symmetric *N,N'*-Dioxide Ligands That Have Been Investigated by Our Group in the Featured Reactions.



Scheme 1. The **L_3-PiMe$_2$** Enabled Propargyl, Allyl, and Allenyl Claisen Rearrangement. *(Ref. 10,11)*

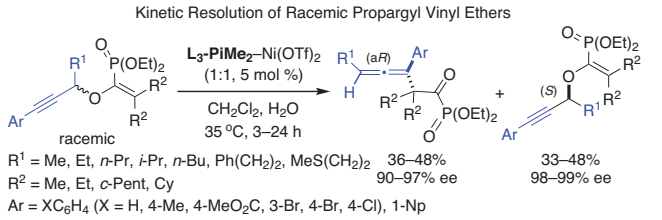
This flexibility in tuning the ligand structure permits the resulting catalyst to satisfy the requirement of enantiocontrol in a variety of reactions. The chiral nickel coordination sphere can restrict how close the reactants can get to the center of the catalytic species by displacing the ancillary solvent or anion during the catalytic process.

2. Catalytic Asymmetric Rearrangement Reactions

2.1. Propargyl, Allyl, and Allenyl Claisen Rearrangement

The Claisen rearrangement and its variants are some of the most powerful stereoselective carbon–carbon bond-forming reactions.[9] If uncatalyzed, it usually requires higher reaction temperatures, while a Lewis acid catalyst might exert a positive influence on the reactivity. *N,N'*-Dioxide–nickel(II) salts offer several advantages in the Claisen rearrangement under mild reaction conditions. For instance, highly efficient and catalytic asymmetric propargyl and allyl Claisen rearrangements of *O*-propargyl and *O*-allyl β-keto esters were effected in the presence of the Ni(II) complexes of the three-carbon-linked *N,N'*-dioxide **L_3-PiMe$_2$**, prepared from L-pipecolic acid and 2,6-dimethylbenzenamine (**Scheme 1**, Parts (a) and (b)).[10] The enantioselective process gave a wide range of allenyl- or allyl-substituted all-carbon quaternary β-keto esters in good yields (up to 99%), high diastereoselectivities (up to 19:1 dr), and excellent enantioselectivities (up to 99% ee). The catalyst loading could be lowered to 0.5 mol % for the asymmetric allyl Claisen rearrangement without deterioration of the yields and stereoselectivities. Moreover, the chiral catalyst system was extended to the allenyl Claisen rearrangement to form branched 1,3-dienyl substituted β-keto esters with high enantioselectivity but at higher reaction temperatures (Scheme 1, Part (c)).[11]

The major pathway of the Claisen rearrangement proceeds via a cyclic chair conformation of the transition state (TS), whereas the minor pathway proceeds via a boat conformation of the TS. Because chiral starting materials could give Claisen rearrangement products of high optical purity, **L_3-PiMe$_2$**–Ni(OTf)$_2$ was successfully applied to the kinetic resolution of racemic propargyl vinyl ethers (**eq 1**).[12] This catalyst system showed a preference for the (*R*)-configured cyclic and linear propargyl vinyl ether through a bidentate bonding manner, leading to a diastereo- and enantioselective [3,3]-sigmatropic rearrangement. Complete central-to-axial chirality transfer occurs in the propargyl Claisen rearrangement, and the chirality of the newly formed stereogenic quaternary carbon is controlled, in some cases, by the chiral catalyst rather than by substrate induction. Moreover, the mismatched *S* isomer of the starting material could be recovered



eq 1 *(Ref. 12)*

in high yield and enantiomeric excess. It is worth noting that enantioselective recognition enabled by chiral *N,N′*-dioxide–nickel(II) complexes has also been observed in visual or fluorescence sensing of chiral α-hydroxycarboxylic acids and *N*-Boc amino acids.[13]

2.2. [2,3]-Wittig Rearrangement

The [2,3]-Witting rearrangement proceeds via a five-membered cyclic transition state and provides a direct route to homoallyl alcohols and related compounds. Using progargylic ethers of oxindole derivatives as substrates, the reaction delivers allene-substituted alcohols, but the reactivity is low due to the distorted transition-state geometries arising from the alkyne sp center. By using **L$_3$-PiCHPh$_2$**–Ni(OTf)$_2$ as catalyst, a highly enantioselective variant was achieved (**eq 2**).[14] Interestingly, a low yield (18%) was obtained in the absence of the *N,N′*-dioxide ligand. Furthermore, kinetic resolution of racemic oxindole derivatives was also achieved with high efficiency and stereoselectivity.[14]

With respect to the modes of asymmetric catalysis of these chiral nickel complexes in the Claisen and [2,3]-Wittig rearrangements, it has been proposed that they occur by similar bidentate activations. The β-keto esters, phosphonates, and oxindoles are 1,4-dioxygen-type substrates, which could bond to the nickel(II) center with the ether oxygen and the carbonyl group, forming a stable five-membered cyclic transition state. The steric hindrance arising from the *N,N′*-dioxide ligand would then direct the subsequent rearrangement enantioselectively to generate the stereogenic center vicinal to the carbonyl group in the products.

2.3. Doyle–Kirmse Rearrangement

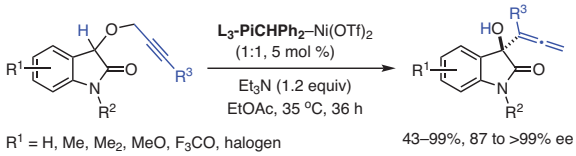
The unique electronic and steric properties of chiral *N,N′*-dioxide–metal complexes prompted us to design α-diazo pyrazoleamides for the asymmetric [2,3]-sigmatropic rearrangement of sulfonium ylides generated from α-diazo compounds and allyl sulfides. The control of enantioselectivity in this type of [2,3]-sigmatropic rearrangement relies on the formation of a metal-bonded ylide intermediate or discrimination of the heterotopic lone pairs on sulfur.[15] The chiral **L$_2$-PiPr$_2$**–Ni(II) complex efficiently catalyzed both the formation of the sulfide ylide intermediate and its subsequent enantioselective rearrangement. Moreover, a combination of **L$_2$-PiPr$_2$**, $NiCl_2$, and $AgNTf_2$ efficiently catalyzed the enantioselective Doyle–Kirmse reaction of a series of aryl- or vinyl-substituted α-diazo pyrazoleamides with allyl aryl sulfides (**Scheme 2**).[16] In most cases, the reactions were completed in 5–20 minutes in high yields and with excellent enantioselectivities (up to 99% yields and 96% ee's). There is an obvious ligand reaction-acceleration effect, as only a trace amount of the product was obtained without the chiral ligand. The introduction of a pyrazoleamide unit into the α-diazo compound enhances its electrophilicity, and facilitates the formation of the chiral Lewis acid bonded ylide intermediate and stereocontrol via bidentate coordination. The latter hypothesis has been supported by the reaction of C_2-symmetric diallyl sulfides with diazo pyrazoleamides, which led to the corresponding products with good enantioselecitivity.

2.4. [2,3]-Stevens and Sommelet–Hauser Rearrangements

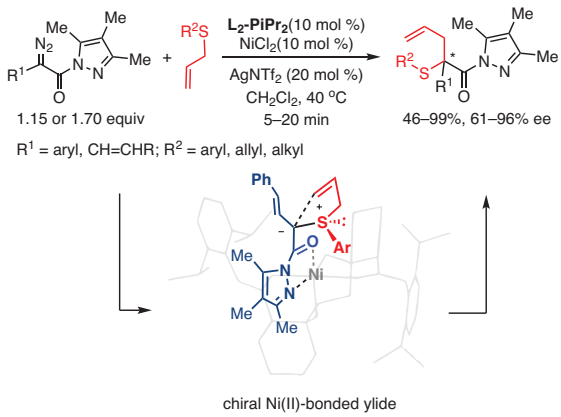
The enantioselective [2,3]-Stevens and Sommelet–Hauser rearrangements of sulfonium ylides—generated from α-diazo compounds and thioacetates—are much more complicated in comparison with the asymmetric Doyle–Kirmse reaction. There are vicinal S- and C-stereogenic centers in the ylide intermediates, racemization or epimerization of ylide tautomers via 1,3-proton shifts, and a remote functionalization in the final [2,3]-rearrangement step.

The **L$_2$-PiPr$_2$**–Ni(II) complex catalyzed the asymmetric [2,3]-Stevens rearrangement of vinyl substituted α-diazo pyrazoleamides and aryl thioacetates. Initially, discrimination of the heterotopic lone pairs on sulfur affords the (*R*)-configured sulfonium ylide species **I**. Added 3-phenylpropanoic acid acts as a mild proton shuttle, enabling the slower diastereoselective tautomerization process to generate the (*R*,*R*)-ylide intermediate **II**, which undergoes an asymmetric [2,3]-rearrangement via an envelope transition state, leading to the desired products with a (*2R*,*3S*,*E*) configuration (**Scheme 3**).[17]

This same chiral nickel complex also efficiently catalyzed the asymmetric Sommelet–Hauser reaction of aryl-substituted α-diazo pyrazoleamides with (phenylthio)methylcarbamoates.[17] This rearrangement is potentially more challenging because dearomatization and rearomatization steps are involved in the process. The desired ortho-thioalkyl-substituted arylacetamides were isolated in 51–78% yield with 60–81% ee. The 1,3-proton shift results from a trace amount of water in the system, and the



eq 2 *(Ref. 14)*

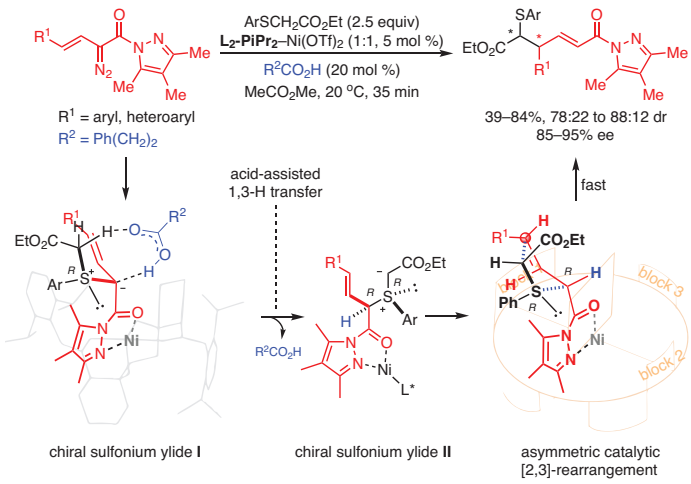


Scheme 2. Doyle–Kirmse Reaction Catalyzed by Ni(II)–*N,N′*-Dioxide Complexes. *(Ref. 16)*

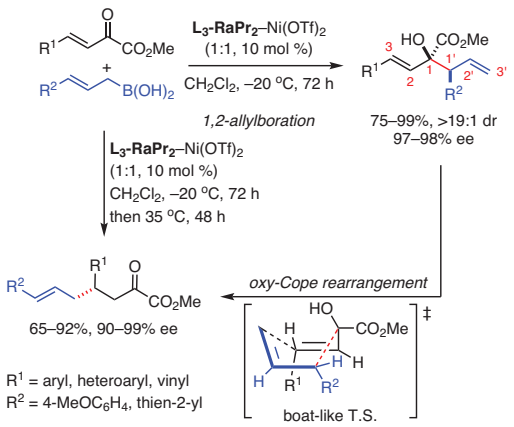
[2,3]-rearrangement process is slow and difficult due to the high activation energy of the dearomatization step.

2.5. Allylboration/Oxy-Cope Rearrangement

Recently, the complex **L$_3$-RaPr$_2$**–Ni(OTf)$_2$ was used to catalyze an allylboration–oxy-Cope rearrangement sequence of β,γ-unsaturated α-keto esters with allylboronic acids under mild conditions (**Scheme 4**).[18] This protocol provides a facile and direct route to γ-allyl-α-keto esters in moderate-to-good yields (65–92%) and excellent enantioselectivity (90–99% ee). The 1,2-allylboration products could also be isolated in good yields and excellent diastereo- and enantioselectivities at lower reaction temperature. The general catalytic mechanism is based on coordination of the β,γ-unsaturated α-keto ester to the nickel center in a bidentate fashion,



Scheme 3. Catalytic, Asymmetric [2,3]-Stevens Rearrangement Enabled by Ni(II)–*N,N'*-Dioxide Complexes. *(Ref. 17)*



Scheme 4. Application of Ni(II)–*N,N'*-Dioxide Complexes as Catalysts for an Asymmetric Allylboration and Oxy-Cope Rearrangement Sequence. *(Ref. 18)*

which is suitable for the face-selective addition of the allylboronic acid. It was found that the subsequent enantioselective oxy-Cope rearrangement is induced by the optically enriched vinyl- and allyl-substituted alcohol intermediates, and the process could be accelerated by the chiral Lewis acid at higher reaction temperature. The chirality transfer in the oxy-Cope rearrangement is via a rare, boat-like transition state.

3. Asymmetric Catalytic Nucleophilic Addition Reactions

3.1. Ene-Type Reactions

Ene-type reactions can provide access to polyfunctionalized compounds that are synthetically versatile intermediates by the further transformation of the carbon–carbon double bond.[19] The asymmetric carbonyl–ene reaction of glyoxals and glyoxylates can be used to construct chiral γ,δ-unsaturated α-hydroxy carbonyl compounds. The chiral *N,N'*-dioxide–nickel(II) complexes can catalyze the asymmetric variant with remarkable results by employing glyoxals, α-keto esters, or isatins as the enophiles, and alkenes, enamides, vinylogous hydrazine, or 5-methyleneoxazolines as the nucleophiles. The common catalytic pathway involves bidentate coordination of the 1,2-dicarbonyl compounds to the nickel center, lowering the LOMO energy of the enophile. Subsequently, the ene component enantioselectively approaches the active carbonyl group via a cyclic transition state to yield the desired adduct.

For example, excellent enantioselectivities (up to >99% ee) were obtained in the **L$_3$-PiPr$_2$**–Ni(BF$_4$)$_2$ catalyzed carbonyl-ene reaction of glyoxals and glyoxylates with various alkenes.[20] The optically active allyl-substituted α-hydroxy carbonyl products can undergo a subsequent, FeCl$_3$–TBSCl catalyzed OH-selective Prins cyclization, leading to a broad range of substituted 4-hydroxytetrahydropyrans highly stereoselectively (**Scheme 5**, Part (a)).[21] The *N,N'*-dioxide–nickel(II) catalysts also show remarkable performance in the carbonyl-ene reaction of glyoxals and glyoxylates with a series of enamides[22] and 5-methyleneoxazolines[23] as nucleophiles. The hetero-ene reaction of glyoxal derivatives and 5-methyleneoxazoline worked well even at 0.5 mol % loading of the catalyst, providing 2,5-disubstituted oxazole derivatives in 60–99% yields and 95 to >99% ee's.

Similarly, the asymmetric ene-type reaction of α-keto esters with 5-methyleneoxazolines also works well under **L$_3$-PiPr$_2$**–Ni(BF$_4$)$_2$ catalysis.[23–24] Moreover, in the presence of **L$_3$-RaEt$_2$**–Ni(ClO$_4$)$_2$ as catalyst, a range of racemic β-halo-α-keto esters were efficiently converted into the chiral β-halo-α-hydroxy esters via dynamic kinetic asymmetric transformations. The corresponding ene products containing vicinal tri- and tetrasubstituted carbon centers were obtained in generally good yields and diastereoselectivity and excellent ee values (Scheme 5, Part (b)).[24]

The valuable nucleophile vinylogous hydrazine underwent an ene-type reaction with glyoxal derivatives. Subsequent treatment with magnesium monoperoxyphthalate hydrate (MMPP·6H$_2$O) gave the valuable, optically active 4-benzoyl-4-hydroxy-2-methylenebutanenitrile in 95% yield and 95% ee.[25] This vinylogous nitrile was elaborated in moderate yield and excellent ee into a bioactive compound that is a potentially cytotoxic agent against human leukemia HL-60 cells.[26] Furthermore, **L$_3$-RaPr$_2$**–Ni(OTf)$_2$

efficiently catalyzed the reaction of vinylogous hydrazine with isatins, and the product of the reaction was transformed in two steps into a spirocyclic lactone that is a potent antineoplastic agent against P-388 lymphocytic leukemia and human carcinoma of the nasopharynx (Scheme 5, Part (c)).[25]

In contrast to the preceding examples of the ene reaction, the asymmetric Alder–ene reaction using alkenes as enophiles remains a challenge due to the low reactivity of the olefins along with the required high activation energy of the ene reaction. Usually, stoichiometric amounts of chiral Lewis acids are required to achieve a satisfactory outcome.[27] In this regard, **L$_3$-RaPr$_2$**–Ni(NTf$_2$)$_2$ efficiently promoted the asymmetric intramolecular Alder–ene reaction, leading to a series of 3,4-disubstituted chromans, thiochromans, tetrahydroquinolines, and piperidines in high yields and with good-to-excellent diastereo- and enantioselectivities.[28]

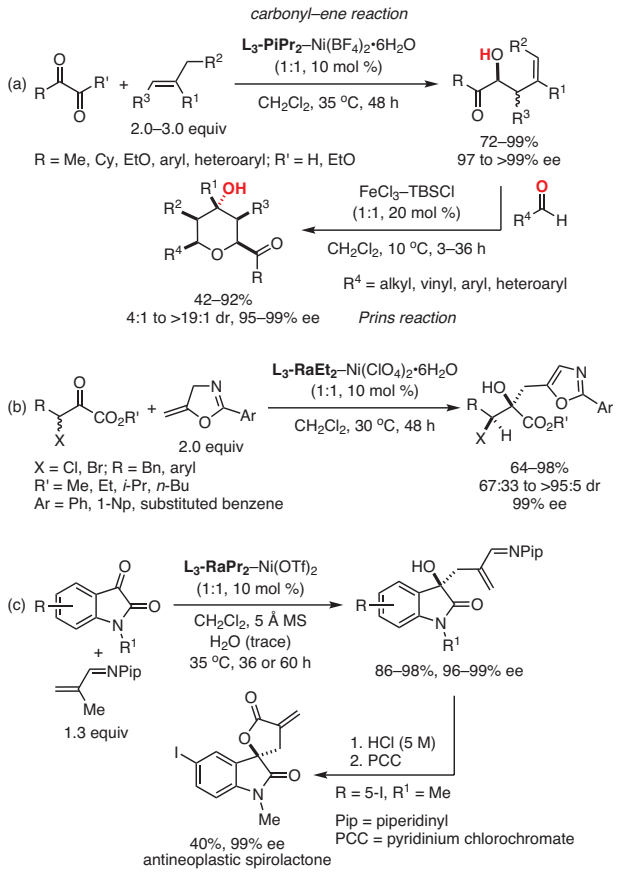
3.2. Friedel–Crafts Reaction

The phenomenon of enantioselectivity reversal is interesting and has important applications in enantiodivergent synthesis.[29] Using the chiral pool and slightly modifying the amide moiety of the *N,N′*-dioxide ligand in chiral *N,N′*-dioxide–Ni(OTf)$_2$ complexes result in an enantiodivergent Friedel–Crafts-type reaction of β,γ-unsaturated α-keto esters with 2,5-dimethylpyrrole or 2-methylindole (**Scheme 6**).[30] For example, **L$_3$-RaPr$_2$**–Ni(OTf)$_2$ catalyzes the addition of 2,5-dimthylpyrrole to β,γ-unsaturated α-keto esters to give the dextran product, while **L$_3$-Ra*m*Bu$_2$**–Ni(OTf)$_2$ catalyzes the same reaction to yield the right-handed enantiomer. The strategy was also successfully implemented in an enantiodivergent synthesis of the corresponding indole adducts. The switch in enantioselectivity results from the markedly different spatial environments in the seesawed amide units of the two catalyst complexes. Steric hindrance around the enantiotopic face of the β,γ-unsaturated α-keto ester causes its differentiation upon bidentate coordination to the nickel center.

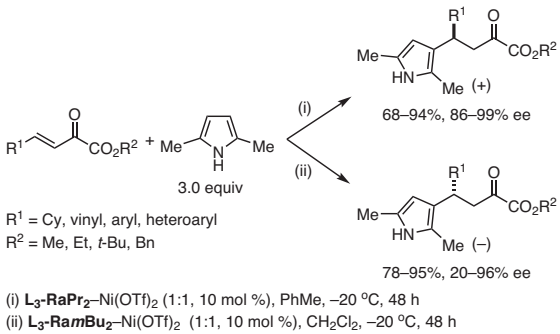
3.3. Michael and Mannich Reactions

Chiral *N,N′*-dioxide–Ni(II) complexes have also been used in classic addition reactions such as the oxa-Michael and Mannich reactions. For example, (2-hydroxyphenyl)propenone derivatives engage in two-point binding to the central metal in **L$_3$-RaPh**–Ni(Tfacac)$_2$, forming a chelate-ordered transition state that results in an intramolecular oxa-Michael addition (**Scheme 7**, Part (a)).[31] The reaction tolerated a relatively wide range of substrates to provide a series of flavanones in excellent yields (90–99%) and moderate-to-excellent enantioselectivities (40–99% ee). Significantly, the optically active flavanones can be converted into versatile building blocks such as hydrazones.[32]

Chiral **L$_3$-PiPr$_2$**-based Ni(II) and Mg(II) complexes are also efficient catalysts for the asymmetric Mannich reaction employing 1,3,5-triazinanes as electrophilic reagents and imine precursors (Scheme 7, Part (b)).[33] The in situ generated imines react smoothly with α-tetralone-derived β-keto esters or amides to give optically active 2-(β-amino)-substituted tetralones in generally good-to-excellent yields and enantioselectivities. However, the five-membered-ring β-keto amide analogue gave the corresponding product in 99% yield but with only 50% ee, while the seven-membered-ring β-keto amide counterpart gave 92% yield of the racemic product.



Scheme 5. Asymmetric Ene-Type Reactions Catalyzed by Ni(II)–*N,N′*-Dioxide Complexes. *(Ref. 20,21,24,25)*



Scheme 6. Enantiodivergent Friedel–Crafts Reaction Promoted by Chiral *N,N′*-Dioxide–Ni(OTf)$_2$ Complexes. *(Ref. 30)*

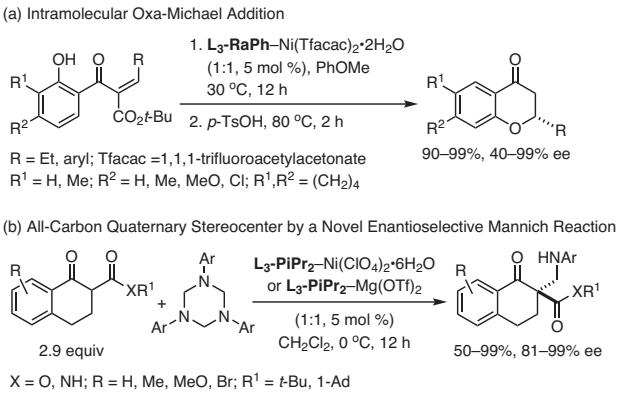
4. Miscellaneous Reactions

4.1. Transformations Involving Hypervalent Iodine Salts

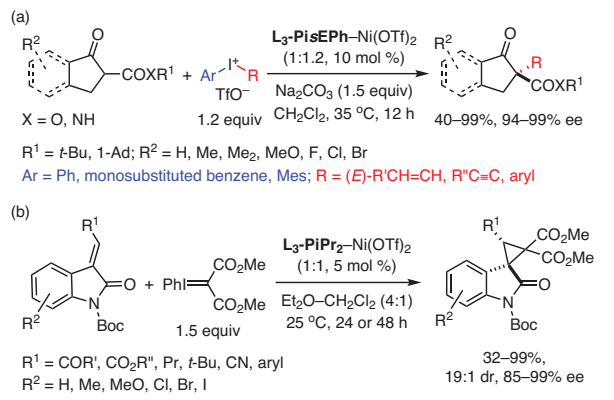
Hypervalent iodine salts, such as vinyl-, alkynyl-, and aryliodonium salts are attractive reagents due to their low toxicity, high reactivity, and high stability. We previously found chiral *N,N'*-dioxide–Sc(OTf)$_3$ complexes to be efficient Lewis acid catalysts for the enantioselective α-arylation of 3-substituted oxindoles with diaryliodonium salts through carbon–iodine bond formation and subsequent [1,2]-rearrangement.[34] When β-keto amides or esters were used as substrates, it was observed that chiral **L$_3$-PisEPh**–Ni(II) was a much more efficient catalyst, which gave good results in the enantioselective vinylation, alkynylation, and arylation (**Scheme 8**, Part (a)).[35] A bidentate coordination of the 1,3-dicarbonyl compound to the nickel center was proposed to rationalize the observed enantioselection.

A new strategy for the catalytic asymmetric cyclopropanation of 3-alkenyloxindoles with phenyliodonium ylide malonate has been developed (Scheme 8, Part (b)).[36] In the presence of **L$_3$-PiPr$_2$**–Ni(OTf)$_2$, a variety of spirocyclopropane-oxindoles with contiguous one tertiary and two quaternary all-carbon centers are generated with excellent yields and stereoselectivities (up to 99% yield, > 19:1 dr, and up to 99% ee). Based on EPR spectroscopic observations, a free, triplet carbene intermediate, ^{3}:C(CO$_2$Me)$_2$, was proposed as resulting from the thermal decomposition of the phenyliodonium ylide. Bidentate coordination of the 3-alkenyloxindole to the chiral nickel center through the two carbonyl groups was also proposed to precede reaction with the triplet carbene. Ring closure of the resulting singlet biradical intermediate leads to the cyclopropane product, with the observed facial selectivity being attributed to the blocking of the nearby amide unit of the ligand.

The catalytic enantioselective C$_{sp3}$–H α-alkylation of β-keto amides with phenyliodonium ylide has been achieved in the presence of the chiral **L$_3$-PiEt$_2$**–Ni(OTf)$_2$ complex.[37] Notably, the catalytic radical process is insensitive to air and moisture, and the resulting products are obtained in good yields and with excellent enantioselectivities even when the reaction is carried out on a gram scale (up to 91% yield and 97% ee).



Scheme 7. Asymmetric Intramolecular Oxa-Michael Addition and Mannich Reaction. *(Ref. 31,33)*



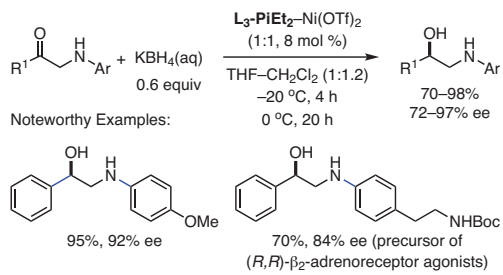
Scheme 8. Chiral *N,N'*-Dioxide–Ni(II) Catalyzed Reactions: (a) α-Vinylation, Alkynylation, and Arylation of β-keto Acid Derivatives. (b) Cyclopropanation of 3-Alkenyloxindoles. *(Ref. 35,36)*

4.2. Reduction Reaction

The asymmetric reduction of secondary and primary α-amino ketones has been achieved using *N,N'*-dioxide–Ni(II) complexes and aqueous KBH$_4$, confirming that such complexes can tolerate reducing agents and aqueous conditions. This approach provides easy access to chiral, β-amino alcohol based natural products and drug candidates, such as β$_2$-adrenoreceptor agonists. For example, chiral **L$_3$-PiEt$_2$**–Ni(OTf)$_2$ catalyzed the reduction of α-(*N*-arylamino)-ketones to chiral β-amino alcohols in good-to-excellent yields (up to 98%) and enantioselectivities (up to 97% ee) (**eq 3**).[38]

5. Application in the Synthesis of Natural Products and Drug Candidates

Hyperolactones A–C and (−)-biyouyanagin A, containing two chiral vicinal quaternary carbon centers, are a family of spirolactone natural products with significant activity against HIV. A short, catalytic, and stereodivergent synthesis of hyperolactones B and C has been achieved starting with an enantioselective dearomatization–Claisen rearrangement of allyl furyl ethers in the presence of chiral **L$_3$-PiMe$_2$**–Ni(BF$_4$)$_2$ or *ent*-**L$_3$-PiMe$_2$**–Ni(BF$_4$)$_2$ (**Scheme 9**).[39] The Ni(II)-catalyzed step was found to be generally applicable to allyl furyl ethers, and, under the optimized conditions, a number of



eq 3 *(Ref. 38)*

γ,δ-unsaturated carbonyl compounds were obtained in up to 99% yield, 19:1 dr, and up to 99% ee. The steric hindrance arising from the bulky amide moiety of the ligand forces the alkene unit of the substrate to preferentially approach the α position of the furan ring from one side. Thus, the stereogenic arrangement of the furanone is catalyst-controlled, while the configuration of the quaternary carbon center is determined by the *Z*/*E* configuration of the allyl substituent. As a result, four enantiomers of the products could be prepared in excellent yields and stereoselectivities by a judicious selection of the configuration of the catalyst and the alkene unit of the substrates.[39]

N,N′-Dioxide–metal complexes have been successfully applied in asymmetric cycloaddition reactions.[7c] One of the noteworthy examples is the *N,N′*-dioxide-Ni(OTf)$_2$ catalyzed regio-, diastereo-, and enantioselective aza-Diels–Alder reaction of 3-vinylindoles with isatin-derived ketimines. The reaction takes place by a concerted reaction pathway, and the regioselectivity and exo selectivity are attributed to the π–π interaction between the two indoline rings of the two reactants. The transformation affords a series of spiroindolone derivatives in good yields and with excellent enantioselectivities.[40] Furthermore, the antimalarial drug candidate NITD609 was obtained in three steps (40.6% overall yield and up to 99% ee) starting with the gram-scale, *ent*-**L$_3$-RaPr$_2$**–Ni(OTf)$_2$ catalyzed aza-Diels–Alder cycloaddition of a suitably substituted 3-vinylindole and isatin-derived ketimine (**Scheme 10**).[40]

6. Conclusion

Chiral *N,N′*-dioxide ligand–Ni(II) complexes are now practical Lewis acid catalysts in several well-known reactions. Additionally, a number of chiral nickel(II) complexes—with ligands possessing functional groups of other heteroatoms as electron-pair donors, such as amines and phosphines—have also been developed. For example, chiral nickel(II)–PyBox or nickel(II)–bis(oxazoline) complexes are efficient catalysts for enantioselective cross-couplings of nucleophiles with racemic alkyl electrophiles via radical pathways.[41] The chiral nickel(II) complexes of diamines, salen, BINAP, and TOX ligands promote various reactions as Lewis acid catalysts. Nickel and several other transition metals, with variable oxidation numbers, have considerable established organometallic chemistry, but the role of the catalyst is only beginning to be understood. Improving our understanding of the geometry, ligands, active site, and activation mode in such reactions would allow the development of more efficient, and useful catalytic asymmetric reactions.

7. Acknowledgments

We are sincerely indebted to a group of talented co-workers whose names are listed in the relevant references. We also thank the National Natural Science Foundation of China (Nos. 21625205 and 21432006) for financial support.

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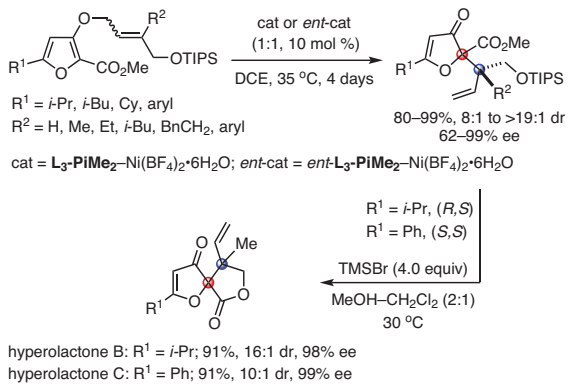
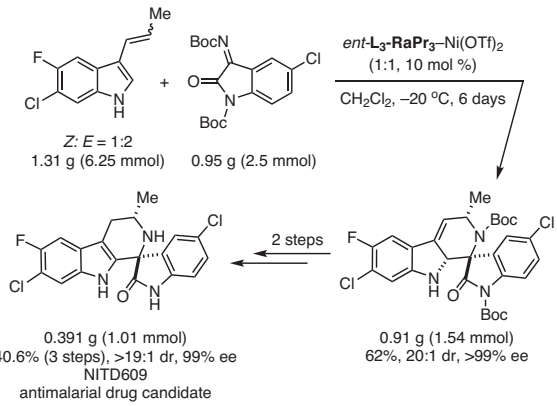


Scheme 9. Application of *N,N′*-Dioxide–Ni(II) Catalysts in a Stereodivergent Synthesis of Hyperolactones B and C. *(Ref. 39)*



Scheme 10. Application of *N,N′*-Dioxide–Ni(II) Catalysts in a Three-Step, Gram-Scale Synthesis of the Antimalarial Drug Candidate NITD609. *(Ref. 40)*

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Asymmetric Allylic Substitutions Catalyzed by Iridium Complexes Derived from C(sp^2)–H Activation of Chiral Ligands


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Keywords. AAS; allylic substitution; asymmetric catalysis; BHPphos; branch selectivity; chiral ligand; C(sp^2)–H activation; enantioselectivity; iridium; N-heterocyclic carbene (NHC); THQphos.

Abstract. The iridium-catalyzed asymmetric allylic substitution reaction has been developed into a reliable method for the synthesis of highly enantioenriched molecules with an allylic stereocenter. The versatility of the reaction is largely attributed to the development of efficient catalysts. Some of these catalysts are iridium complexes derived from C(sp^2)–H activation of chiral ligands including THQphos (1,2,3,4-tetrahydroquinoline phosphoramidite), BHPphos (*N*-benzhydryl-*N*-phenyldinaphthophosphoramidite), and NHCs (N-heterocyclic carbenes). These catalysts exhibit exceptionally high regio-, diastereo-, and enantioselectivities as well as good tolerance of sterically hindered substrates. In this article, we briefly review the design and mechanism of action of these chiral ligands, and highlight their applications in the Ir-catalyzed allylic substitution of various nucleophiles.

Outline

1. Introduction

Transition-metal-catalyzed asymmetric allylic substitution (AAS) reactions are among the most important transformations that allow the construction of carbon–carbon or carbon–heteroatom bonds in an enantioselective fashion.[1] Early examples mainly focused on palladium catalysis, which is compatible with a wide range of nucleophiles and electrophiles and generally favors linear selectivity for mono-substituted allylic electrophiles. Catalysis by other metals has been less studied, but has shown promising control of selectivity. In particular, Ir-catalyzed asymmetric allylic substitutions have received a lot of attention in the past two decades owing to their unique reactivity profile that includes a remarkably high branch selectivity for mono-substituted allylic electrophiles and nearly perfect enantioselective control.[2]

Since the first report by Janssen and Helmchen,[3a] various chiral ligands—including oxazolinylphosphines, phosphoramidites, and dienes—have been utilized in Ir-catalyzed allylic substitution reactions.[3] Of these ligands, the phosphoramidites have contributed significantly to the development of this area, and have enabled a large number of valuable transformations with high levels of regio- and enantioselectivity. For instance, Carreira's

bidentate P,olefin coordination ligands have demonstrated the robustness of this approach by using unprotected allylic alcohols as substrates in the presence of an acidic additive.[2l,4] Under non-acidic conditions, the Feringa ligand[5a,b] and the Alexakis ligand[5c–e] are the most frequently employed ones in iridium-catalyzed allylic substitutions. Mechanistically, the active iridacycle catalyst is formed by bidentate P,C(sp³) coordination to Ir of the ligand, which is generated through C(sp³)–H activation of its methyl group.[2d,6]

Our research efforts have been focused on developing a class of ligands that undergo C(sp²)–H activation during the formation of the active catalytic iridium species. Specifically, we have developed THQphos (1,2,3,4-tetrahydroquinoline phosphoramidite),[7] BHPphos (*N*-benzhydryl-*N*-phenyldinaphthophosphoramidite),[8] and NHC (N-heterocyclic carbene)[9] ligands for the Ir-catalyzed asymmetric allylic substitution reactions (**Figure 1**). This class of chiral ligands exhibits unique performance characteristics with respect to selectivity control and substrate scope. Herein we highlight the evolution of these ligands with an emphasis on their applications in Ir-catalyzed allylic substitutions with various nucleophiles.

2. Chiral Ligand Design

The first iridium-catalyzed allylic substitution was reported by Takeuchi and Kashio in 1997.[10] The allylic substitution reactions of allylic acetates with sodium malonates proceeded with iridium complexes generated in situ from $[Ir(cod)Cl]_2$ and various phosphites. It was also observed that utilization of the better π-acceptor $P(OPh)_3$ as ligand resulted in enhanced reactivity and favored the formation of branched products. In 2002, Helmchen and co-workers investigated the possible active species and found that **K1**, generated by mixing $[Ir(cod)Cl]_2$ and $P(OPh)_3$, is unreactive.[11] Upon addition of $NaCH(CO_2Me)_2$ and $P(OPh)_3$ to **K1**, complex **K2** is formed via activation of the ortho C(sp²)–H bond of one of the phenyl groups of $P(OPh)_3$ (**Scheme 1**, Part (a)). Subsequent dissociation of $P(OPh)_3$ from **K2** delivers the catalytically active species. Based on these early findings, we developed a series of binaphthol-derived, P,C(sp²)-coordination phosphoramidite ligands, as exemplified by THQphos[7] and BHPphos,[8] which incorporate chiral elements. Later on, structurally distinct NHCs, bearing an N-aryl group at the ortho position (e.g., the D-camphor-derived NHC[9b]) were found to be suitable ligands for iridium-based catalytic systems following the same C(sp²)–H activation mode (Scheme 1, Part (b)).[9]

3. Mechanistic Studies

Among THQphos-type ligands,[7] (R,R_a)-Me-THQphos (**L1b**) outperforms in most cases. For example, its cinnamyliridium complex, **K3**,[7b] was prepared following the procedure developed by Helmchen and co-workers.[12] It is worth noting that an exclusive exo isomer was formed at the very beginning; however, after equilibration, a 4:1 mixture of exo and endo isomers was finally isolated (**Scheme 2**, Part (a)). Using **K3** in the allylic alkylation reaction of sodium dimethyl malonate with cinnamyl methyl carbonate led to comparable results with those obtained with the in situ generated catalyst, which supported the proposal that the (π-allyl)–Ir complex **K3** is the catalytically active species (Scheme 2, Part (b)). Moreover, the crystal structure of **K3** showed that: (i) The iridacycle complex is formed via a C(sp²)–H bond insertion of the phenyl group rather than C(sp³)–H bond activation of a methyl group in the ligand. (ii) Compared with the Ir-C(1) bond of **K3**, the Ir-C(3) bond is longer by 0.173 Å. The strong trans influence of the phosphorus atom, as well as the stabilizing ability of the attached phenyl ring, render C(3) more electropositive than C(1). As a result, nucleophiles prefer to attack at the C(3) position to afford highly branched allyl alkylation products. (iii) Since the *Re*-face of C(3) is well shielded by the chiral pocket of the ligand, nucleophilic substitution

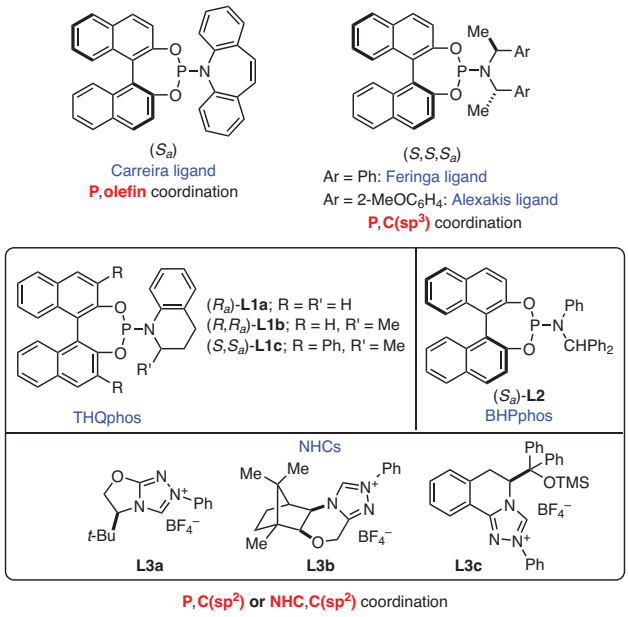
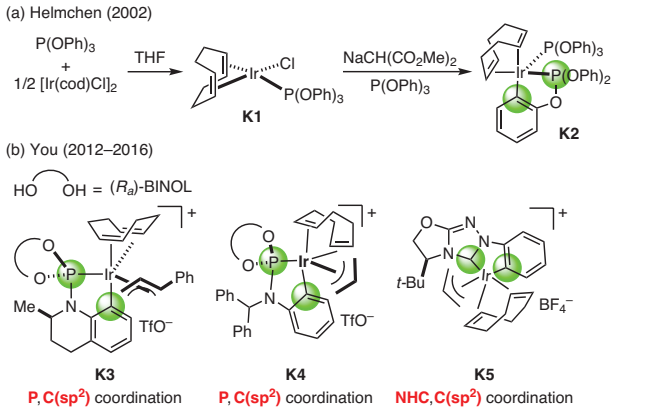


Figure 1. Representative Ligands for the Ir-Catalyzed Asymmetric Allylic Substitution Reactions. *(Ref. 7–9)*



Scheme 1. Representative Iridium Complexes Formed by C(sp²)–H Activation of Ligands. *(Ref. 7b,8,9d,11)*

would occur from the *Si*-face to give the *R* configuration of the branched product. Compared with Ir complexes derived from Feringa-type ligands, **K3** has a bigger pocket for the allyl ligand, thus permitting a good tolerance of sterically bulky substrates. One possible explanation for the observed high enantioselectivity is that the kinetically favorable exo form of **K3** could be captured by nucleophiles prior to π–σ–π interconversion. The absolute configuration of the chiral products is determined by the BINOL scaffolds. Interestingly, the reactions with THQphos and the Feringa ligand derived from the same configuration of BINOL afford the products with opposite absolute configurations. Further investigations disclosed that the same C(sp^2)–H activation mode operates in the iridium complexes derived from BHPphos and the NHCs bearing an *N*-Ar group.[8,9] These three types of ligand have found wide applications in iridium-catalyzed asymmetric allylic substitution reactions.

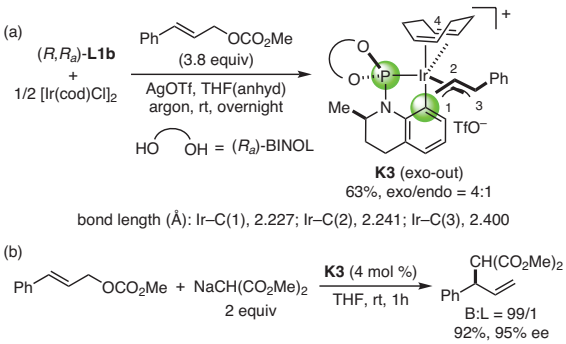
4. Ir-Catalyzed Asymmetric Allylic Substitutions with Carbon Nucleophiles

4.1. Enolates

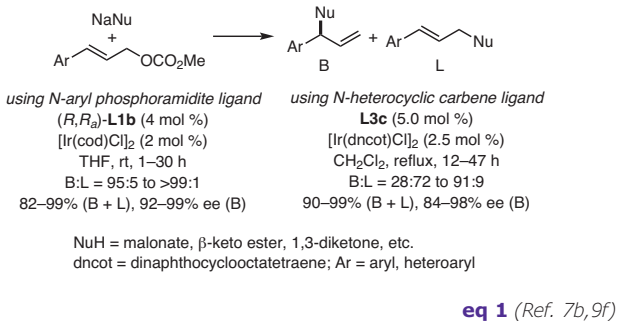
In 2012, our group introduced a series of *N*-aryl phosphoramidites, such as THQphos and BHPphos, as ligands for the iridium-catalyzed asymmetric allylic alkylation of sodium dimethyl malonates.[7b] (R,R_a)-Me-THQphos (**L1b**) proved to be the optimal ligand, with the corresponding reactions giving good yields and excellent regio- and enantioselectivities. It is worth noting that ortho-substituted cinnamyl carbonates, which are typically unfavored substrates in iridium catalysis with Feringa-type ligands, were well accommodated in this reaction.[7b] Recently, a chiral dihydroisoquinoline-type NHC was used as ligand for the same transformation, resulting in excellent enantioselectivity but moderate regioselectivity being achieved for a wide range of allylic substrates.[9f] Preliminary mechanistic studies have suggested that the key active species results from the same C(sp^2)–H activation mode. The modest regioselectivity is presumed to be due to electronic effects, since the phosphorus in THQphos is a stronger electron donor than an NHC (**eq 1**).[7b,9f]

An iridium-catalyzed asymmetric allylic alkylation of cyclic β-keto esters has been reported by Stoltz and co-workers.[13] The corresponding α-quaternary β-keto ester products bearing vicinal stereocenters were obtained in good yields and excellent stereoselectivities. Although diastereoselective control by a catalyst is problematic within this domain, the iridium complex derived from (R,R_a)-Me-THQphos (**L1b**) resulted in diastereoselectivities (>20:1 dr) that are much greater than those from other privileged ligands (1:1 or 1:2 dr in each case).[13,14] Stoltz's group extended the use of the Ir/**L1b** catalytic system further to address asymmetric transformations involving the more challenging acyclic β-keto esters.[15] Employing LiO*t*-Bu as base, a wide variety of nucleophiles—bearing substituents such as alkyl, allyl, propargyl, heteroaryl, and ketone functionalities at the α position—were tolerated, affording the expected products in excellent yields and selectivities. When an electron-withdrawing group was incorporated into the cinnamyl carbamate substrates, a diminished regioselectivity was observed. When the logarithm of the B/L value was plotted vs the corresponding Brown σ^+ constant, a linear relationship was revealed, which corresponded well with the experimental observations.

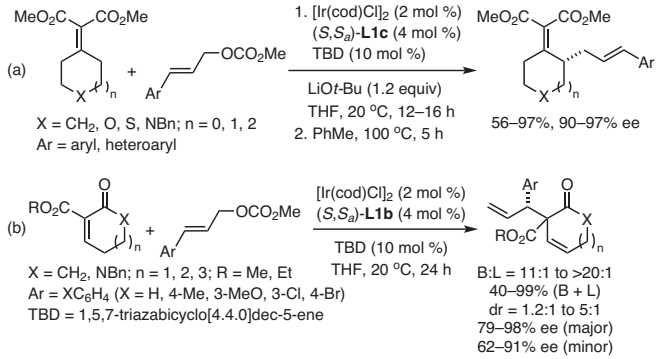
Stoltz's group later employed enolates derived from α,β-unsaturated malonates or α,β-unsaturated keto esters as substrates, and found that sequential α-alkylation and Cope rearrangement afforded linear γ-alkylated products in good yields and with excellent ee's.[16] (S,S_a)-diPh-THQphos (**L1c**) was identified as the optimal ligand for α-alkylation (**Scheme 3**, Part



Scheme 2. Synthesis and Application of Iridium–THQphos Complex **K3**. *(Ref. 7b)*



eq 1 *(Ref. 7b,9f)*

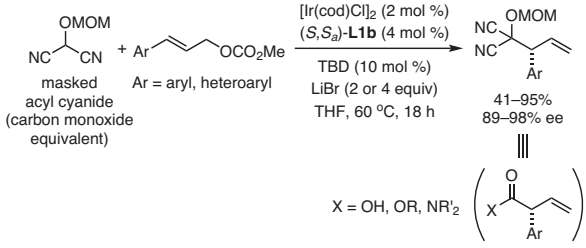


Scheme 3. Ir-Catalyzed Asymmetric Allylic γ-Alkylation of α,β-Unsaturated Malonates and Keto Esters. *(Ref. 16)*

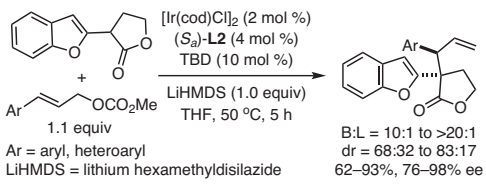
(a)).[16] The Cope rearrangement occurred with a high degree of chirality transfer via a chair-like transition state. However, the reactions of endocyclic α,β-unsaturated β-keto esters only gave modest dr values (Scheme 3, Part (b)). Moreover, the pure diastereomers from the α-alkylation were isolated and subjected to the Cope rearrangement individually. The major isomer delivered the product in a relatively better yield through a chair-like transition state, while the minor isomer furnished a much lower yield via a boat-like transition state.

Alkyl-substituted allylic electrophiles are challenging substrates in iridium-catalyzed asymmetric allylic substitutions. Nevertheless, the Ir-catalyzed asymmetric allylic alkylation of β-keto esters with crotyl derivatives has been achieved by Stoltz and co-workers.[17] Due to the counterion effect, crotyl chloride provided better regioselective control than crotyl carbonate. With diPh-THQphos (**L1c**) as ligand, the corresponding alkylated products were furnished in good-to-excellent yields and selectivities. The same laboratory later reported that masked acyl cyanide reagents were suitable nucleophiles in the asymmetric allylic alkylation catalyzed by the iridium catalyst derived from (*S*,S_a)-**L1b**. This led to vinylated α-aryl carbonyl derivatives with high enantioselectivity (**eq 2**).[18]

Bos and Riguet reported that benzofuran-substituted γ-lactones are competent substrates in Ir-catalyzed asymmetric allylic substitutions in the presence of strong base such as LiHMDS that is required to generate the corresponding enolates. By using BHPphos (S_a)-**L2** as the optimal ligand, 1,5-hexadienes were delivered in good-to-excellent yields and selectivities (**eq 3**).[19] Interestingly, a heteroaromatic Cope rearrangement of the resultant 1,5-hexadienes followed by rearomatization permitted the efficient alkylation of the benzofuran ring at the 3 position.



eq 2 *(Ref. 18)*



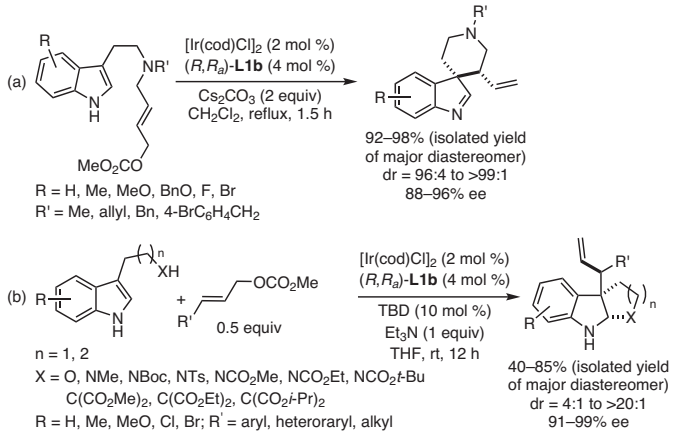
eq 3 *(Ref. 19)*

4.2. Electron-Rich Arenes

4.2.1. Indoles

Apart from soft carbon nucleophiles, aromatic compounds are also suitable substrates in iridium-catalyzed asymmetric allylic substitutions with ligands capable of undergoing C(sp²)–H activation. We reported the earliest examples back in 2009, when (*R*,R_a)-**L1b** and its analogues were synthesized and applied in the Ir-catalyzed asymmetric Friedel–Crafts reaction of indoles with allylic carbonates.[7a] High levels of regioselectivity for the branched alkylation product as well as high levels of enantioselectivity were observed. In particular, **L1b** exhibited superior performance to the Feringa-type ligands when ortho-substituted cinnamyl carbonates were used. When reacting with substrates bearing an allylic carbonate side chain at the C(3) position of indoles, an intramolecular nucleophilic attack at the more-substituted C(3) of indoles took place resulting in a spirocyclic product.[20] Systematic evaluation of various reaction parameters established that the iridium catalyst generated in situ from $[Ir(cod)Cl]_2$ and **L1b** affords the desired dearomatized products bearing all-carbon quaternary stereogenic centers in high yields and with remarkably high diastereo- and enantioselectivity (up to >99:1 dr and 97% ee) (**Scheme 4**, Part (a)).[20] The resultant spiroindolenines were amenable to further elaboration without loss of enantiomeric purity. Subsequently, an unprecedented Ir-catalyzed asymmetric allylic dearomatization–*N*-Bn iminium migration sequence was unlocked when the electronic property of the tether was tuned.[21] Synthesis of chiral tetrahydro-β-carbolines was achieved in a highly enantioselective fashion with readily accessible **L2** as the chiral ligand. An aza-spiroindolenine intermediate was proposed and detected via in situ infrared spectroscopy.

Interestingly, by employing symmetric bis(indol-3-yl)-substituted allylic carbonates as substrates, the desymmetrizing allylic dearomatization of indoles was achieved.[22] The spiroindolenines containing three contiguous stereogenic centers



Scheme 4. Ir-Catalyzed Asymmetric Allylic Alkylation of Indole Derivatives. *(Ref. 20,24)*

were obtained as single diastereoisomers with exceptionally high enantioselectivity (up to 99% ee). The combination of $[Ir(dbcot)Cl]_2$ (dbcot = dibenzocyclooctatetraene)[23] and (S,S_a)-**L1c** exerted crucial influence on the reaction outcome. When the products were subjected to a catalytic amount of *p*-toluenesulfonic acid in refluxing THF, a ring expansion of a six- to a seven-membered-ring occurred to deliver hexahydroazepino[4,5-*b*]indoles with high diastereoselectivity. The configuration of the migrating carbon stereocenter was reversed, indicating a possible stepwise migration mechanism involving a free vinyliminium intermediate.

The intermolecular allylic dearomatization of indoles was also explored using the iridium catalyst derived from (R,R_a)-**L1b**. Allylic substitution with allylic carbonates was selective for the branched product and yielded polycyclic indolines possessing contiguous tertiary and all-carbon quaternary stereocenters in a highly chemo-, regio-, diastereo-, and enantioselective fashion.[24] Tryptophols, tryptamines, indoles with a carbon nucleophile side chain, and tryptophan derivatives were demonstrated to be suitable substrates (Scheme 4, Part (b)).

4.2.2. Pyrroles

Similarly, the $[Ir(cod)Cl]_2$–(R,R_a)-**L1b** complex catalyzed the asymmetric allylic dearomatization of pyrroles tethered with an allylic carbonate. With THF as solvent, six-membered, spiro-2*H*-pyrrole derivatives were obtained in good yields with high levels of regio-, diastereo- and enantioselectivity (**Scheme 5**, Part (a)).[25] Further transformations of the resultant products afforded diverse pharmaceutically important spirocycles. When (R_a)-**L2** was used instead of (R,R_a)-**L1b** and the tether between the pyrrole ring and the allylic carbonate moiety was shortened by one CH_2 group, a sequential dearomatization–in situ migration of the substituent from the C(2) to the C(3) position of the pyrrole ring occurred in a fashion similar to that of indoles.[21] In combination with DFT calculations, it was found that the *N*-Bn linkage enhances the migratory aptitude of the methylene group. Employing (R_a)-**L2** again and switching the substrates to the gem-diester-tethered analogues afforded stable five-membered-ring spiro-2*H*-pyrroles in good yields with excellent diastereo- and enantioselectivity.[8] Upon treatment with a catalytic amount of TsOH, stereospecific allyl migration took place smoothly, yielding the enantioenriched polycyclic pyrrole derivatives with preserved ee's. It is worth highlighting that the Ir-complex derived from $[Ir(cod)Cl]_2$ and (R_a)-**L2** is critical for excellent control of both diastereo- and enantioselectivity. As a consequence, the corresponding π-allyl iridium complex was prepared and characterized, further confirming the C(sp^2)–H activation mode of the ligand.[8]

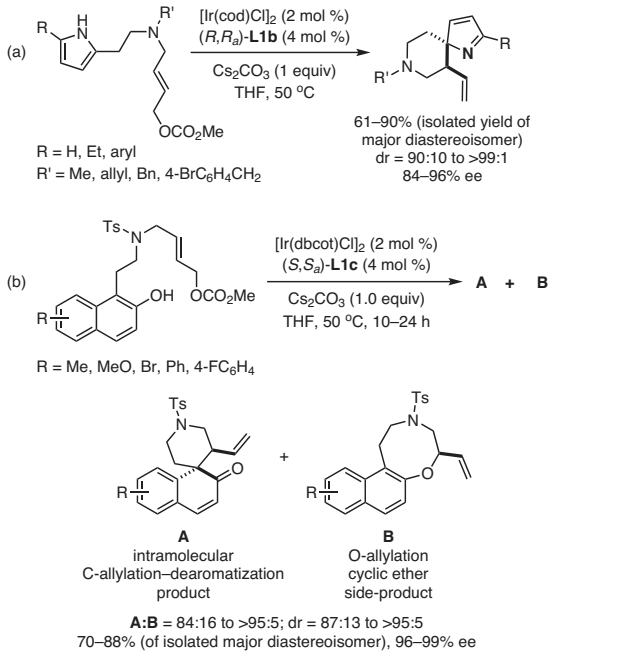
4.2.3. Naphthols

α-Substituted β-naphthols are challenging substrates in the Ir-catalyzed asymmetric allylic dearomatization, since etherification could be a facile competing reaction. Gratifyingly, by using $[Ir(dbcot)Cl]_2$ as the iridium precursor and (S,S_a)-diPh-THQphos (**L1c**), the allylic etherification pathway was largely inhibited. The dearomatized spironaphthalenones bearing two contiguous stereogenic centers were furnished with good-to-excellent chemo-, diastereo-, and enantioselectivity (Scheme 5, Part (b)).[26] It is believed that the high C/O alkylation ratio might be caused by the restriction on ring size, as formation of six-membered rings is more facile than that of eight-membered rings. It is worth noting that superior selectivities were achieved when the nitrogen atom was protected with electron-deficient and sterically hindered groups.

5. Ir-Catalyzed Asymmetric Allylic Substitutions with Nitrogen Nucleophiles

5.1. Aliphatic Amines and Arylamines

In 2016, our research laboratory investigated the Ir-catalyzed asymmetric intermolecular allylic amination using various nitrogen nucleophiles—namely, anilines, indolines, benzylamines, and 2-vinylanilines—in the presence of (S,S_a)-**L1c**.[7c] To our delight, we observed a significant advantage over the Feringa ligand with respect to regio- and enantioselective control when challenging ortho-substituted cinnamyl carbonates were employed as substrates. Remarkably, the utilization of either (S,S_a)-**L1c**, its diastereomer (R,S_a)-**L1c**, or a mixture of equal amounts of the two resulted in the same reaction outcome, indicating that the stereocenter of 2-methyl-THQ was not essential in this case. X-ray crystallographic analysis of the catalyst complex further supported the proposal that the active iridacycle was generated via C(sp^2)–H bond activation of the THQ moiety of the ligand.[7c]



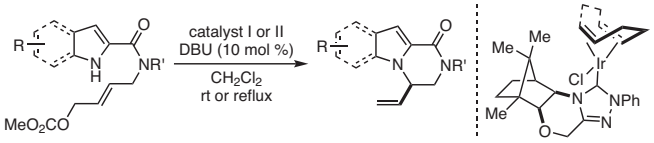
Scheme 5. Ir-Catalyzed Asymmetric Allylic Alkylation of (a) Pyrrole and (b) Naphthol Derivatives. *(Ref. 25,26)*

5.2. Nitrogen-Containing Heterocycles

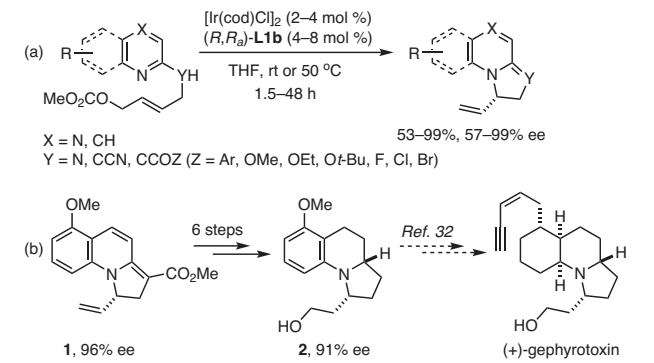
Our research efforts had demonstrated that indoles and pyrroles with electron-donating or electron-neutral groups attached to the core would undergo a dearomatization–migration reaction sequence. However, when an electron-withdrawing group is installed at the C(2) position, a highly enantioselective intramolecular allylic amination of indoles and pyrroles is enabled by an iridium complex generated in situ from $[Ir(cod)Cl]_2$ and L-*tert*-butylalaninol-derived triazolium salt (**L3a**), first introduced by the research group of Enders.[9a] For the first time, chiral NHC carbenes were demonstrated as suitable ligands for Ir-catalyzed asymmetric allylic substitutions.[9d] Preliminary mechanistic studies suggested that C(sp²)–H activation takes place at the ortho C(sp²)–H bond of the N-aryl group of the ligand. Later, Ir–**L3b** prepared from $[Ir(cod)Cl]_2$ and D-camphor-derived **L3b**, was successfully applied in the same transformation. In both cases, the corresponding indolopiperazinones and piperazinones were furnished in good yields and high enantioselectivities (**eq 4**).[9e] To further broaden the substrate scope for pyrroles, the iridium catalysts derived from chiral phosphoramidites were exploited. Particularly, the utilization of THQphos (**L1b** or **L1c**) significantly improved the enantioselectivity of the reactions involving bromo-substituted pyrroles.[27]

C(sp²)–H activation ligands are also capable of promoting asymmetric allylic dearomatization reactions with nitrogen-containing, electron-deficient heteroarenes.[28–30] With (R,R_a)-**L1b** as the optimal ligand, a variety of heterocycles including pyrazines, quinolines, isoquinolines, benzoxazoles, benzothiazoles, and benzimidazoles underwent asymmetric allylic dearomatization reactions smoothly, affording highly functionalized products in good-to-excellent yields with excellent enantioselectivity (**Scheme 6**, Part (a)).[28,29] In accordance with well-established Ir-catalysis pathways, the allylic carbonate reacts first with the chiral iridium catalyst. The liberated methoxide anion abstracts the α proton in the substrate, rendering the N-attack feasible due to delocalization of the negative charge. Alternatively, N-alkylation occurs prior to deprotonation. As supporting evidence, and under certain conditions, the intermediate resulting from direct N-attack has been captured in situ and isolated. The synthetic utility of this method has been demonstrated by a facile synthesis of compound **2**,[29] which can be easily converted into (+)-gephyrotoxin[31] through known reaction steps[32] (Scheme 6, Part (b)).

The reaction was then extended to the more challenging hydroxyquinoline derivatives.[33] However, the frequently used phosphoramidites—including the Feringa and the Alexakis ligands, Me-THQphos, and BHPphos—failed to give satisfactory results. However, to our great delight, the anticipated intramolecular allylic alkylation reactions of 5- and 7-hydroxyquinolines were achieved with good-to-excellent yields and enantioselectivities with the iridium catalyst generated in situ from $[Ir(dbcot)Cl]_2$ and the Enders NHC (**L3a**) (**eq 5**).[33] Theoretical calculations supported the hypothesis that the aromatic character of the two consecutive rings of the hydroxyquinoline was weakened. Remarkably, performing the reaction directly in air and using undistilled THF as solvent led to comparable results, further highlighting the robustness of Ir–NHC catalysis. Based on this method, a key intermediate (a phenol variant of *ent*-**2**) for the synthesis of (+)-gephyrotoxin was delivered in only two steps from the product of the reaction. This method is also a rare example of allylic chlorides being viable precursors in the Ir-catalyzed asymmetric allylic substitution reaction.



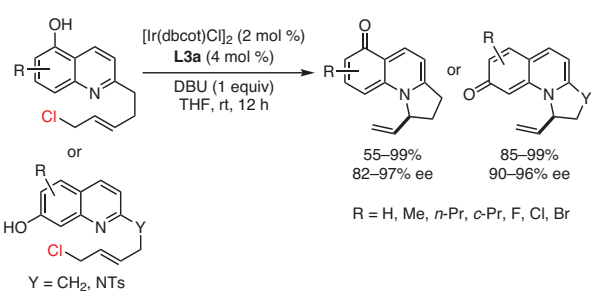
eq 4 *(Ref. 9d,9e)*



Scheme 6. (a) The Iridium-Catalyzed Asymmetric Allylic Dearomatization of Nitrogen-Containing Heterocycles and (b) Its Application to a Formal Synthesis of (+)-Gephyrotoxin, a Naturally Occurring Histrionicotoxin. *(Ref. 28,29)*

6. Ir-Catalyzed Asymmetric Allylic Substitutions with Oxygen Nucleophiles

The catalytic, enantioselective construction of chiral N,O-heterocycles remains a challenging task in organic synthesis.



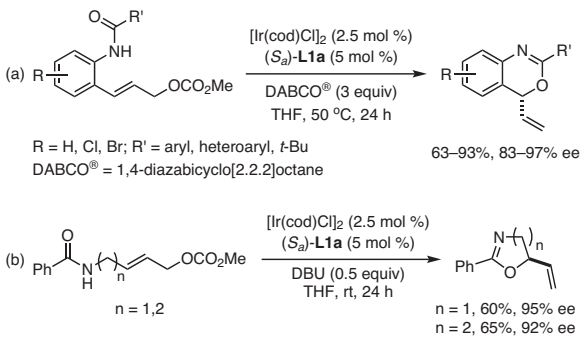
eq 5 *(Ref. 33)*

In 2014, Feringa and co-workers reported an unprecedented synthesis of such scaffolds through a highly efficient iridium-catalyzed intramolecular allylic substitution with the amide group providing the oxygen nucleophile.[34] By employing the catalyst generated from $[Ir(cod)Cl]_2$ and (S_a)-**L1a**, Feringa's team was able to prepare differentially substituted oxazolines, oxazines, and benzoxazines in good-to-excellent yields and with high enantiomeric purity (**Scheme 7**).[34]

7. Conclusion and Outlook

Chiral phosphoramidite and NHC ligands capable of undergoing C(sp^2)–H activation have been widely employed in Ir-catalyzed asymmetric allylic substitution (AAS) reactions. Among them, THQphos and BHPphos participate in P,C(sp^2) coordination with the Ir center. As a result of both electronic and steric influences, high levels of branched regioselectivity and asymmetric induction are generally observed. Intriguingly, the newly developed catalysts tolerate well ortho-substituted cinnamyl carbonates, which were challenging substrates in prior similar studies. The catalysts also display remarkable diastereoselective control when prochiral nucleophiles are employed. Furthermore, the C(sp^2)–H activation mode has been extended to structurally distinct N-heterocyclic carbene ligands, whereby the active iridium catalyst results from a bidentate NHC,C(sp^2) coordination. With NHC as the chiral ligand, Ir-catalyzed asymmetric allylic substitution reactions can occur in a highly enantioselective fashion. However, regioselective control is still problematic for the intermolecular variants. Nevertheless, NHCs show significant advantages in some instances, as exemplified by the asymmetric allylic alkylation of challenging hydroxyquinolines.

Despite considerable progress, the substrate scope for currently available methods is still limited to commonly used nucleophiles, such as enolates or aromatic compounds, and activated allylic electrophiles. In this regard, expanding the substrate scope is an important goal in our current investigations. On the other hand, efforts will also be directed to exploring structurally distinct ligands capable of C(sp^2)–H activation, as well as exploring new types of asymmetric reactions beyond the Ir-catalyzed AAS.[35]



Scheme 7. Feringa's Ir-Catalyzed Intramolecular Asymmetric Allylic Substitution Reaction with Amide Oxygen Nucleophiles. *(Ref. 34)*

8. Acknowledgments

We thank the National Key R&D Program of China (2016YFA0202900), National Natural Science Foundation of China (91856201, 21572252, 21821002), Strategic Priority Research Program (XDB20000000) and Key Research Program of Frontier Sciences (QYZDY-SSW-SLH012) of the Chinese Academy of Sciences, and the Science and Technology Commission of Shanghai Municipality (16XD1404300) for their generous financial support.

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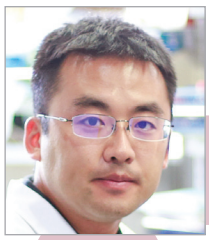
Recent Advances in Sulfuration Chemistry Enabled by Bunte Salts


Prof. M. Wang


Ms. Y. Li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Keywords. Bunte salt; *S*-aryl(alkyl) thiosulfate sodium salts; sodium thiosulfate; sulfuration reagent; sulfide; sulfur-containing heterocycles; dithiocarbamates; thiophosphates; metal nanoparticles; glycosyl.

Abstract. Bunte salts are easy-to-handle crystalline solids, even when incorporating highly lipophilic organic moieties, and generally have little-to-no odor. Due to the unique properties of Bunte salts, they have been frequently utilized in the synthesis of sulfides, sulfur-containing heterocycles, thiophosphates, other compound classes, and metal nanoparticles. This short review focuses on recent applications of Bunte salts in the synthesis of sulfur-containing compounds with particular emphasis on the synthesis of sulfides.

Outline

1. Introduction

Alkyl and aryl thiosulfate sodium salts are known as Bunte salts, after Hans Bunte who first reported them in 1874.[1] He prepared the first such salt by reactiing ethyl bromide with sodium thiosulfate ($Na_2S_2O_3$) to yield *S*-ethyl thiosulfate sodium salt as a crystalline solid. Bunte salts, as the easy-to-handle crystalline solids, generally have little-to-no odor.[2–3] The sulfur trioxide group in Bunte salts could be viewed as an electron-withdrawing group preventing strong coordination of the sulfur atom to metals. Moreover, we obtained the crystal structure of a Bunte salt in 2015 and found that its sulfur–sulfur bond is longer than the traditional S–S bond, which may be activated easily.[4] Over the past few years, enormous efforts have been devoted to developing synthetic methodologies for the application of Bunte salts. The present article concisely reviews recently reported methodologies for the application of Bunte salts, with particular emphasis on the synthesis of sulfides. The presentation is organized according to the structures of the reaction partners of Bunte salts.

2. Preparation of Bunte Salts

2.1. Alkyl Bunte Salts

Alkyl Bunte salts have traditionally and conveniently been prepared by reaction of the inexpensive and odorless sodium thiosulfate ($Na_2S_2O_3$) with alkyl halides.[5–8] More recently, various modifications of the reaction conditions have been developed for

a diversity of alkyl halides. Both primary and secondary halides are compatible with the transformation, and the desired Bunte salt products are obtained in generally excellent yields.

2.2. Aryl Bunte Salts

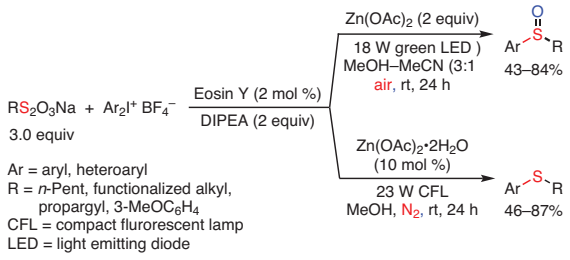
Janeba and co-workers reported a novel and facile route to polysubstituted aryl and heteroaryl Bunte salts by reaction of aromatic thiocyanates with sodium sulfite.[9] Their synthesis could be conducted under catalyst-free and room temperature conditions to generate the desired Bunte salts in good yields. Monosubstituted thiocyanatobenzothiazole and polysubstituted thiocyanatopyrimidines, which contain labile hydrogens such as NH_2 and OH, were compatible with the reaction conditions.

A year later, Reeves's group disclosed the first direct and general method for the synthesis of a variety of aryl, heteroaryl, and vinyl Bunte salts in 66–89% yields.[8] The approach involves a Cu(I)-catalyzed reaction of the widely available halide precursors with sodium thiosulfate (1.5 equiv) in DMSO at 80 °C for 2–6 h. It is worth noting that, in the case of vinyl halides, the geometry of the carbon–carbon double bond was preserved in the reaction. This synthetic method is currently one of the most efficient routes to such Bunte salts because of the wide availability and broad compatibility of the halide starting materials.

In addition to the above strategies, several other original methods have been developed for the synthesis of aryl Bunte salts. For example, aryl Bunte salts were obtained by sulfonylation of aryl thiols with *N*-pyridinium sulfonic acid ($C_5H_5NSO_3H$)[10] or with chlorosulfonic acid ($ClSO_3H$),[11] and by reaction of sodium sulfite with aryl disulfides (or aryl sulfenyl chlorides).[12]

2.3. Glycosyl Bunte Salts

Very recently, glycosyl Bunte salts (*S*-glycosyl thiosulfates) have been developed by Shoda and co-workers as a new class of synthetic intermediates in carbohydrate chemistry[13] The one-pot reaction is carried out in H_2O–CH_3CN, and it involves the direct condensation of unprotected mono-, di-, and polysaccharides with $Na_2S_2O_3$ in the presence of 2-chloro-1,3-dimethylimidazolinium chloride (DMC) as dehydrating agent. Glucose, allose, xylose, mannose, rhamnose, and galactose all underwent this mild reaction efficiently, giving rise to the corresponding glycosyl Bunte salts in up to 94% yields. The utility of these *S*-glycosyl thiosulfates was then demonstrated by converting β-D-glucosyl Bunte salt into 1-thio-β-D-glucose, glucosyl disulfide, 1,6-anhydroglucose, and ethyl α-D-glucopyranoside.



Scheme 1. Photocatalytic Sulfoxide and Sulfide Formation through Controlled Sulfoxidation and Sulfenylation of Diaryliodonium Salts. *(Ref. 14)*

3. Bunte Salts for the Synthesis of Sulfides

The main application of Bunte salts is in the synthesis of sulfides, since these salts are stable, odorless, and green when compared with thiols as substrates.

3.1. Coupling through C–X Bond Cleavage

In 2017, we developed a controlled sulfoxidation of diaryliodonium salts with Bunte salts in air and under photocatalytic conditions in which dual electron- and energy-transfer as well as single-electron-transfer processes were involved (**Scheme 1**).[14] When the reaction was carried out under a nitrogen atmosphere, sulfenylation products were conveniently obtained. This approach could be used in the late-stage modification of pharmaceuticals and sugar derivatives, which were highly compatibile with the reaction conditions.

In the proposed mechanism, the excited-state catalyst Eosin Y* (EY*) reacts with the diaryliodonium salt via a single-electron transfer process to generate an aryl radical. The aryl radical then couples with the Bunte salt to afford a sulfide radical. The electron-transfer process between the sulfide radical (ArS•R) and $EY^{+\bullet}$ provides the sulfide product (ArSR) and regenerates the photosensitizer EY. In the presence of air, an energy-transfer process takes place between $^3O_2$ and EY* to generate $^1O_2$, the key active oxygen species, which was confirmed by fluorescent quenching experiments. Reaction of the in situ generated sulfide (ArSR) with $^1O_2$ forms a persulfoxide intermediate (R(Ar)-S^+–O–O^-), which is stabilized by $Zn(OAc)_2$. Reaction of the persulfoxide with a second in situ generated sulfide leads to two molecules of the observed sulfoxide product (ArS(=O)R).

In 2014, our group developed a Pd-catalyzed double C–S bond forming reaction for the synthesis of aryl alkyl sulfides. Aryl and heteroaryl iodides efficiently reacted with alkyl chlorides to provide the desired sulfides in excellent yields. In this transformation, $Na_2S_2O_3{\cdot}5H_2O$ was employed as an environmentally friendly and odorless sulfur atom source to generate the Bunte salt in situ.[15] Late-stage modification of pharmaceutical molecules was also achieved to demonstrate the synthetic potential of this protocol.

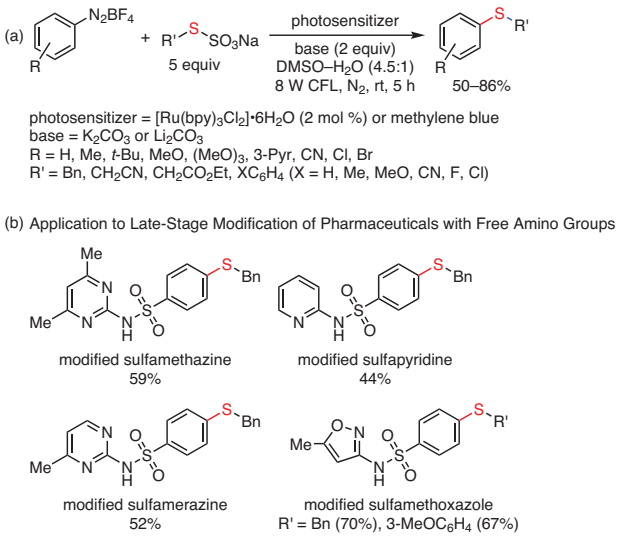
3.2. Coupling through C–N Bond Cleavage

An analogous Cu-catalyzed double C–S bond forming reaction has been developed for the synthesis of aryl alkyl sulfides from aromatic amines and alkyl halides via in situ generated Bunte salts.[16] Heterocyclic substrates and active-hydrogen-containing substrates were tolerated in this transformation, which permitted the late-stage sulfuration of functionalized aryl amines, including such interesting amines as sulfamethoxazole, sulfadiazine, and the antitumor drug lenalidomide. Axially chiral (*R*)-(+)-2,2′-diamino-1,1′-binaphthalene could also be

transformed into the corresponding bis(benzyl sulfide) product without racemation (38% yield, 99% ee), which offers a facile strategy for the synthesis of chiral, sulfur-containing ligands. Moreover, amine derivatives of glucose and amino acids were tolerated in the reaction, hinting at its potential usefulness in bioorthogonal reactions.

Subsequently, we successfully extended this protocol to the Cu-catalyzed reaction of substituted 1-aryltriazenes and alkyl chlorides in water at room temperature and in the absence of any surfactant with the aim of developing an environmentally friendly variant.[17] We were also delighted to discover that the outcome of the reaction was not significantly affected by the addition of such biomolecules as amino acids, nucleosides, oligosaccharides, proteins, and HeLa cell lysates, highlighting again the promise of its potential applications in bioorthogonal studies.

A photocatalytic variant involved reacting diazonium salts with alkyl or aryl Bunte salts in the presence of $Ru(bpy)_3Cl_2$ (**Scheme 2**).[18] The reaction did not proceed when the Bunte salt was replaced with BnSH or BnSSBn, demonstrating the unique behavior of the Bunte salt in this system. Both alkyl and aryl Bunte salts were well-tolerated in this transformation. Both an oxidative and a reductive quenching process were possible in the transformation. At first, the Ru(II) catalyst is activated by visible light to generate $^{3*}[Ru(bpy)_2(bpy^{\bullet-})Cl_2]$, which undergoes an oxidative quenching process with the diazonium salt to form Ru^{3+} and an aryl diazonium radical ($Ar–N^{\bullet}\equiv N\ BF_4^-$). Bunte salt $R'SSO_3Na$ releases an electron to the solvent and affords a thiosulfate radical cationic species, which couples with the aryl diazonium radical to provide the sulfide products. The solvent shuttles an electron to Ru^{3+} and regenerates the Ru(II) catalyst. A similar catalytic cycle is proposed to operate in the reductive quenching process.



Scheme 2. Photocatalytic Sulfide Formation from Diazonium Salts and Alkyl and Aryl Thiosulfates and Its Application to the Late-Stage Modification of Pharmaceuticals. *(Ref. 18)*

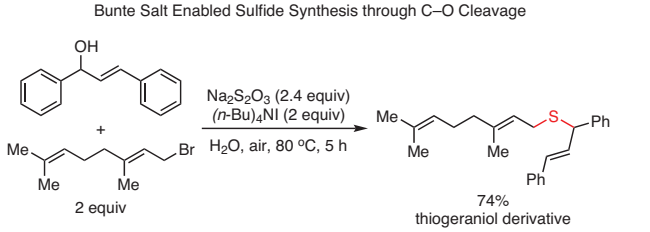
An interesting extension of this approach has been disclosed by Jiang, Yi, and co-workers.[19] In this instance, aromatic primary amines were subjected to an efficient, Cu-catalyzed Sandmeyer-type monofluoromethylthiolation by employing the Bunte salt sodium *S*-(fluoromethyl)sulfurothioate ($FH_2CS–SO_2–ONa$). The intermediate aryldiazonium salts were generated in situ using *tert*-butyl nitrite (*t*-BuONO) and a variety of aryl and heteroaryl primary amines, leading to the desired sulfides in moderate-to-good yields (43–77%). The late-stage monofluoromethylthiolation of biologically relevant sulfonamides and the gastroprokinetic agent mosapride were also achieved in acceptable isolated yields (41–73%). Interestingly, Bunte salt $FH_2CS–SO_2–ONa$ was also utilized in the monofluoromethylthiolation of substituted aryl thiols under similar conditions to provide the corresponding aryl monofluoromethyl disulfides in 58–78% isolated yields.

3.3. Coupling through C–O Bond Cleavage

An efficient, catalytic, and metal-free sulfide synthesis from allyl or propargyl alcohols and organic halides was reported by Chu et al.[20] The reaction takes place at 80 °C in air and in aqueous medium in the presence of two equivalents of tetra-*n*-butylammonium iodide (TBAI), leading to the formation of the two C–S bonds of the sulfide. TBAI plays the dual role of phase-transfer agent and a hydrolysis promoter of the Bunte salt initially formed from the halide. The hydrolysis gives rise to a key intermediate mercaptan species, which then combines with the carbocation derived from the allylic or propargylic alcohol to provide the final sulfide product. A wide variety of functionalized terminal and internal allylic alcohols as well as propargylic alcohols and organic halides proved compatible with the eco-friendly reaction conditions. These authors also demonstrated the value of their novel protocol by sulfurating important molecules (**eq 1**),[20] including sulfur-modified epiandrosterone.

A year later, the same laboratory described the efficient reaction of a wide variety of benzyl alcohols—including diarylmethanol, triphenylmethanol, propynols, and allylic alcohols—and alkyl halide derived Bunte salts in water at 100 °C.[21] Both in situ generated Bunte salts and pre-prepared ones reacted smoothly to provide unsymmetrical sulfides in moderate-to-excellent yields.

Very recently, Ma, Xu, and collaborators developed a scalable, one-pot reaction between alcohols, $Na_2S_2O_3·5H_2O$, and heteroaryl chlorides under catalyst-, additive-, and solvent-free



eq 1 *(Ref. 20)*

conditions at 140 °C.[22] Primary and secondary benzylic alcohols, heteroarylmethanols, and primary aliphatic alcohols were competent substrates, giving rise to 31 desired unsymmetrical heteroaryl sulfides in 16–86% yields.

3.4. Coupling through C–C Bond Cleavage

An interesting, copper-catalyzed decarboxylative cross-coupling of alkynyl carboxylic acids with Bunte salts for the synthesis of alkynyl chalcogenides has been disclosed by Liu and Yi.[23] A wide range of Bunte salts including benzyl, aryl, and alkyl ones, worked well to furnish the products in moderate-to-good yields. Alkyl Bunte salts provided only moderate yields due to the formation of the disulfide as byproduct. Both (hetero)aryl- and alkylpropiolic acids were suitable partners, affording the desired alkynyl sulfides in good-to-excellent yields. Interestingly, seleno Bunte salts also proved applicable in the reaction, leading to the construction of unsymmetrical alkynyl selenosulfides (**eq 2**).[23]

3.5. Coupling through C–H Bond Cleavage

Two efficient and C(3)-selective protocols for the sulfenylation of 1*H*-indoles[24,25] and 1*H*-pyrrolo[2,3-*b*]pyridine[25] with Bunte salts has been achieved under eco-friendly and metal-free conditions, leading to the corresponding 3-alkyl- and 3-arylthioindoles in moderate-to-high yields. In the first protocol, a stoichiometric amount of tetra-*n*-butylammonium iodide is used, while in the second 20 mol % of elemental iodine is utllized. In the proposed mechanisms of both protocols, the catalytic cycle is initiated by reaction of adventitious water with the Bunte salt (RS–SO_3Na) to form bisulfate (HSO_4^-) and an intermediate thiol species, which is then oxidized by I_2 to the actual thiolating species, RSI. The latter then attacks the 3 position of the indole, giving rise to the observed 3-thioindole products. The usefulness of the second protocol was demonstrated by a facile synthesis (**eq 3**) of methyl 5-methoxy-3-((3,4,5-trimethoxyphenyl)thio)-1*H*-indole-2-carboxylate,[25] a potent tubulin polymerization inhibitor, in 67% isolated yield (after chromatography), in stark contrast to a prior method in which the carboxylate was obtained in only 4% yield. More recently, a very similar mechanism has been proposed for the transition-metal-free and regioselective sulfenylation of 4-anilinocoumarins catalyzed by potassium iodide (20 mol %).[26] This method provides access to 3-alkylthio-4-anilinocoumarins with potential biological activities in moderate-to-excellent yields.

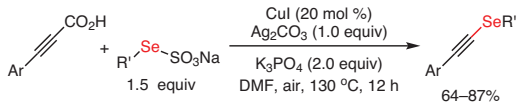
3.6. Reactions with Grignard Reagents and Boronic Acids

Reeves and co-workers developed the reaction of Bunte salts with Grignard reagents as a mild (THF, 0 °C to rt) and general route to sulfides that avoids using air-sensitive and malodorous thiols as starting materials.[8] The reaction is compatible with a broad range of alkyl, aryl, and vinyl Bunte salts and alkyl, (hetero)aryl, vinyl, and alkynyl Grignard reagents and provides the sulfides in 68–99% isolated yields. The authors demonstrated the usefulness of their approach by a straightforward and high yield (82%) synthesis of a combretastatin analogue. It is also worth noting that an alkynyllithium, instead of the corresponding Grignard Reagent, was also effective in the transformation. In 2015, the Cu-catalyzed direct oxidative cross-coupling between boronic acids and Bunte salts for the synthesis of unsymmetrical sulfides was developed by our group (**eq 4**).[27] Silver carbonate and di-*tert*-butyl peroxide (DTBP) were used as the oxidants, and a CO_2 atmosphere was required to suppress formation of the disulfide byproduct. This strategy was readily applied to the late-stage diversification of biologically active molecules. Moreover, the unsymmetrical diaryl sulfide products can undergo an oxidative dehydrogenative cyclization process to provide unsymmetrical dibenzothiophenes (DBTs), which form the core of photoactive compounds and conducting polymers.

3.7. Reaction with Organosilicon Reagents

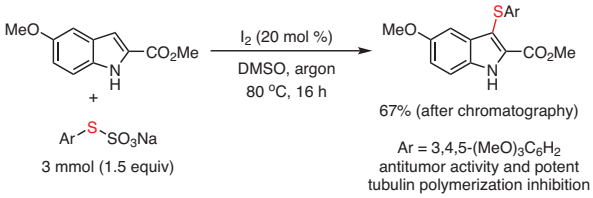
A novel and tunable Pd-catalyzed oxidative cross-coupling of Bunte salts with aryl- or heteroaryl(triethoxy)silanes was recently disclosed by our group (**Scheme 3**).[28] The selectivity

Decarboxylative Cross-Coupling of Seleno Bunte Salts with Propiolic Acids

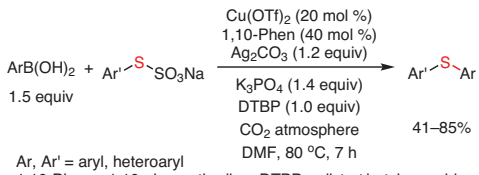


Ar = 4-XC_6H_4 (X = Me, MeO, CF_3, Cl, Br)
R' = Cy, *c*-Hep, $YC_6H_4CH_2$ (Y = H, Me, Cl, Br, CN, NO_2), 2-Me-5-FC_6H_3

eq 2 *(Ref. 23)*

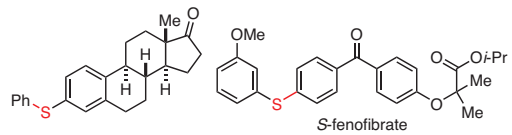


eq 3 *(Ref. 25)*



Ar, Ar' = aryl, heteroaryl
1,10-Phen = 1,10-phenanthroline; DTBP = di-*tert*-butyl peroxide

Noteworthy Application Products:



S-estratrien
(67% from estratrien Bunte salt)

S-fenofibrate
(73% from bis(pinacolato)boron
fenofibrate)

eq 4 *(Ref. 27)*

for Hiyama-type coupling or one-carbon (C1) insertion was controlled by the absence or presence of palladium ligand: Sulfides were afforded under ligand-free conditions, whereas thiol esters were formed with bidentate phosphine ligands under a carbon monoxide atmosphere. Aryl and alkyl Bunte salts were competent reactants in both protocols, providing the corresponding products in moderate-to-excellent yields. PhS-modified estratrien was also obtained by the Hiyama-type coupling reaction. Mechanistic studies of the C1-insertion reaction led to proposing a plausible pathway for thiol ester formation. In this pathway, a chelated $PdCl_2$ species is generated with the bis(diphenylphosphino)alkane ligand. Transmetalation through Cl^- displacement by the Bunte salt is followed by CO insertion. Loss of SO_3, organosilicon transmetalation, and reductive elimination lead to the observed thiol ester product.

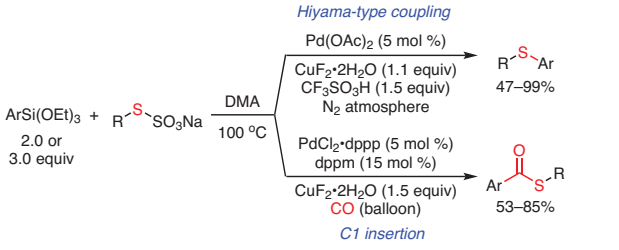
3.8. Sulfuration of Isoxazoles

An interesting, atom- and step-economical, one-pot, three-component reaction cascade employing acetylenic oximes, $Na_2S_2O_3$, and aryl iodides has been reported by Li et al (**eq 5**).[29] The reaction sequence is carried out in air and in 1-(3-cyanopropyl)-3-methylimidazolium chloride ([Cpmim]Cl) ionic liquid under Pd-NHC catalysis. A variety of substituted aryl iodides and acetylenic oximes reacted smoothly with $Na_2S_2O_3$ to afford highly substituted 4-arylthio-1,2-oxazoles in moderate-to-high isolated yields. In contrast, alkyl iodides did not react and, in the case of 1-iodobutane, the starting material was recovered completely. In the proposed mechanism for the reaction cascade, the isoxazole ring is formed first in a trans oxypalladation of the oxime. The resulting palladium–isoxazole intermediate undergoes a chloride–$ArSSO_3^-$ exchange with the Bunte salt generated in situ from the aryl iodide. The final two steps consist of loss of SO_3 and reductive elimination to form the observed isoxazole products.

4. Synthesis of Dithiocarbamates and Thiophosphates

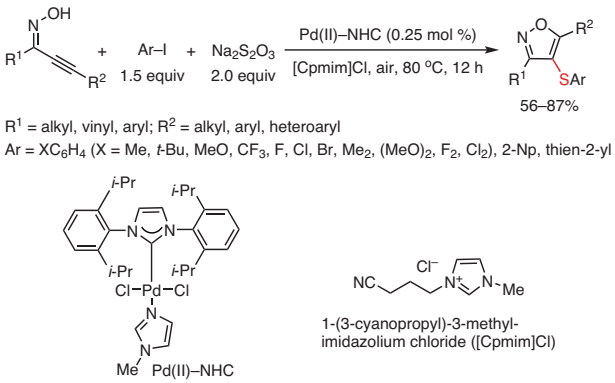
Recently, we developed a novel, efficient, and one-pot method for the construction of dithiocarbamates from Bunte salts, secondary amines, and a thiocarbonyl surrogate (K_2S + $CHCl_3$).[30] A wide range of amines—including 5- and 6-membered cyclic amines, dialkylamines, and methylaniline—reacted with alkyl and aryl Bunte salts in the presence of potassium sulfide and chloroform, furnishing the dithiocarbamates in moderate-to-high isolated yields (**eq 6**).[30] Interestingly, some of the dithiocarbamates exhibited promising selective bioactivity against human histone deacetylase 8 (HDAC8), highlighting the potential of this method for the development of novel HDAC8 inhibitors with a dithiocarbamate core. This stoichiometric process is believed to occur via initial dichlorocarbene (generated from $Ba(OH)_2$ and $CHCl_3$) insertion into the N–H bond of the amine to give a dichloromethylamine intermediate that is readily converted into the corresponding monochloromethylimine cation. Addition of the alkyl or aryl thiol derived from the Bunte salt to this imine cation generates an α-alkyl/arylthioimine cation. Trisulfur radical anion ($S_3^{\bullet-}$)—formed from K_2S in NMP—addition, intramolecular hydrogen atom transfer (HAT), and homolytic S–S bond cleavage (with loss of S_2^-) affords the dithiocarbamate in the presence of base.

Lin, Yan, and co-workers have reported an efficient and eco-friendly NaBr-catalyzed coupling reaction of Bunte salts with phosphonates ($R_2P(O)H$, where R = alkoxy or aryl) in the presence of two equivalents of H_2O_2 as the oxidant and AcOH as additive.[31] The corresponding thiophosphates were obtained in 40–92% yields by a pathway that is initiated by the generation of the active alkyl/arylthiol species through hydrolysis of the Bunte salt with water at 80 °C.



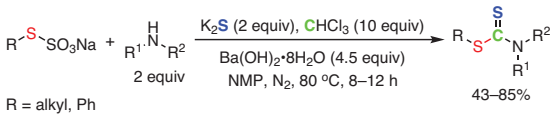
Ar = XC_6H_4 (X = H, Me, F, Cl, MeO), thien-3-yl, 9*H*-fluoren-2-yl, estratrien-3-yl
R = XC_6H_4 (X = H, Me, MeO, Me_2, CF_3, Cl), Me, *n*-Bu, *n*-$C_{12}H_{25}$, Bn, 1-Np, 2-Np
dppp = 1,3-bis(diphenylphosphino)propane; dppm = bis(diphenylphosphino)methane

Scheme 3. Divergent Cross-Coupling of Organosilicon Reagents with Bunte Salts. *(Ref. 28)*



R^1 = alkyl, vinyl, aryl; R^2 = alkyl, aryl, heteroaryl
Ar = XC_6H_4 (X = Me, *t*-Bu, MeO, CF_3, F, Cl, Br, Me_2, $(MeO)_2$, F_2, Cl_2), 2-Np, thien-2-yl

eq 5 *(Ref. 29)*



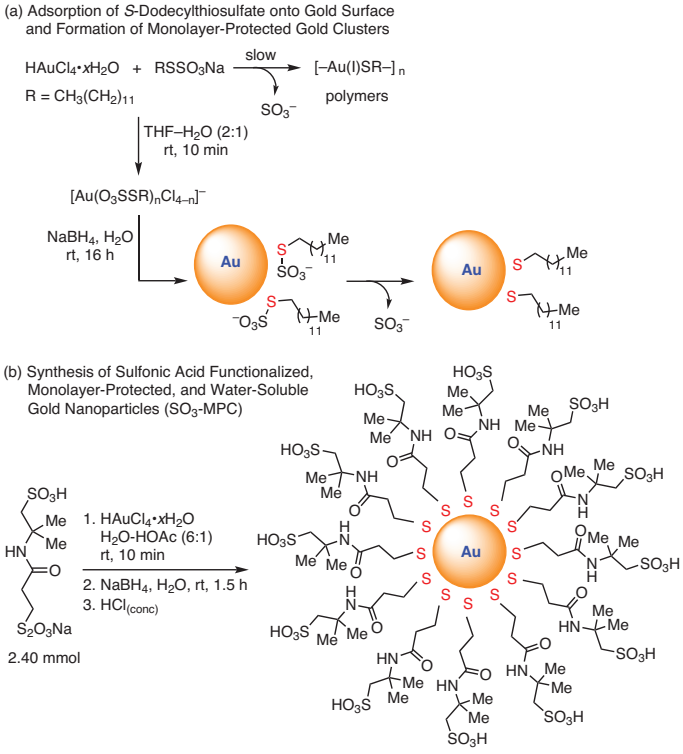
R = alkyl, Ph
R^1,R^2 = Me,Ph; Me,Bn; Bn_2; Et_2; heterocycle
NMP = 1-methyl-2-pyrrolidinone

eq 6 *(Ref. 30)*

5. Application in Metal Nanoparticles

Metal nanoparticles (MNPs) are used in biomedical assays and treatments and for the construction of microscale optical devices. A number of chemical strategies have been devised for synthesizing functionalized metal nanoparticles of various sizes.[32] Since Bunte salts have no odor and lower reactivity than thiols, they are generally utilized for the synthesis of metal nanoparticles with a sulfur-containing headgroup. Lukkari and co-workers found that Bunte salts can generate self-assembled monolayers (SAMs) on gold under anaerobic conditions, and chemisorb forming an Au–S bond.[33] The S–SO_3^- bond in Bunte salts (RS–SO_3^-) is cleaved during adsorption of the RS moiety onto the gold surface, releasing the SO_3^- group. The following year, Murray's group reported the first example of metal nanoparticles, in which alkanethiolate-protected AuNPs were prepared by Bunte salts as ligand precursors (**Scheme 4**, Part (a)).[34] Employing the same protocol, they later explored the preparation of water-soluble, monolayer-protected nanoparticles (SO_3–AuNP) by using the strong-acid-functionalized Bunte salt of 2-acrylamido-2-methyl-1-propanesulfonic acid as precursor (Scheme 4, Part (b)).[35]

A thiosulfate approach was also utilized by Shon and Cutler for the one-pot preparation of alkanethiolate-capped silver nanoparticles (AgNPs) in aqueous media.[36] The AgNPs, produced by borohydride ($NaBH_4$) reduction of silver nitrate, were stabilized by adsorption of *S*-dodecylthiosulfate (*n*-$C_{12}H_{25}S$–SO_3^-) onto the particle surface followed by elimination of the SO_3^- fragment. Later, Shon and other co-workers reported a two-phase synthesis of water-soluble, carboxylate-functionalized, and alkanethiolate-capped palladium nanoparticles (PdNPs) from Bunte salts (ω-carboxyl-*S*-alkanethiosulfate sodium salt).[37,38] These PdNPs were then investigated as catalysts for the hydrogenation of allyl alcohol to 1-propanol versus its isomerization to propanal. Their results showed that the sulfur ligand structure, its conformation, and its degree of surface coverage were crucial in determining the activity and selectivity of the PdNP catalysts.



Scheme 4. The Synthesis of Gold Nanoparticles from Bunte Salts. *(Ref. 34,35)*

6. Conclusion

The fact that Bunte salts are stable, easy-to-handle crystalline solids with generally little-to-no odor and unique chemical properties has made them attractive thiol sources and desirable substrates for a wide variety of chemical reactions. Not only have Bunte salts served as an important component of new protocols for shorter and more efficient syntheses of known sulfur-containing compounds, but also as key precursors in the synthesis of novel and bioactive sulfur-containing molecules and sulfur-modified drugs. Although quite a few effective strategies have so far been devised for the application of Bunte salts in many types of reaction, there is still a need for even more efficient and practical methods for their use in facilitating the synthesis of structuraly diverse sulfur-containing compounds. Drug discovery is one area that we believe Bunte salts, as optimal sulfurating agents, are poised to play an increasingly important role in.

7. Acknowledgments

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P-Chiral Phosphorus Ligands for Cross-Coupling and Asymmetric Hydrogenation Reactions


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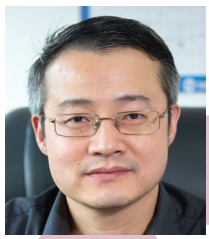
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Keywords. P-chiral; phosphorus ligands; asymmetric cross-coupling; Suzuki–Miyaura coupling; axial chirality; asymmetric dearomative coupling; α-arylation; asymmetric hydrogenation; all-carbon quaternary stereocenters.

Abstract. The asymmetric cross-coupling and asymmetric hydrogenation reactions are highly relevant to synthetic organic chemists in both academia and industry. Chiral phosphorus ligands have played a central role in improving the efficiency, selectivity, and scope of these transition-metal-catalyzed asymmetric transformations. Nevertheless, the invention of new phosphorus ligands and their applications in these two types of reaction are still urgently needed to further expand their scope and improve their efficiency and enantioselectivity. This mini-review summarizes our recent efforts in developing P-chiral, mono- and bisphosphorus ligands that possess unique structural motifs. It also highlights their powerful applications in promoting the asymmetric Suzuki–Miyaura coupling, asymmetric dearomative cross-coupling, asymmetric α-arylation, and various asymmetric hydrogenations, with particular emphasis on practicality and efficiency of the transformations (low catalyst loading, good atom economy, and high enantioselectivity).

Outline

1. Introduction

P-Chiral phosphorus ligands have played a significant role in the advancement and industrialization of asymmetric catalysis.[1,2] For example, Knowles developed CAMP and DiPAMP ligands in the early 1970s, which not only set the bar high for highly enantioselective rhodium-catalyzed asymmetric hydrogenation, but also ushered in the era of asymmetric catalytic transformations for industrial applications[3,4] Imamoto later developed a series of P-chiral bisphosphorus ligands—BisP*,[5] MiniPhos, and QuinoxP*®[6]—which are highly effective for various Rh- or Pd-catalyzed carbon–carbon and carbon–hydrogen bond-forming reactions. In the meantime, Zhang developed a series of 1,2-bisphospholane ligands, TangPhos,[7] DuanPhos,[8] and ZhangPhos,[9] which were successfully applied in asymmetric hydrogenation, hydroformylation, and other reactions. Despite these advances, the development of chiral phosphorus ligands with new structural motifs to address numerous unsolved challenges in asymmetric catalysis remains a necessary and

worthy pursuit. This mini-review highlights our group's recent efforts to design and synthesize novel P-chiral mono- and bisphosphorus ligands based on the 2,3-dihydrobenzo[*d*][1,3]-oxaphosphole (DHBOP) motif and to apply them in asymmetric cross-coupling and hydrogenation reactions.[2,10,11]

2. Design and Development of P-Chiral Phosphorus Ligands Based on the 2,3-Dihydrobenzo[*d*][1,3]-oxaphosphole Motif

The inspiration for employing this structural motif originated with TangPhos, a highly efficient but air-sensitive chiral bisphospholane ligand.[7] Preparation of both enantiomers of TangPhos has remained a challenge owing to the use of sparteine as the chiral reagent in the synthesis. Not only is the natural (+)-sparteine expensive and in limited supply, but an effective surrogate of its antipode, (–)-sparteine, is also scarce. To overcome the synthetic challenge and air-sensitivity of TangPhos, we sought an air-stable, operationally simple, and modular version of TangPhos. Introducing two aryl rings into the oxaphosphole structure thus led to the DHBOP motif, which could be prepared from readily available starting materials in only three steps and could be resolved easily to provide both enantiomers on a kilogram scale. Additionally, most ligands derived from this structure are air-stable solids and thus operationally simple to handle. Furthermore, the excellent modularity and tunability of this unique structure have allowed us to develop a series of chiral mono- and bisphosphorus ligands that have shown excellent reactivities and enantioselectivities in various asymmetric catalytic reactions.

Chiral monophosphorus ligands have played increasingly important roles in developing new and efficient asymmetric catalytic reactions.[12] However, designing efficient chiral monophosphorus ligands is much more difficult than designing bisphosphorus ligands due to the lack of a conformationally defined and systematically tunable ligand framework. We have been fortunate to have developed a library of conformationally well-defined and electron-rich P-chiral biaryl monophosphorus ligands based on the DHBOP motif (**Figure 1**). Structurally, these are more stable and electron-rich ligands than chiral monophosphoramide ligands, and most are also air-stable crystalline solids, which are relatively easy to handle. Additionally, the high tunability of the steric and electronic properties of the P-chiral biaryl monophosphorus ligand structure enables the broad application of such ligands in various catalytic systems.

The chiral, BIBOP-type bisphosphorus ligands also have unique structural features when compared to the well-known bisphosphorus ligands such as BINAP and DuPhos. Variation of the R' groups at the 4,4′ positions led to a series of chiral bisphosphorus ligands (Type I)—e.g., BIBOP, MeO-BIBOP, WingPhos, and ArcPhos—with various depths, shapes, and electronic properties of the chiral pocket. Another group of chiral bisphosphorus ligands (Type II)—e.g., BABIBOP, Me-BABIBOP, and *i*Pr-BABIBOP—are formally constructed by dimerization at the 4 position of DHBOP (Figure 1). One interesting non-C_2-symmetric bisphosphorus ligand is MeO-POP, which has proven a highly efficient ligand in rhodium-catalyzed asymmetric hydrogenations. In addition to these mono- and bisphosphorus ligands, a series of P,P=O ligands

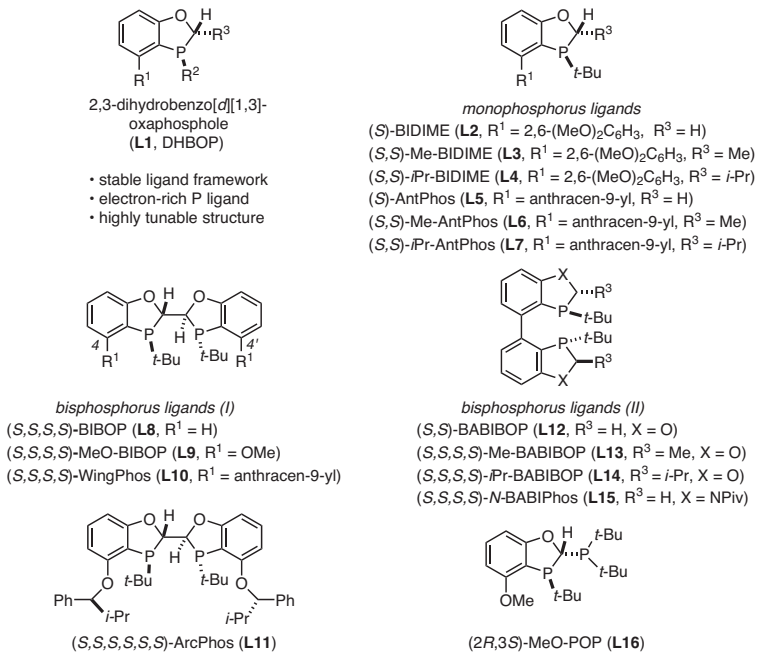


Figure 1. The Highly Tunable and Stable 2,3-dihydrobenzo[*d*][1,3]oxaphosphole (DHBOP) Motif and Novel, Air-Stable, Crystalline, and Highly Efficient Mono- and Bisphosphorus Ligands Derived from It.

have been developed. The P=O moiety is designed to provide a hemilabile coordination to the metal center, thus inhibiting a β-hydride elimination or a second transmetalation, and promoting an effective aryl–alkyl cross-coupling.

3. Chiral Monophosphorus Ligands for Cross-Coupling

Cross-coupling is one of the most important carbon–carbon bond-forming reactions, and has been widely applied in the electronics, materials, and pharmaceutical industries. Thanks to the recent development of phosphorus ligands, the scope of the cross-coupling reaction has been significantly expanded. Nevertheless, significant challenges remain such as tolerance of steric hindrance, compatibility of various functional groups, and excellent stereocontrol in forming axial chirality or all-carbon quaternary centers. To overcome these challenges, we developed a series of sterically hindered and electron-rich P-chiral monophosphorus ligands for the purpose of investigating the sterically hindered aryl–aryl and aryl–alkyl cross-couplings.[13] Moreover, an efficient, sterically hindered aryl–isopropyl coupling has also been developed for the first time by employing a sterically hindered P,P=O ligand.[14] In the rest of this article, we will concisely highlight our recent results for the asymmetric Suzuki–Miyaura coupling,[15–20] asymmetric dearomative cross-coupling,[21–23] and α-arylation.[24–25]

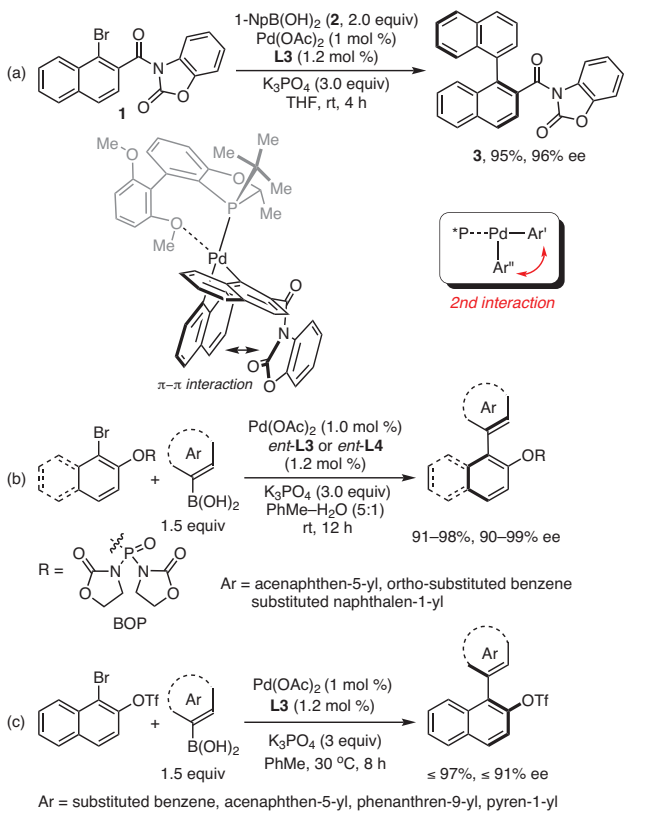
3.1. Asymmetric Suzuki–Miyaura Coupling

Axially chiral biaryl structural motifs are found in a large number of biologically important natural products as well as in thousands of ligands for asymmetric catalysis. Although there have been quite a few reported methods for the construction of chiral biaryl units,[26] the asymmetric Suzuki–Miyaura coupling remains of significant interest in this regard owing to its mild reaction conditions, broad functional group compatibility, and nontoxic nature of the starting materials.[11] To that end, we have demonstrated the advantages of utilizing monophosphorus ligands such as (*S*)-BIDIME (**L2**) and (*S*)-AntPhos (**L5**) in the Pd-catalyzed, sterically demanding Suzuki–Miyaura coupling leading to tetra-ortho-substituted biaryls among others.[15]

We initially pursued the asymmetric construction of chiral tri-ortho-substituted biaryls[16] for which, and despite considerable research efforts prior to our work, an efficient and practical synthetic protocol utilizing the asymmetric Suzuki–Miyaura coupling remained elusive. Our approach involved incorporating a noncovalent π–π interaction between the two aryl partners at the reductive elimination stage. Employing this approach and monophosphorus ligand (*S*,*S*)-Me-BIDIME (**L3**), an efficient, mild, and enantioselective Suzuki–Miyaura coupling between naphthyl bromide **1** and 1-naphthylboronic acid (**2**) was achieved, providing the biaryl coupling product **3** in 95% yield and 96% ee (**Scheme 1**, Part (a)).[16]

Since a large number of natural products feature chiral *ortho*-hydroxy- or *ortho*-methoxybiaryl structures, we then developed an efficient asymmetric Suzuki–Miyaura coupling between arylboronic acids and aryl bromides bearing an ortho oxygen-protecting group (OPG).[17] To achieve high enantioselectivity, an effective noncovalent second interaction needed to be introduced. After screening a series of OPG's, we found that excellent enantioselectivity was achieved when the bis(2-oxo-3-oxazolidinyl)phosphinyl (BOP) protecting group was employed. The significant increase in enantioselectivity in going from O–P(O)Ph_2 to O–BOP pointed to an important noncovalent interaction with the O–BOP group. The substrate scope further revealed the importance of the extended π system of the arylboronic acid for high enantioselectivity. All these observations suggested the presence of a significant polar–π interaction between the highly polarized BOP group and the extended π system of the arylboronic acid during the reductive elimination step. The chiral *ortho*-*O*–BOP biaryl products were subsequently applied to concise and stereoselective total syntheses of the biologically active natural products korupensamine A and B, and michellamine B (Scheme 1, Part (b)).[17]

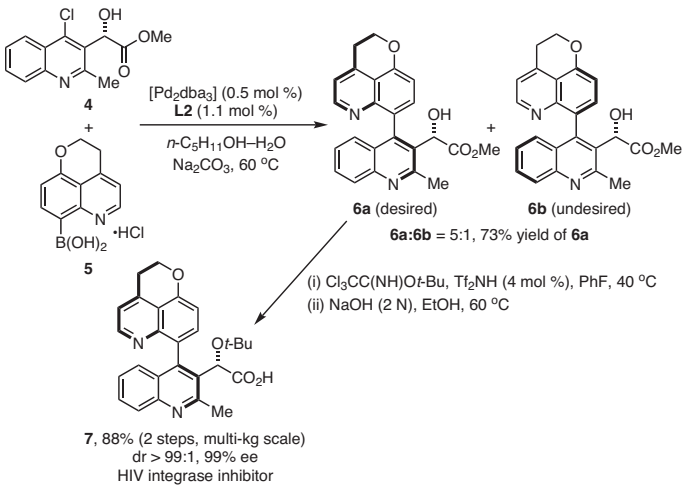
The trifluoromethanesulfonyl group can also be an effective ortho OPG group in the asymmetric Suzuki–Miyaura coupling that uses Pd-(*S*,*S*)-Me-BIDIME (**L3**) as the catalyst system (Scheme 1, Part (c)).[18] Utilizing this protocol, a series of chiral biaryl triflates were synthesized in excellent ee's and yields.



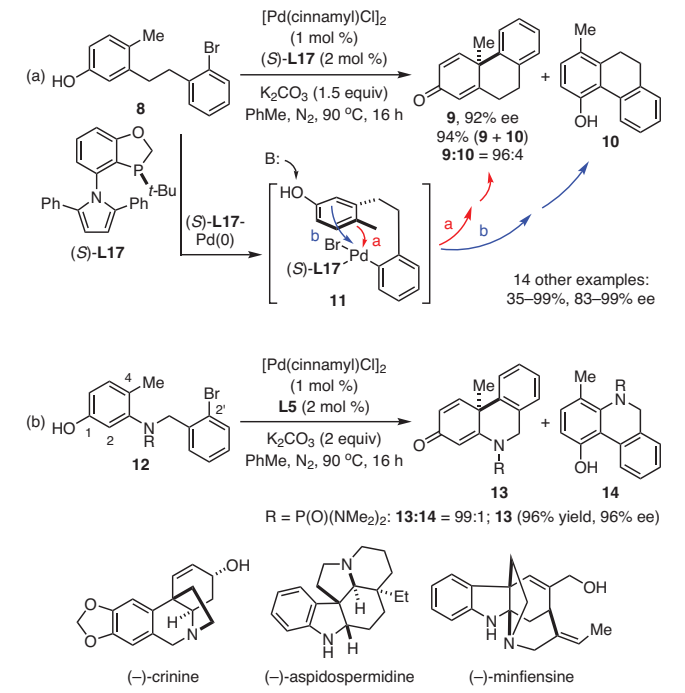
Scheme 1. Construction of Highly Sterically Hindered Biaryls by a Mild, Efficient, and Highly Enantioselective Suzuki–Miyaura Coupling Enabled by Chiral, Monophosphorus Ligands. *(Ref. 16–18)*

The biaryl triflate products underwent further elaborations such as carbonylation, Suzuki–Miyaura coupling, Miyaura borylation, and Sonogashira coupling to forge a variety of chiral biaryl derivatives.

Tetra-ortho-substituted biaryls can also be accessed by the asymmetric Suzuki–Miyaura or Negishi coupling by employing a chiral monophosphorus ligand.[19] Although high enantioselectivities were obtained for a few substrates with the employment of sterically hindered ligands, the asymmetric Suzuki–Miyaura cross-coupling did not prove to be general. Low or no yield was obtained with slight variation of substrate structure. The corresponding Negishi cross-coupling provided only slightly better yields of the tetra-ortho-substituted biaryls, but with lower enantioselectivities.[19]



Scheme 2. Ligand (*S*)-BIDIME (**L2**) Enabled Suzuki Cross-Coupling as a Key Step in a Concise, Robust, Safe, Economical, and Asymmetric Synthesis of an HIV Integrase Inhibitor. *(Ref. 20)*



Scheme 3. P-Chiral Biaryl Monophosphorus Ligands Enabling the Efficient and Stereoselective Intramolecular Dearomative Cross-Coupling, a Key Step in the Synthesis of Fused Tricyclic Cores of Biologically Active Natural Products. *(Ref. 21–24)*

Compound **7** is a quinoline-based allosteric integrase inhibitor, whose structure features an axially chiral biaryl backbone with an attached *ortho*-(α-(*tert*-butoxy)acetic acid) side chain. A robust and practical synthesis was needed to support its advancement through the drug development process. Thus, a diastereoselective Suzuki–Miyaura coupling of aryl chloride **4** and arylboronic acid **5** was exploited to install the chiral biaryl backbone, with the best result being obtained with ligand (*S*)-BIDIME (**L2**) (**Scheme 2**).[20] Under the optimized reaction conditions (1-pentanol–water and 60 °C) a 5:1 diastereomeric ratio of **6a** to **6b** was achieved, and the desired precursor (**6a**) to **7** was isolated in 73% yield, which is significantly better than the 40% yield and 2:1 ratio of **6a** to **6b** obtained with SPhos.[20]

3.2. Asymmetric Dearomative Cross-Coupling

Fused tricyclic skeletons containing chiral, all-carbon quaternary centers, such as chiral phenanthrenones, are found in numerous complex terpenes and steroids that exhibit interesting biological activities.[21,22] Complementing the asymmetric Heck reaction, the enantioselective intramolecular dearomative cross-coupling has become an important strategy to assemble these chiral skeletons. Over the past several years, our research group has undertaken the total synthesis of terpenoids, steroids, alkaloids, and polyketide natural products by taking advantage of the powerful, intramolecular, and enantioselective dearomative cross-coupling reaction.

The program originated with the study of the asymmetric palladium-catalyzed cyclization of bromine-substituted phenol **8**, which can lead to the formation of the desired coupling product **9**—containing a chiral, all-carbon quaternary center—as well as the achiral molecule **10** (**Scheme 3**, Part (a)).[22] Products **9** and **10** arise from a common intermediate, **11**, and, although **9** is thermodynamically less stable than **10**, its formation could be kinetically more favorable in the presence of a suitable catalyst. Among all the ligands screened, P-chiral biaryl monophosphorus ligand (*S*)-**L17** was found to promote the formation of the desired product, **9**, smoothly in high yield and with the highest enantioselectivity (92% ee). In the proposed stereochemical model for the cyclization, the high stereoselectivity observed with (*S*)-**L17** is rationalized by stipulating that the 2,5-diphenylpyrrole moiety of (*S*)-**L17** and its bulky *tert*-butyl group dictate the orientation of substrate coordination. Substrate **8**, after oxidative addition to palladium to form **11** and nucleophilic substitution, could adopt two major conformations, with the less strained one being more favored and leading to the observed *R* configuration of **9**.[22] By using this methodology, a series of biologically important

terpenes, such as triptoquinone H,[21] and (–)-totaradiol[22] were efficiently synthesized. In addition, this approach proved crucial in a nine-step, enantioselective synthesis of the strong immunosuppressant (+)-dalesconol A that relied on the use of chiral (*R*)-AntPhos (*ent*-**L5**) as the chiral ligand.[23] A steroid skeleton was also constructed efficiently by using this method.[21]

The success we achieved in the all-carbon, fused tricyclic systems prompted us to explore nitrogen-containing polycyclic frameworks also incorporating a chiral, all-carbon quaternary center (Scheme 3, Part (b)).[24] While the anticipated structural difference was simply the formation of a dihydrophenanthridinone unit instead of a phenanthrenone one, it turned out that such a minor structural variation had a dramatic effect on the chemoselectivity of the reaction. Substrate **12a** (R = H) did not undergo the cyclization, while substrate **12b** (R = Piv) provided the undesired nonchiral compound **14b**. We reasoned that the chemoselectivity could be altered by changing the *N*-R protecting group. Interestingly, after screening Piv, Ms, Ts, Tris, Nos, Tf, SO_2NMe_2, and $P(O)(NMe_2)_2$ as the nitrogen protecting group, we discovered that the bulky phosphoramide group $P(O)(NMe_2)_2$ led to the desired coupling product, **13**, in excellent yield. When (*S*)-AntPhos (**L5**) was employed as ligand, the desired chiral dehydrophenanthridin-3(5*H*)-one product **13** [R = $P(O)(NMe_2)_2$] was isolated in 96% yield and 96% ee.

DFT calculations helped rationalize the dramatic effect of the *N*-R protecting group on the chemoselectivity. In substrate **12** [R = $P(O)(NMe_2)_2$], the C-2′ position (CBr) is in closer proximity to the C-4 position than is the case with substrate **12** (R = Piv). NBO analysis also showed that the charge on C-4 in **12** [R = $P(O)(NMe_2)_2$] was –0.071, more negative than that on C-2 (–0.017). Thus the higher nucleophilicity of the C-4 position in substrate **12** [R = $P(O)(NMe_2)_2$] leads preferentially to the desired intramolecular dearomative cyclization forming compound **13**.[24]

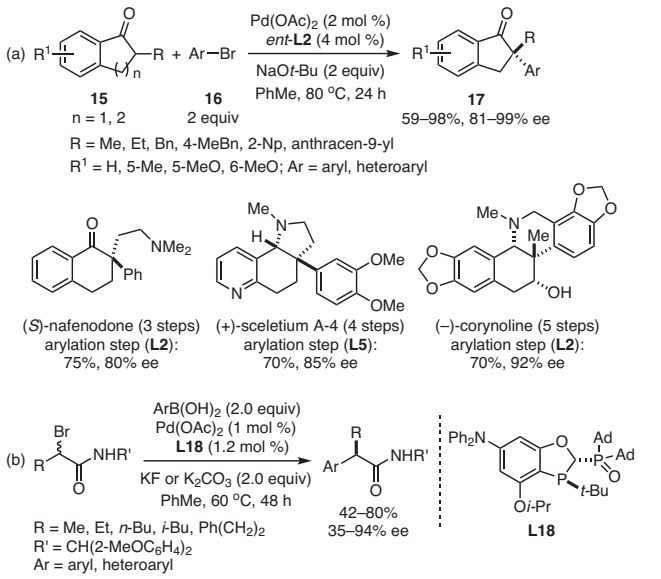
Finally, the asymmetric dearomative cross-coupling enabled the enantioselective synthesis of three distinct and challenging biologically important polycyclic alkaloids:[24] concise and gram-scale total synthesis of (–)-crinine, an efficient total synthesis of indole alkaloid (–)-aspidospermidine, and a formal total synthesis of (–)-minfiensine.

3.3. Asymmetric α-Arylation of Carbonyl Compounds

The search for efficient asymmetric catalytic methods to construct all-carbon quaternary stereocenters is gaining significant momentum. The palladium-catalyzed, asymmetric α-arylation of carbonyl compounds remains one of most efficient and powerful methods to assemble chiral all-carbon quaternary stereocenters, and the type of chiral ligand on palladium is key to achieving the desired reactivity and enantioselectivity. Our group has found that (*R*)-BIDIME (*ent*-**L2**) is an exceptional ligand for the asymmetric α-coupling of indanones **15** with ortho-substituted 2-bromoarenes **16.** The ketone products, **17**, incorporating a chiral quaternary carbon center, are generated in up to 98% yield and 99% ee (**Scheme 4**, Part (a)).[25] Taking advantage of this methodology, we achieved the efficient and enantioselective synthesis of the antidepressant (*S*)-nafenodone (3 steps), the sceletium alkaloid (+)-sceletium A-4 (4 steps), (–)-corynoline (5 steps), and (–)-deN-corynoline (3 steps).[25]

Carrying out an efficient cross-coupling between α-bromo carbonyl compounds and arylboron reagents under palladium catalysis remains a tough challenge.[26] Although such a transformation has been realized with chiral Ni[27] or Fe[28] catalysts, palladium catalysis often features much lower catalyst loading and is amenable to industrial applications. Nevertheless, the palladium-catalyzed coupling of benzyl 2-bromopropionate with phenylboronic acid in the presence of known ligands afforded the undesired des-bromo ester and biphenyl in all cases without forming the desired cross-coupling product.[29] Since monophosphorus ligands based on the DHBOP motif have been successfully applied in the coupling between aryl halides and aryl- or alkylboronic acids, we surmised that the enantioselective palladium-catalyzed coupling of α-bromo carbonyl compounds with arylboronic acids could be accomplished by a judicious choice of ligand. The key to success would be the effective inhibition of the homocoupling of the arylboronic acids, which results from a second transmetalation.[30] Thus, we postulated that a bulky P,P=O ligand could offer a secondary hemilabile interaction besides the Pd–P coordination, which would make the second transmetalation difficult due to steric hindrance.[30]

Careful ligand engineering and screening identified a bulky P,P=O ligand, **L18**, as optimal.[30] Using **L18**, the desired aryl–alkyl cross-coupling product was isolated in moderate yield and a decent ee. Because, in this case, the racemic α-bromo carboxamide was employed as substrate, the cross-coupling

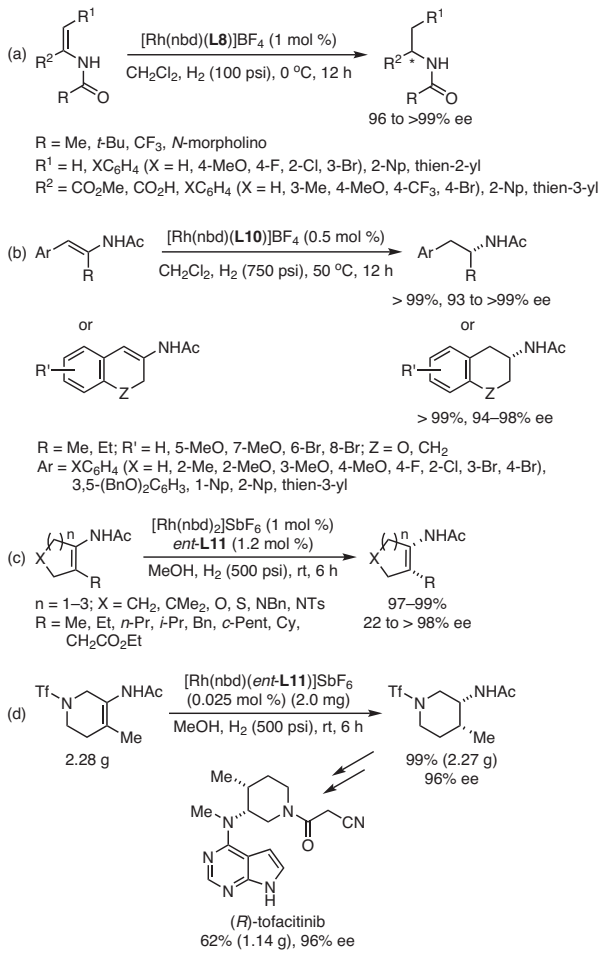


Scheme 4. Chiral Quaternary Carbon Formation by the Catalytic, Asymmetric α-Arylation Employing P-Chiral Biaryl Monophosphorus Ligands. *(Ref. 25,30)*

was essentially a dynamic kinetic resolution (DKR) process. The base and the acidity of the substrates were important parameters for both yield and enantioselectivity. Optimization of the reaction parameters revealed that KF as the base and $CH(2\text{-}MeOC_6H_4)_2$ as the nitrogen protecting group were optimal for both yield and enantioselectivity (Scheme 4, Part (b)).[30]

4. Chiral Bisphosphorus Ligands for Asymmetric Hydrogenation

The past few decades have seen significant advances in the asymmetric hydrogenation, and a number of important industrial processes have been implemented based on this reaction.[1] Since cost is a significant factor in judging whether a chemical reaction is viable or not on an industrial scale, turnover numbers (TONs) must be considered for it and should be as high as possible. Our belief that bisphosphorus ligands based on the DHBOP motif could address these issues and other unmet challenges led us to develop three ligand frameworks for the catalytic asymmetric hydrogenation. Our efforts led to BIBOP (**L8**), which could be prepared in two stereoisomeric forms and tuned both sterically and electronically by changing the substituents at the 4 and 4′ positions.[31] Some of the novel bisphosphorus ligands that were developed in this way—e.g., BIBOP, MeO-BIBOP, and others—have proved to be excellent ligands for the enantioselective catalytic hydrogenation reaction.



Scheme 5. Efficient Enantioselective Olefin Hydrogenations Enabled by Chiral Bisphosphorus Ligands. *(Ref. 31,33,34)*

Rh–BIBOP (Rh–**L8**) exhibited excellent catalytic efficiency in the asymmetric hydrogenation of various functionalized olefins such as α-(acylamino)acrylic acid derivatives, α-aryl enamides, β-(acylamino)acrylic acid derivatives, and dimethyl itaconate (**Scheme 5**, Part (a)).[31] Various functionalities were tolerated, and excellent enantioselectivities (up to 99% ee) and TONs (up to 2,000) were achieved in the synthesis of chiral α- and β-amino acids, chiral amines, and chiral carboxylic acid derivatives.

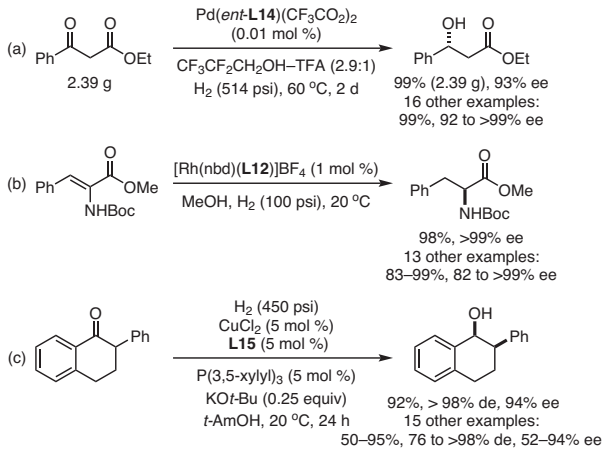
MeO-BIBOP (**L9**) is another air-stable but more electron-donating ligand. With Rh-**L9** as the catalyst, a 200,000 TON was achieved in the rhodium-catalyzed hydrogenation of *N*-(1-(4-bromophenyl)vinyl)acetamide, which was the highest TON reported then for the hydrogenation of α-aryl enamides. Similarly, a pyridine-substituted enamide was also hydrogenated with a Rh–MeO-BIBOP catalyst to provide the hydrogenation product in quantitative yield and 97% ee.[32] By installing two 9-anthryl groups at the 4 and 4′ positions, a structurally interesting chiral bisphosphorus ligand—WingPhos (**L10**) was designed and synthesized. The salient feature of WingPhos is the position of the two 9-anthryl groups that protrude directly toward the coordinated substrate, forming a deep chiral pocket capable of long-range stereochemical control. Notably, the two diagonal quadrants bearing two *tert*-butyl groups no longer provided a direct influence on substrate coordination, and the anthryl groups in the other two quadrants presumably influence substrate coordination, leading to high enantioselectivities. The Rh–WingPhos complex was a highly efficient catalyst for the rhodium-catalyzed hydrogenation of (*E*)-β-aryl enamides, forming a variety of chiral cyclic and acyclic β-arylamines with different functionalities in excellent enantioselectivities at low catalyst loadings (TONs up to 10,000) (Scheme 5, Part (b)).[33] Because (*E*)-β-aryl enamides could be conveniently synthesized, this method provided a practical synthesis of various chiral β-arylamine derivatives.

ArcPhos (**L11**) is a conformationally defined, electron-rich, C_2-symmetric, P-chiral bisphosphorus ligand. It is highly efficient in the rhodium-catalyzed asymmetric hydrogenation of carbocyclic and heterocyclic tetra-substituted enamides. Excellent enantioselectivities (up to 98% ee) and up to 10,000 TON were achieved, which was the highest reported up until then (Scheme 5, Part (c)).[34] NMR experiments and X-ray diffraction studies revealed that *ent*-**L11** had a conformational preference whereby the flexible isopropyl groups are directed toward the rhodium center due to both stereoelectronic and steric effects. Moreover, the asymmetric hydrogenation of a heterocyclic starting material with [Rh(nbd)(*ent*-**L11**)]SbF_6 as catalyst led to *N*-trifluoromethanesulfonyl *cis*-3-acylamino-4-methylpiperidine (99% yield, 96% ee), and enabled an efficient and practical synthesis of the Janus kinase inhibitor (*R*)-tofacitinib (Scheme 5, Part (d)).[34]

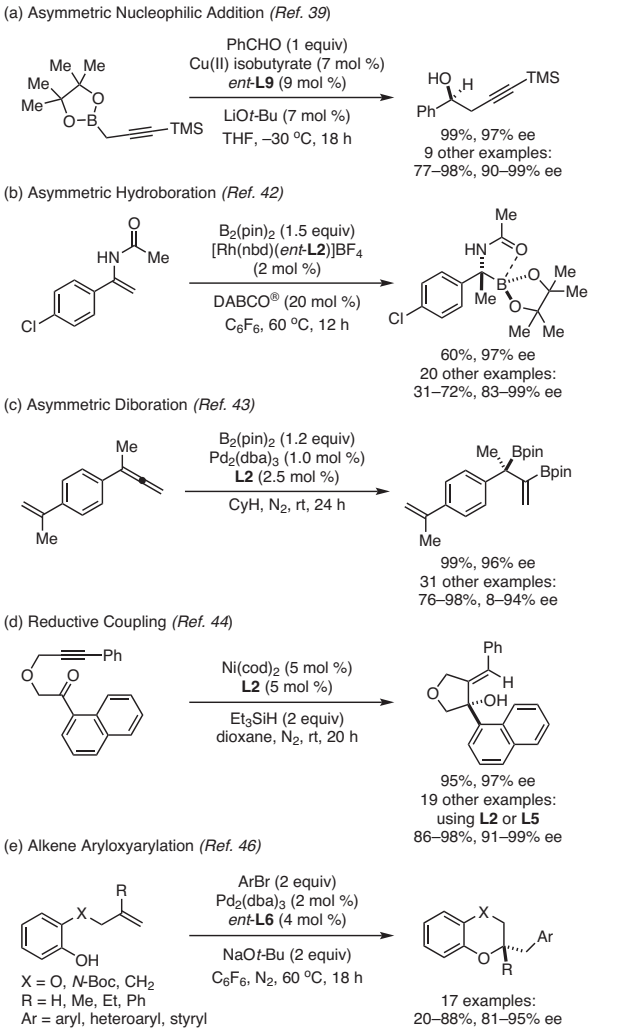
Our group has also developed a series of novel bisphosphorus ligands, **L12**–**L14**.[35] This type of ligand possesses the following characteristics: (i) The chirality of the ligand arises from the central P-chirality instead of from the biaryl axial chirality. (ii) The ligand adopts coordination modes with the metal similar to those of BINAP- or BIPHEP-type ligands. (iii) Its steric and electronic properties can be highly modulated by varying the R^3 group at the 2 and 2′ positions. By employing Pd–*i*Pr-BABIBOP (Pd–*ent*-**L14**) as catalyst, the hydrogenation of ethyl 3-oxo-3-phenylpropanoate proceeded in pentafluoropropanol–TFA under 514 psi of H_2 to form the chiral alcohol product in 93% ee and 99% yield with a TON of up to 10,000 (**Scheme 6**, Part (a)).[35] Besides applications in palladium-catalyzed asymmetric hydrogenation, other BABIBOPs have also been successfully used in the rhodium-catalyzed asymmetric hydrogenation of di- and tri-substituted enamides (Scheme 6, Part (b))[36] and the copper-catalyzed hydrogenation of 2-substituted 1-tetralones via dynamic kinetic resolution (Scheme 6, Part (c)).[37] The novel, C_1-symmetric bisphosphorus ligand, MeO-POP, is an operationally convenient solid. It has proven equally effective or even superior to the preceding C_2-symmetric bisphosphorus ligands in the rhodium-catalyzed asymmetric hydrogenation of α-(acylamino)acrylates and β-(acylamino)acrylates, providing excellent enantioselectivities (up to >99% ee) and high TONs (up to 10,000).[38] For example, in the presence of 0.01 mol % [Rh(nbd)(**L16**)]BF_4, methyl 2-acetamido-3-(2-chlorophenyl)-acrylate was hydrogenated in methanol to provide the corresponding chiral α-amino acid derivative in 98% ee.

5. Miscellaneous Asymmetric Transformations

In addition to applications in the asymmetric cross-coupling and asymmetric hydrogenation, chiral phosphorus ligands incorporating a DHBOP moiety have been extensively utilized in a variety of other asymmetric transformations (**Scheme 7**). BIBOP-type ligands have been successfully used in nucleophilic additions of boron reagents to aldehydes, ketones, and imines, to generate chiral homopropargylic alcohols,[39] tertiary alcohols,[40] and α-tertiary amines[41] in excellent enantioselectivities. The Rh–(*R*)-BIDIME catalyst, Rh–*ent*-**L2**, enabled the asymmetric hydroboration of α-aryl enamides with $B_2(pin)_2$, providing a series of chiral α-amino tertiary boronic esters in excellent ee's and satisfactory yields.[42] In the Pd-catalyzed diboration of 1,1-disubstituted allenes, (*S*)-BIDIME (**L2**) performed the best among several chiral mono- and bisphosphorus ligands tested, and led to the formation of a series of chiral tertiary diboronic esters in excellent yields and ee's.[43] Using (*S*)-AntPhos (**L5**) or (*S*)-BIDIME (**L2**), our group effected the first Ni-catalyzed reductive coupling to generate, in high yields and high ee's, chiral tertiary allylic alcohols attached to a tetrahydrofuran[44] or to a pyrrolidine ring.[45] The reaction had a broad scope and permitted the efficient asymmetric synthesis of the lignan dehydroxycubebin as well



Scheme 6. Asymmetric Hydrogenations Catalyzed by Biaryl Bisphosphorus Ligands. *(Ref. 35–37)*



Scheme 7. Miscellaneous Efficient Asymmetric Transformations Enabled by P-Chiral Phosphorus Ligands Based on the DHBOP Motif.

as chiral dibenzocyclooctadiene skeletons. Finally, chiral biaryl monophosphorus ligand (*R,R*)-Me-AntPhos (*ent*-**L6**) led to good yields and excellent enantioselectivities in the asymmetric alkene aryloxyarylation.[46]

6. Conclusion and Outlook

Over the last ten years, our research group has designed and developed chiral phosphorus ligands based on the 2,3-dihydrobenzo[*d*][1,3]oxaphosphole (DHBOP) motif in order to address unmet challenges in asymmetric organic synthesis. High enantioselectivities and turnover numbers, low catalyst loadings, and generally mild conditions have been achieved in a number of reactions by the judicious use of one of these ligands and the metal catalyst. In this way, efficient asymmetric cross-coupling, hydrogenation, hydroboration, cyclization, and nucleophilic addition, among others, have been readily carried out on a very wide range of substrates. Our continued efforts to design and develop novel and efficient phosphorus ligands for new applications in synthetic organic chemistry will help transform the fields of catalysis and synthesis and make useful contributions to the agrochemical and pharmaceutical industries.

7. Acknowledgments

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