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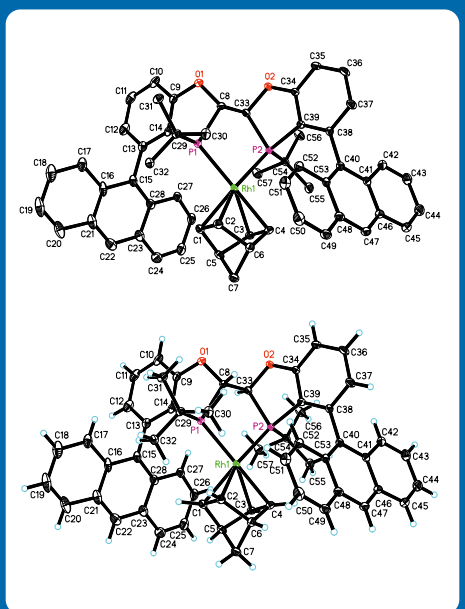

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寄稿論文

Development of Novel P-chiral Phosphorus Ligands for Efficient Transition-Metal Catalyzed Reactions

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Abstract: We have developed four categories of air-stable and operationally convenient phosphorus ligands on the basis of a benzooxaphosphole backbone. The bulky biaryl monophosphorus ligands BI-DIME and AntPhos are efficient for sterically hindered aryl-aryl cross-couplings; two new P,P=O ligands are developed and applicable for sterically hindered aryl-isopropyl cross-couplings; several P-chiral monophosphorus ligands are highly efficient for asymmetric aryl-aryl cross-couplings and various chiral cyclizations; a structurally unique P-chiral bisphosphorus ligand WingPhos is versatile for asymmetric hydrogenation as well as asymmetric addition of arylboron reagents to aryl ketones. The high reactivity, chemoselectivity, as well as enantioselectivity achieved with these phosphorus ligands have allowed practical applications in construction of various therapeutic agents and natural products.

Keywords: P-chiral phosphorus ligand, cross-coupling, reductive cyclization, dearomative cyclization, natural products

1 Introduction

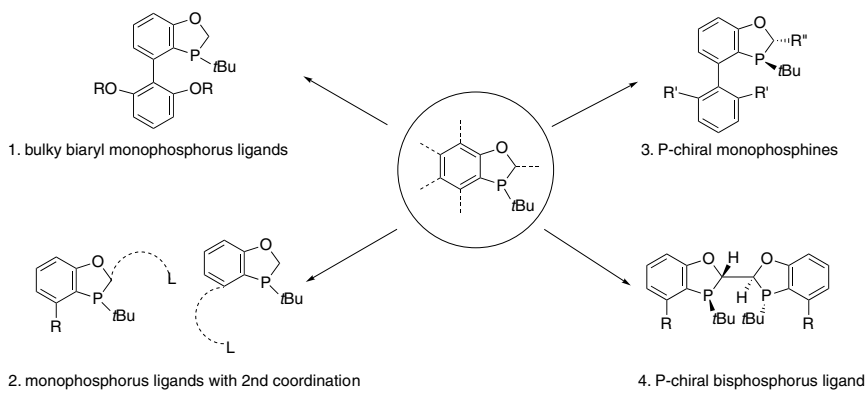
Over past several decades, the development of efficient transition-metal catalyzed reactions has become one of the most active area in organic chemistry and transition-metal catalysis has made significant impacts on almost every chemical fields including natural product synthesis, medicinal chemistry, material chemistry, fine and agrochemical industry, chemical biology, and etc.[1] Numerous efficient transition-metal catalysts have been developed, which have not only greatly improved synthetic efficiency, but also provided opportunities to explore new research fields and ideal synthetic chemistry. Significant efforts have been taken recently in developing highly efficient, cost-effective, and environmentally benign catalytic reactions. Consequently, a few practical processes in particular asymmetric hydrogenations and cross-couplings[2] are developed and operated at industrial scales with excellent chemo-, regio-, and enantioselectivities at extremely high substrate/catalyst ratios (over 1,000,000). It is without any doubt that transition-metal catalyzed transformations will continue to play increasingly important roles in construction of new molecules, and bring incredible benefits to our life and society.

In transition metal catalysis, the catalyst generally consists with a transition metal and one or several ligands. In search for a new and efficient catalyst for a specific reaction, the judicial choice of a transition metal is naturally of utmost importance. However, the electronic and steric properties of ligands can significantly influence the reactivity and selectivity of the reaction. Since Wilkinson and co-workers discovered $RhCl(PPh_3)_3$

as the catalyst for alkene hydrogenation, phosphorus ligands have received great attention.[3] Up today, thousands of various phosphorus ligands have been designed and developed and a few of them have proven to be very useful and have become indispensable tools in asymmetric hydrogenation and other related areas.[4] It is fair to say that the development of phosphorus ligands has promoted the progress of transition metal catalysis. Conversely, the number of well-designed phosphorus ligands will continue to grow rapidly and more efficient catalytic processes are expected to be discovered in the future.

Ligands dictate the electronic and steric properties of the transition metal catalyst. As a result, they have often played significant role for the reactivity and selectivity of the catalytic reaction. An excellent catalyst often features a well-defined and predictable conformation, which requires its ligating ligands to possess an unambiguous, fixed, and rigid structural conformation. Therefore, the rational design and development of a ligand with a stable configuration and a rigid structure is often a very effective way for the development of efficient catalytic reaction.

Our research group has embarked a program on exploring efficient and practical catalytic reactions by inventing novel and highly-efficient phosphorus ligands in recent years. We designed and developed a series of phosphorus ligands based on a benzoheterophosphole as the backbone structure[5] with the following features: 1) The 5-membered bisdihydrobenzooxaphosphole ring system makes such ligands conformationally rigid, which help predict the conformation of its metal complex in a real reaction; 2) The physical properties of such ligands were improved as air-stable solid by the introduction of the benzene ring, leading to great operational convenience; 3) Ease of changing the substituents on various locations of such structure allows systematic variation of its steric and electronic properties; 4) The capability of introducing P-chirality in its structure allows such ligands applicable for asymmetric catalysis.

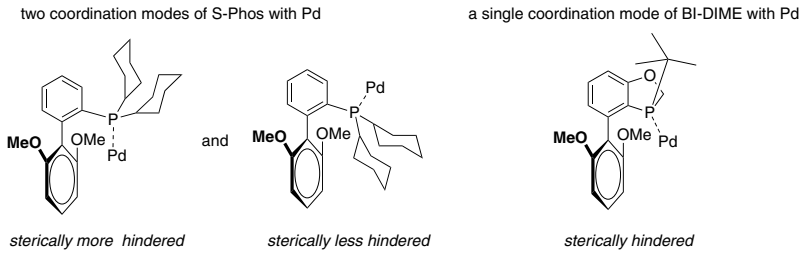


Scheme 1. Four categories of ligands developed in our Lab

Thus, we have developed four categories of ligands for various purposes (Scheme 1): 1) bulkyl biaryl monophosphorus ligands that have enabled sterically hindered aryl-aryl cross-couplings; 2) monophosphorus ligands with 2nd coordination that have provided greater functional group tolerance or enabled sterically hindered aryl-isopropyl cross-couplings; 3) P-chiral monophosphorus ligands that have enabled efficient asymmetric aryl-aryl cross-couplings or asymmetric cyclizations; 4) P-chiral bisphosphorus ligands that are applied successfully in asymmetric hydrogenations and asymmetric additions of arylboronic reagents. In this article, we outline some of our recent progress in exploring the application of those novel phosphorus ligands in transition metal catalysis.

2 Sterically Hindered Aryl-Aryl Suzuki-Miyaura Cross-Couplings

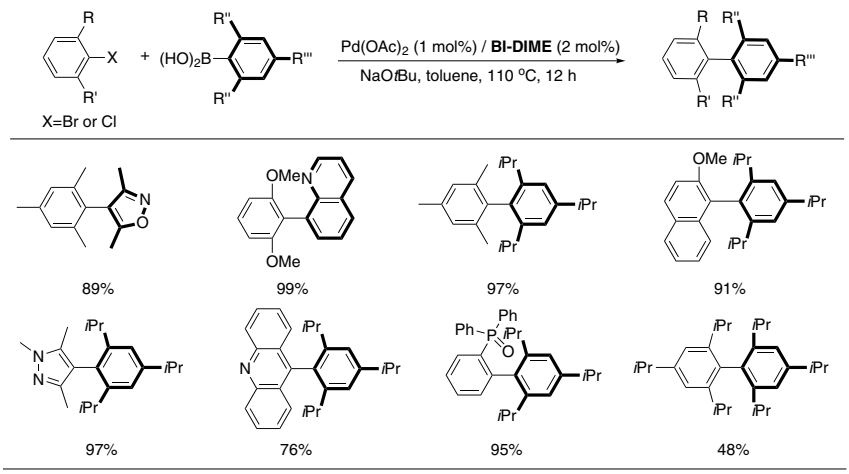
In the past several decades, transition-metal catalyzed cross-couplings have received significant attention.[6] Today, it has become one of most powerful method for constructing carbon-carbon bonds for the synthesis of various chemical compounds such as drugs, pesticides and materials. In particular, significant progresses have been achieved on Suzuki-Miyaura cross-couplings thanks to the stable and environmentally benign properties of organoboron reagents. The last twenty years have witnessed the even-broader substrate scope of Suzuki-Miyaura cross-couplings with excellent functional group compatibility at low catalyst loading (<0.1 mol%). Despite the significant advances, there have been only few reports on sterically hindered Suzuki-Miyaura couplings between di-*ortho*-substituted aryl halides and di-*ortho*-substituted arylboronic acids. Biaryl monophosphorus ligands such as S-Phos, X-Phos, and others developed from Buchwald's group have shown good reactivity on some sterically hindered substrates.[7] However, the exact capabilities of steric tolerance and functional group compatibilities are unknown. It has been proven that a single electron-rich and steric bulky monophosphorus ligand is beneficial to palladium catalyzed cross-couplings.[8] Electron-rich phosphorus ligands increase the oxidation power of transition metals and hence facilitate reactions where the oxidative addition step is rate-limiting; while the steric hindrance of the monophosphorus ligand allows to form a single-ligand-coordinated palladium species, which is believed to be active for the transmetallation step as well as reductive elimination. On the basis of these principles, we have developed a conformationally rigid monophosphorus ligand BI-DIME for steric hindered Suzuki-Miyaura coupling reactions. Structurally, BI-DIME eliminates any conformational ambiguity caused by rotation of the C–P bond as observed in Buchwald's S-Phos system (Scheme 2). The sterically more hindered nature of BI-DIME has provided great advantages in Suzuki-Miyaura couplings of sterically hindered arylboronic acids.[9]



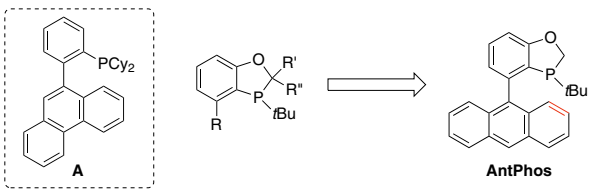
Scheme 2. Comparison of SPhos and BI-DIME

With BI-DIME as ligand, a series of *ortho*-disubstituted arylboronic acids were successfully coupled with *ortho*-disubstituted aryl bromides to form corresponding tetra-*ortho*-substituted biaryls in excellent yields under strong basic conditions (NaO*t*Bu as base). Tetra-*ortho*-substituted biaryls bearing secondary alkyl *ortho*-substituents such as isopropyl groups were synthesized for the first time through cross-coupling reactions (Scheme 3). Substituents such as methyl, methoxy and phosphine oxide were well tolerable, heteroaryls such as pyrazole, quinolone and acridine were also compatible. At 2.5 mol% Pd loading, a tetra-*ortho*-isopropyl substituted biaryl was also successfully formed for the first time in moderate yield by Suzuki-Miyaura coupling. Sterically hindered aryl chlorides could also be employed. The Pd-BI-DIME/NaO*t*Bu system has significantly expanded the scope and utility of sterically hindered aryl-aryl cross-couplings. Mechanistic studies revealed that the NaO*t*Bu might have accelerated the dissociation of the inactive Pd(II) dimer species to form the active Pd(II) monomer species during the reaction, which might have significantly improved the rate of the transmetallation step.

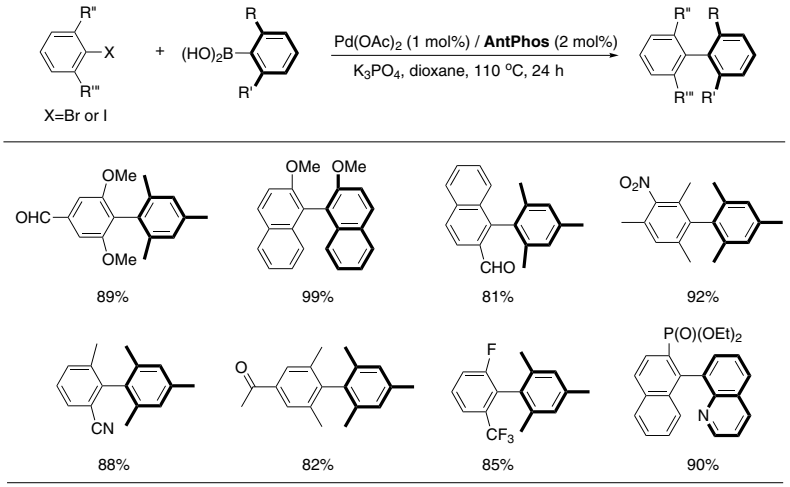
Construction of the functionalized tetra-*ortho*-substituted biaryls is very important for the synthesis of biaryl natural products and ligands.[10] Many of important functional groups such as aldehyde, ester, ketone and nitro are not tolerable to the strong basic conditions with NaO*t*Bu as base. Furthermore, the protodeboronation of the functionalized arylboronic acids is greatly accelerated under strong basic conditions. Only a mild base such as K_3PO_4 can be employed for those substrates and BI-DIME was not effective. For this, a more reactive and functional group compatible phosphorus ligand was needed. In 2002, Buchwald reported a biaryl monophosphine ligand **A** bearing with a phenanthrene moiety, which provided excellent yields for a series of tetra-*ortho*-substituted biaryls with K_3PO_4 as the base.[11] Interestingly, a π coordination of the phenanthrene moiety with the palladium center was observed in its complex. Inspired by this work, we designed and synthesized a new ligand AntPhos with an anthryl group in its framework (Scheme 4).[12] Gratifyingly, various functionalized substrates were coupled efficiently by AntPhos as ligand with K_3PO_4 as base. Functionalities such as aldehyde, ketone, phosphate, cyano, fluoro, and trifluoromethyl group were all well tolerated. This catalytic system provides an effective method for the synthesis of a series of sterically hindered, functionalized biaryls (Scheme 5).



Scheme 3. Substrates scope of sterically hindered Suzuki-Miyaura Coupling with BI-DIME as ligand

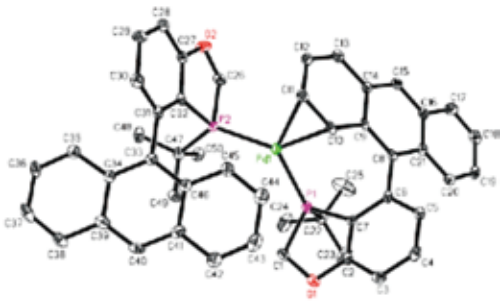


Scheme 4. Design of AntPhos



Scheme 5. Substrates scope of functionalized sterically-hindered cross-coupling by AntPhos as ligand

The X-ray crystal structure of [Pd(0)((*R*)-AntPhos)$_2$] revealed an interesting π-coordination between the Pd center and the anthracene ring at 1,2 positions (Scheme 6). We believe that this coordination may not only contribute to stabilize the [Pd(0)((*R*)-AntPhos)] complex, but also help inhibit the dimerization of its Pd(II) complex and increase the stability of its monomeric palladium(II) complex, which well explains its good activity in functionalized sterically hindered cross-couplings.

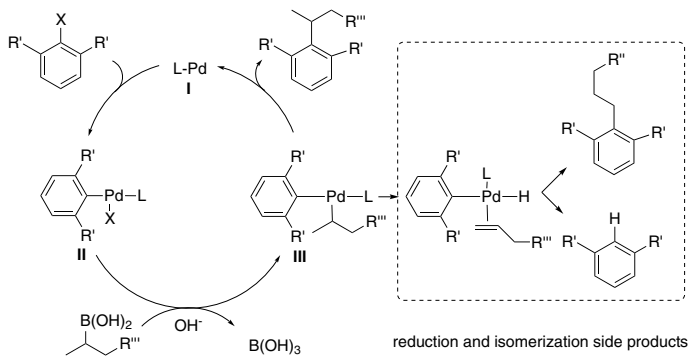


Scheme 6. X-ray structure of [Pd(0)((*R*)-AntPhos)$_2$]

3 Sterically Hindered Aryl-Alkyl Suzuki-Miyaura Cross-Couplings

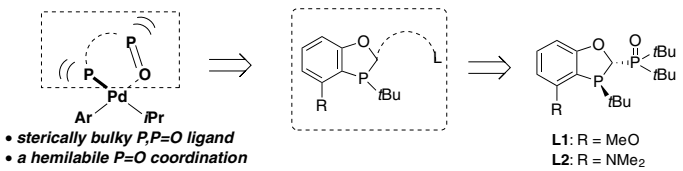
The transition-metal catalyzed cross-couplings between aryl halides and alkylmetallic reagents have become an important method for the construction of substituted aryls.[13] In particular, aryl-alkyl Suzuki-Miyaura cross-couplings have received much attention thanks to the readily availability of aryl halides as well as the good stability of alkylboronic acids. However, few efficient catalytic systems were reported due to several challenging

innate issues: a) the sp^3-hybridized alkylboronic acids are much bulkier and slower for transmetallation in contrast to the sp^2-hybridized arylboronic acids; b) the presence of β-hydrogen in alkylboronic acid allows the β-hydride elimination pathway, leading to the reduction of aryl halides and the formation of the regio-isomer during cross-coupling. These issues become more prominent in cross-couplings between sterically hindered aryl halides and secondary alkylboron reagents (Scheme 7). Biscoe and co-workers reported a highly selective aryl-isopropyl Suzuki-Miyaura coupling of non-hindered substrates,[14] but isomerization and low yields were particularly observed in aryl-isopropyl Suzuki-Miyaura couplings of *ortho*-substituted aryl halides.[15] An efficient method leading to high yields and selectivities was yet to be developed for the Suzuki-Miyaura coupling between di-*ortho*-substituted aryl halides and acyclic secondary alkylboronic acids. Such method would be highly desirable for late-stage introduction of alkyl groups to aromatic molecules.



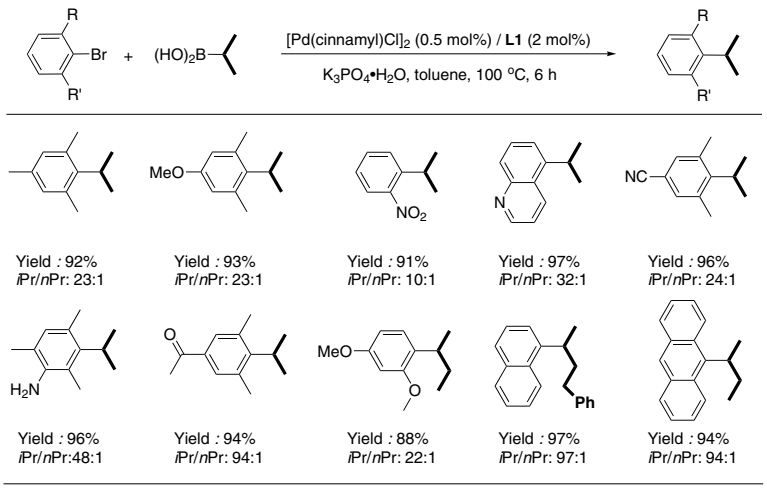
Scheme 7. Reduction and isomerization in Suzuki-Miyaura cross-couplings

We envisioned that the introduction of a hemilabile coordination by installing a P=O group adjacent to a bulky phosphorus ligand would be beneficial to steric hindered aryl acyclic secondary alkyl coupling. Our proposal was: a) the hemilabile coordination can block an empty coordination site of the palladium center to help inhibit β-hydride elimination; b) the bulky conformation of the ligand could promote facile reductive elimination step. After intensive design and synthesis, we were pleased to develope two novel bulky P,P=O ligands **L1** and **L2** on the basis of 2,3-dihydrobenzo[*d*]-[1,3]oxaphosphole framework (Scheme 8).[16] Both of them were easily prepared within 5 steps in gram scales.



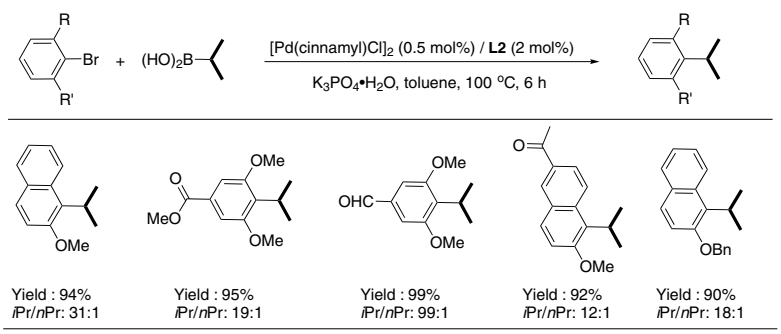
Scheme 8. The design of steric bulky P,P=O ligand

With **L1** as the ligand, a series of mono or di-*ortho*-substituted aryl bromides were coupled with acyclic secondary alkylboronic acids in excellent yields and selectivities under 1 mol% palladium loading (Scheme 9). Noteworthy was the excellent functional group compatibility, where methoxy, nitrile, cyano, ketone, amine and quinoline moieties were well tolerated. This method offered advantages over traditional Negishi and Kumada aryl alkyl cross-couplings.



Scheme 9. Substrate scope of sterically hindered aryl secondary alkyl cross-coupling

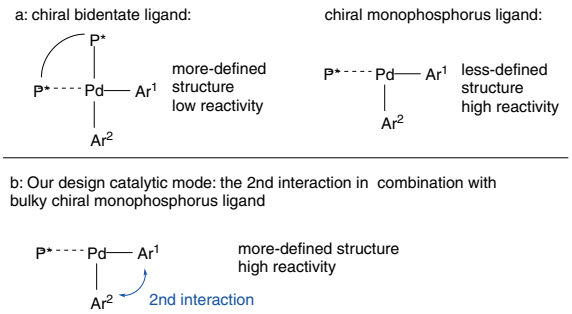
Since the isopropyl *ortho*-alkoxy di-*ortho*-substituted arene moieties exist in numerous bioactive natural products,[17] a highly efficient cross-coupling between *ortho*-alkoxy di-*ortho*-substituted aryl halides and isopropylboronic acids is yet to be accomplished. Although ligand **L1** provided only moderate yield and poor *i*Pr/*n*Pr selectivity, we were pleased to find the ligand **L2** led to excellent yields and *i*Pr/*n*Pr selectivities for those challenging transformations. A series of isopropyl *ortho*-alkoxy di-*ortho*-substituted arenes were efficiently synthesized in high yields and selectivities. Various functionalities such as aldehyde, ketone and ester were all tolerable (Scheme 10). This protocol was successfully employed in the late-stage modification of estrone at gram scale and applied in a new synthetic route toward gossypol by introduction of the isopropyl group by cross-coupling,[16] demonstrating the power of this methodology.



Scheme 10. Substrate scope of sterically hindered aryl secondary alkyl cross-coupling

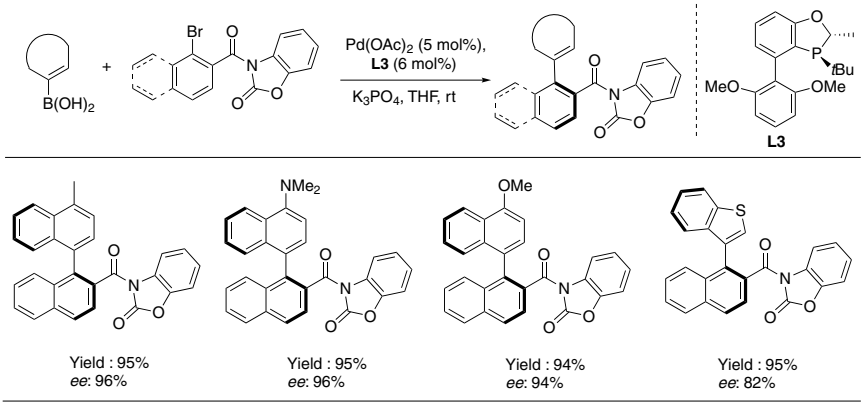
4 Asymmetric Suzuki-Miyaura Cross-Coupling

Chiral biaryl structures exist in numerous biological interesting natural products as well as serve as privileged frameworks for efficient ligands. As one of the most direct and effective method, the development of cross-couplings for construction those chiral biaryls have received much attention during the past several years.[18] Although much study on asymmetric cross-couplings including Kumada, Negishi, Suzuki-Miyaura have been reported in high yields and stereoselectivities,[19] most current methods focus on the development of unfunctionalized substrates with little synthetic interest. We sought to explore an efficient catalytic system that would be compatible to various functional groups and be applicable to the synthesis of chiral biaryl natural products. Our previous study has proven that the steric bulky and conformationally rigid monophosphorus ligands could promote the reactivity of sterically hindered aryl-aryl couplings. The presence of P-chirality in BI-DIME and related ligands encouraged us to investigate asymmetric Suzuki-Miyaura cross-coupling with these chiral ligands. There remains a significant challenge to achieve high enantioselectivity for cross-coupling with a chiral monophosphorus ligand. Unlike bidentate phosphorus ligands, chiral monophosphorus ligands allow more space at the palladium center, resulting in a less-defined Pd structure and more difficulty in enantiocontrol (Scheme 11a). To provide a solution to this problem, we designed a new catalytic mode by introducing a secondary interaction between the two aryl coupling partners in combination with the employment of a well-defined chiral monophosphorus ligand (Scheme 11b).[20] The choice of an auxiliary should follow the two principles: 1) The auxiliary can be easily introduced and transformed; 2) The auxiliaries should have the capabilities to offer a noncovalent interaction to the other aryl group such as π-π, polar-π, hydrogen bonding, and cation-π interactions.



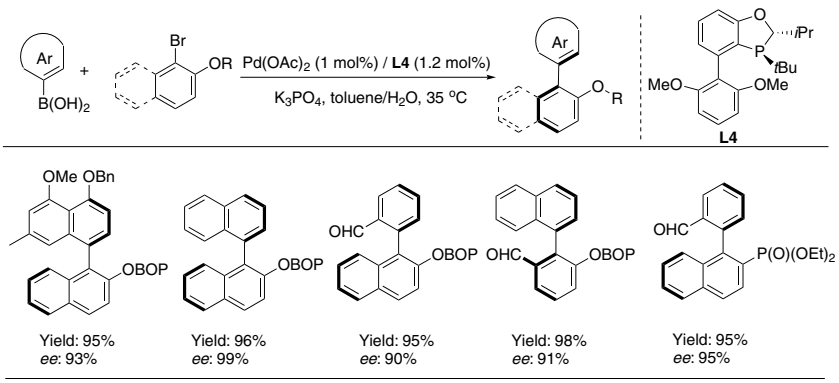
Scheme 11. New catalytic mode for highly reactive and enantioselective Suzuki-Miyaura cross-couplings

Following this strategy, we first investigated the synthesis of *ortho*-carbonyl substituted biaryls by Suzuki-Miyaura cross-coupling. Gratifyingly, excellent enantioselectivity was achieved when 2-benzoxazolinonyl imide group was employed with **L3** as the ligand. Functional groups such as methoxy and dimethylamino groups were well tolerated. Heteroaryl substrates with strong coordinating abilities such as benzothiazole were also applicable, providing excellent yield and good *ee* value (Scheme 12). It is noteworthy that the biaryl products were easily derivatized to form acids and alcohols by hydrolysis or reduction, respectively.[21] DFT calculations revealed the existence of a π-π interaction between the oxazolidinonyl group and the naphthyl group from the boronic acid. This secondary interaction played a significant role in achieving the high enantioselectivity.



Scheme 12. Substrate scope of asymmetric cross-couplings with *ortho*-carbonylbenzooxazolidinone substituents

Since numerous biaryl natural products contain *ortho*-hydroxyl/methoxy substituents, efficient construction of *ortho*-oxygen functionalized biaryls by asymmetric Suzuki-Miyaura couplings is highly desirable and yet to be developed. In contrast to *ortho*-carbonyl groups, the *ortho*-oxygen functional groups are more flexible and much more difficult to offer a reliable noncovalent interaction for high enantioselectivity. Fortunately, we found that OBOP (BOP = bis(2-oxo-3-oxazolidinyl)phosphinyl) group could provide excellent reactivity and enantieselectivity when **L4** was employed as ligand. It was noteworthy that the *ortho*-aldehyde substituted substrates were well-tolerable providing high yields and *ee* values, and *ortho*-phosphonate functional biaryls could also be synthesized efficiently (Scheme 13), indicating the compatibility of this cross-coupling with various functional groups.[22] Using this efficient methodology, we successfully finished the total synthesis of biaryl natural products korupensamine A & B, and their heterodimer michellamine B for the first time in a concise and highly stereoselective fashion. This work further demonstrated the practical utility in total synthesis of natural products.

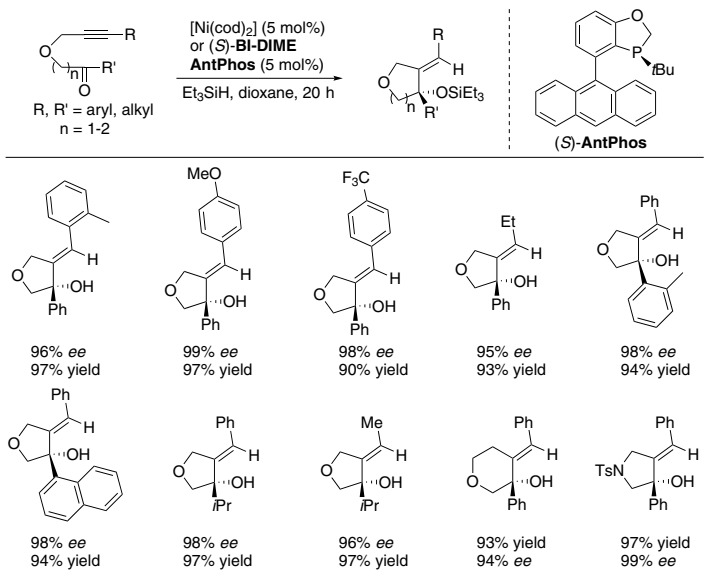


Scheme 13. Substrate scope of asymmetric cross-couplings with OBOP substituents

Recently, we reported an asymmetric Suzuki-Miyaura coupling of *ortho*-bromo aryl triflates with various arylboronic acids with **L3** as the ligand, affording a series of chiral biaryl triflates in high yields and up to 91% *ee*. The aryl triflates were easily transformed to various chiral biaryl products via simple derivatizations.[23]

5 Efficient Cyclizations Promoted by Chiral Monophosphorus Ligands

Chiral tetrahydrofuran/tetrahydropyran moieties exist in a broad range of bioactive natural products.[24] As one of most convenient and powerful methodology for constructing those chiral structures, the transition metal catalyzed intramolecular cyclization of alkynals/alkyones has received great interests.[25] Recent years have witnessed the ever expanding scope of such cyclizations along with the employment of various transition-metal catalysts including Ni, Pd, Rh, Ru and Ir catalytic systems. Among those metals, the application of cost-effective Ni in reductive cyclization is particularly attractive.[26] Although a number of Ni-catalyzed cyclizations of alkynals/alkynones with high reactivities are developed, no efficient enantioselective reductive/alkylative cyclization of alkynones has been reported. Encouraged by early work from Jamison's group,[27] we envisioned that P-chiral monophosphorus ligands developed in our laboratory could be applicable for enantioselective Ni-catalyzed cyclizations. With these easily prepared alkynones as substrates, we were pleased that the reductive cyclizations proceeded smoothly with chiral monophosphorus ligand (*S*)-BI-DIME or (*S*)-AntPhos as the ligand, providing cyclic allylic alcohols in excellent yields and *ee* values.[28] A series of aromatic and aliphatic alkynes were all suitable for this system. Aromatic ketones with various substituents such as methyl, methoxy and trifluoromethyl were compatible with the reaction conditions. In addition, various aliphatic ketones were also converted efficiently to chiral 2-alkyl furanols. Besides the chiral tetrahydrofuran products, a chiral tetrahydropyran product was also synthesized in high yield and 94% *ee* (Scheme 14).

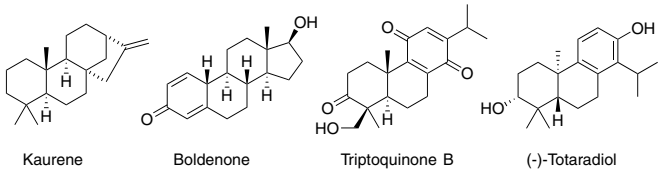


Scheme 14. Substrate scope of asymmetric reductive cyclization of alkynones

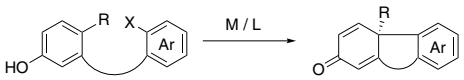
This asymmetric cyclization was applied in the efficient synthesis of the lignan dehydroxycubebin as well as the facile construction of chiral dibenzocyclooctadiene skeletons,[28] which demonstrated its utility in natural product syntheses.

Tricyclic skeletons bearing all-carbon quaternary centers exist in numerous biological interesting natural products, such as complex terpenes and steroids (Scheme 15).[29] Although various methods were successfully

applied in synthesis of those compounds, there remains great demand for developing more powerful and efficient strategies in the construction of such chiral skeletons. We believed that the asymmetric intramolecular dearomative cyclization can offer good synthetic efficiency owing to the availability of aryl systems as well as the convenience in the derivatization of the cyclized products (Scheme 16).[30]

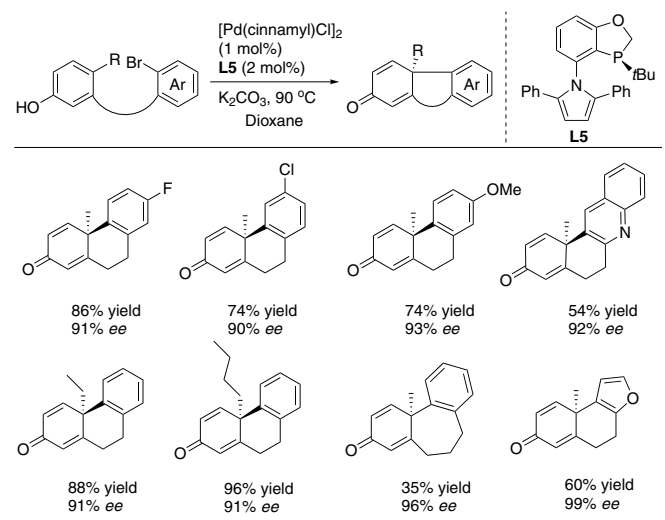


Scheme 15. Terpenes and steroids bearing all-carbon quaternary centers



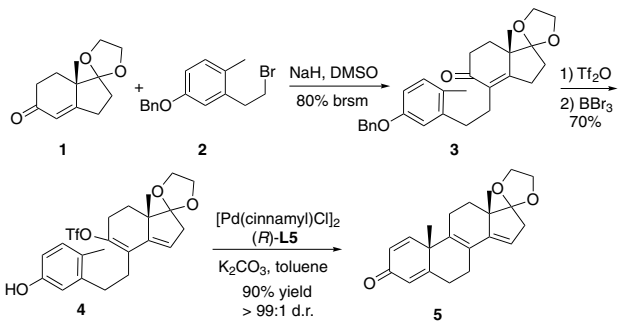
Scheme 16. Novel asymmetric dearomative cyclization

According to this design, we screened a series of chiral monophosphorus ligands developed in our group. Interestingly, high yield and excellent enantioselectivity was obtained when a new ligand **L5** bearing a 2,5-diphenylpyrrole moiety was employed and $[Pd(cinnamyl)Cl]_2$ as the catalyst precursor.[31] A series of tricyclic phenanthrenone derivatives bearing an all-carbon quaternary center were efficiently synthesized with this protocol. Various functional groups such as fluoro, chloro, and methoxy substituents were well tolerated. Quinone and furan heteroaryls were also compatible with the catalytic conditions (Scheme 17).

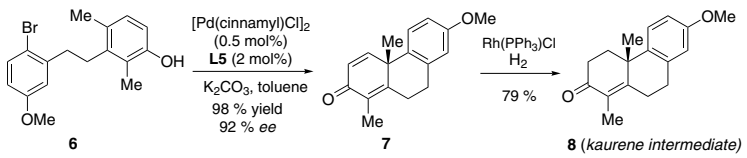


Scheme 17. Substrates scope of asymmetric dearomative cyclizations

The cyclization was applied to the construction of the skeleton of the anabolic steroid boldenone (Scheme 18). Thus, chiral ketal **1** was reacted with bromide **2** in the presence of NaH to form **3** in an unoptimized yield of 80% based on recovered starting material. Then, conversion of **3** into the cyclized precursor vinyl triflate **4** by two steps. Cyclization of triflate **4** by our protocol provides boldenone skeleton **5** in 90% yield and a diastereomeric ratio of > 99:1. This strategy was also applied in the synthesis of enone **8**, a key chiral intermediate[32] for the synthesis of kaurene, abietic acid, and a bruceantin analogue. Up to 98% yield and 92% *ee* value of tricyclic product was obtained by the key dearomative cyclization (Scheme 19). At the same time, we also finished the total synthesis of (-)-totaradiol by the employment of this efficient strategy.[31]



Scheme 18. Efficient synthesis of boldenone skeleton **5**



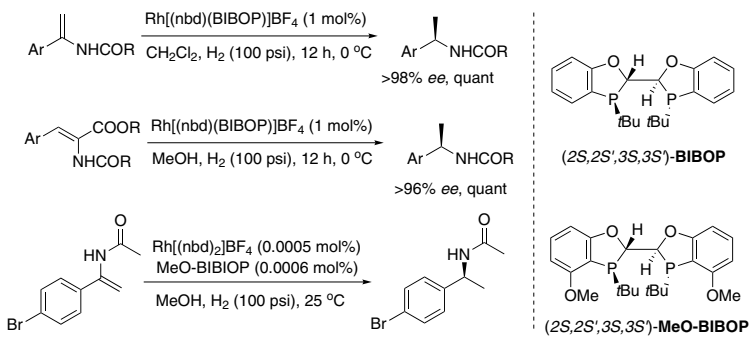
Scheme 19. Efficient synthesis of kaurene intermediate **8**

6 Asymmetric Hydrogenation

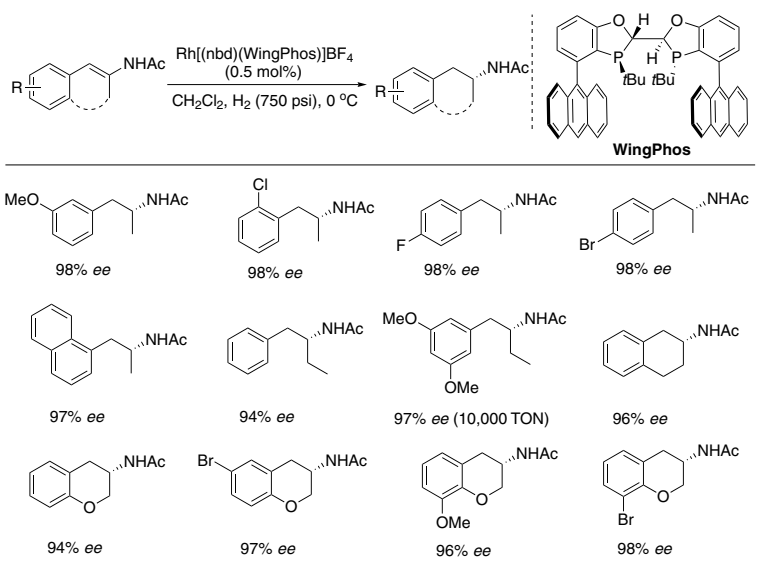
Although tremendous progress has been achieved in asymmetric hydrogenation, there remains numerous unsolved problems that call for developing new and efficient catalytic systems. P-chiral phosphorus ligands has demonstrated several advantages owing to its innate features,[3a] and a number of well-known, efficient ligands and catalysts were developed in recent years.[33] However, many of these are inconvenient to operate as oily or air-sensitive ligands. From the practical point of view, and in order to meet the increasing demand of green chemistry, highly efficient and operationally convenient phosphorus ligands are needed to be developed. Our group designed a novel skeleton with benzooxaphosphole as backbone in 2010, and then synthesized a series of C_2-symmetric P-chiral phosphorus ligands BIBOP and MeO-BIBOP (Scheme 20). Both of them are air-stable, crystalline solid that has been provide a great deal of operational convenience. With BIBOP as ligand, various α-arylenamides and α-(acylamino)acrylic acid derivatives can be hydrogenated in excellent yields and enantioselectivities with $Rh(nbd)_2BF_4$ as the metal precursor.[5] To our delight, MeO-BIBOP has provided 200,000 TON in rhodium-catalyzed asymmetric hydrogenation of *N*-[1-(4-bromophenyl)vinyl]acetamide,

which has been considered as the most efficient processes in rhodium-catalyzed asymmetric hydrogenation of α-arylenamides up to date.

We further modified the BIBOP by introducing anthracenyl groups and thus synthesized the new ligand WingPhos. In contrast to the traditional bisphosphorus ligands, WingPhos contains anthracenyl groups that protrude directly forward to the substrate coordination and provide a well-defined and deep chiral pocket, which could enable efficient asymmetric hydrogenation for some challenging substrates. Since chiral β-arylamines exist in numerous biologically interesting natural products and therapeutic agents,[34] we embarked a program on searching for efficient phosphorus ligands to synthesize chiral β-arylamines by asymmetric hydrogenation. Gratifyingly, we found WingPhos was an efficient ligand for asymmetric hydrogenation of both (*E*)-β-arylenamides and cyclic β-arylenamides. A series of chiral β-arylisopropylamines, 2-aminotetralines, and 3-aminochromans were easily accessed by using this method (Scheme 21). Hydrogenation of (*E*)-*N*-[1-(3,4-dimethoxyphenyl]-prop-1-en-2-yl)acetamide as substrate showed that the highest TON could be reached up to 10,000 without erosion of the *ee* value, thus demonstrating the high efficiency and reactivity of WingPhos for this transformation.[35]

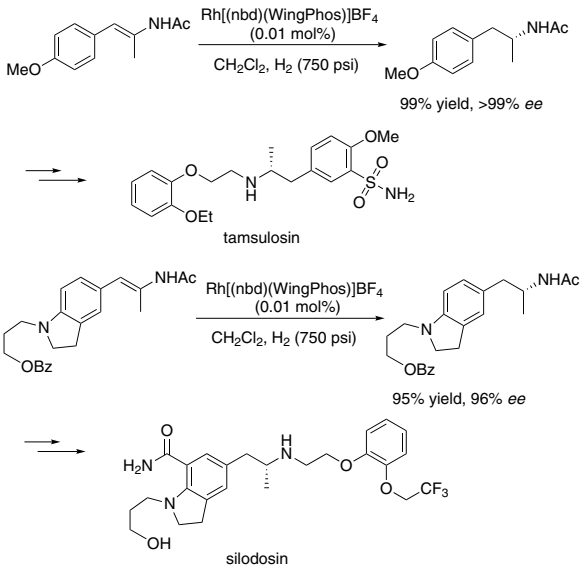


Scheme 20. Asymmetric hydrogenation by BIBOP and MeOBIBOP



Scheme 21. Substrate scope of asymmetric hydrogenation by WingPhos

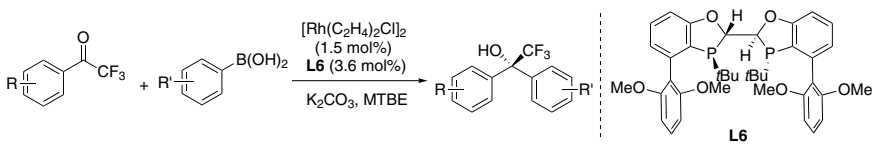
By using this method, several key chiral intermediates for therapeutic agents such as the α-blocker tamsulosin and α_1-adrenoceptor antagonist silodosin, can be efficiently synthesized by asymmetric hydrogenation (Scheme 22).



Scheme 22. The application in the synthesis of key intermediates for therapeutic agents

7 Enantioselective Addition of Arylboron Reagents to Arylketones

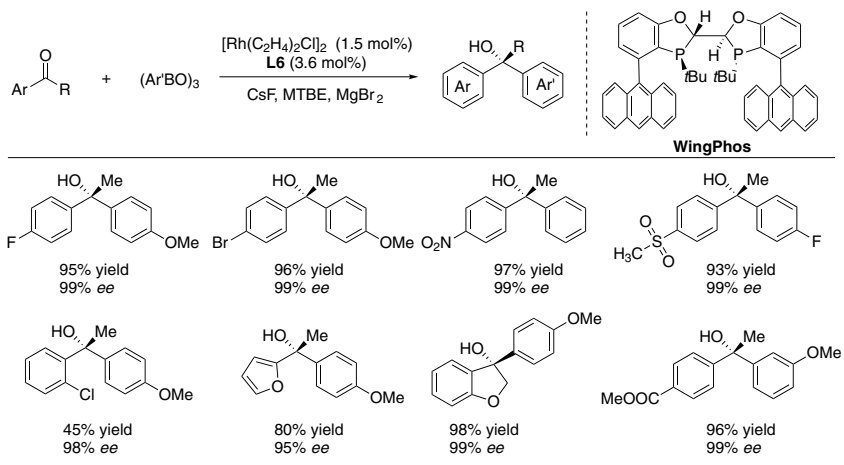
Chiral tertiary carbinol moieties bearing diaryl and alkyl groups exist in a number of therapeutic agents and natural products,[36] such as the antidepressant escitalopram, antihistamine clemastine, and cough suppressant chlophedianol. The efficient synthesis of these chiral tertiary alcohols have received significant attention. The asymmetric addition of nontoxic, stable and operationally convenient aryl boron reagents to simple aryl ketones is highly attractive yet remains challenging. In 2013, we described a highly enantioselective Rh-catalyzed addition of trifluromethyl ketones by arylboronic acids[37] by using **L6** as ligand. A series of chiral tertiary trifluoromethyl alcohols were synthesized in good to excellent yields and excellent *ee* values (Scheme 23).



Scheme 23. Highly enantioselective addition of arylboronic acids to aryl trifluoromethyl ketones

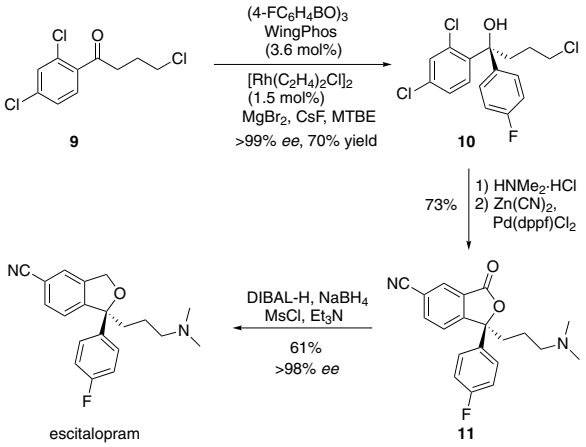
Low yield (25%) was observed for the addition of 4-methoxyphenylboronic acid to acetophenone when **L6** was employed as ligand, albeit with an excellent *ee* (96%). This promising result encouraged us to search for

more efficient catalytic system. After intensive optimization of the reaction conditions, we were pleased that an excellent yield and enantioselectivity were obtained in the addition of phenylboroxine to acetophenone with WingPhos as Ligand. The employment of magnesium bromide as additive is very important to enhance the yield presumably by activating the ketone substrate. With this new protocol, a range of chiral tertiary carbinols were synthesized in excellent *ee* values and yields.[38] Functional groups such as halide, nitro, ester, and sulfone were well tolerated. Notably, the *ortho*-substituted aryl ketones were also compatible and provided tertiary alcohols with excellent enantioselectivities, albeit with diminished yields. In addition, the Rh/WingPhos system could also be employed in enantioselective addition to benzofused five-membered cyclic ketones, providing cyclic tertiary alcohols in excellent *ee* values (Scheme 24).



Scheme 24. Substrate scope of asymmetric addition of arylboroxines to aryl ketones

This catalytic methodology was successfully applied in enantioselective synthesis of antidepressant drug escitalopram (Scheme 25). 4-Fluorophenylboroxine was added to 4-chloro-1-(2,4-dichlorophenyl)butan-1-one (**9**) with the Rh/(*R*,*R*,*R*,*R*)-WingPhos catalyst, providing the desired tertiary alcohol **10** on gram scale with 70% yield and >99% *ee* value. Introduction of dimethylamine by displacement of the chloride in **10** and subsequent palladium-catalyzed dicyanation-lactonization afforded the lactone **11** in 73% overall yield. After reduction of lactone **11** and subsequent cyclization, providing escitalopram in 61% overall yield and with greater than 98% *ee*. Thus, a new highly enantioselective synthesis of escitalopram was successfully developed with this methodology.[38]



Scheme 25. Synthesis of escitalopram

8 Summary

In this article, we outlined our recent efforts in the development of novel phosphorus ligands and its applications in efficient transition metal catalyzed reactions. In particular, we developed four categories of new phosphorus ligands on the basis of a benzooxaphosphole backbone. All of those novel ligands are air-stable and operationally convenient solids. In search of highly efficienct and practical catalyst, we have developed the bulky biaryl monophosphorus ligands BI-DIME and AntPhos that have enabled sterically hindered aryl-aryl cross-couplings; two P,P=O.

Ligands have been successfully applied in sterically hindered aryl-isopropyl cross-couplings; several P-chiral monophosphorus ligands have been synthesized and employed successfully in efficient asymmetric aryl-aryl cross-couplings or cyclizations; several P-chiral bisphosphorus ligands are applied in highly enantioselective asymmetric hydrogenation as well as asymmetric addition of arylboron reagents. The high reactivity, chemoselectivity, and enantioselectivity achieved in these catalytic systems allow practical applications in construction of therapeutic agents and natural products. Despite those progresses, the current applications remains very limited with respect to the increasing demand of numerous catalytic reactions. We are convinced that the development of novel phosphorus ligands will continue to be an important method for discovering efficient and practical catalytic reactions and the future is bright down this path.

Acknowledgment

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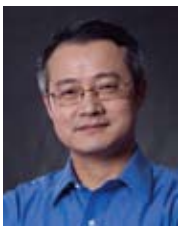
Guangqing Xu was born in 1987 in Shandong Province, China. He received his Bachelor of Science from Qingdao University of Science and Technology in 2009. After one year of experience in pharmaceutical company, he then joined in Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, and received his Ph.D. in 2015 under the guidance of Prof. Wenjun Tang. Now, he is working on development of efficient asymmetric catalyst and reactions in Prof. Wenjun Tang's group as assistant researcher.



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Wenjun Tang was born in 1974 in Zhejiang Province, China. He received his B. Eng. degree in 1995 from East China University of Sciences and Technology, his M.S. degree in 1998 from Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, and his Ph.D. in 2003 from the Pennsylvania State University. After two-year postdoctoral research at the Scripps Research Institute, he worked six years as a process chemist at Boehringer Ingelheim Pharmaceuticals Inc. In 2011, he took his current position as a research professor at Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences. His research interests are in the areas of asymmetric catalysis, total synthesis of natural products, and development of efficient chemical processes.

化学よもやま話 ～身近な元素の話～

典型元素の新しい同素体（2）

佐藤　健太郎

前々回に続き，近年登場した典型元素の新しい同素体を紹介しよう。

ケイ素

ケイ素はクラーク数25.8で，地殻上に酸素に次いで多く存在する。最もよく知られている同素体は，ケイ素原子がダイヤモンド型につながったもので，暗灰色の硬くてもろい固体だ。半導体材料としてあらゆる場所で使われ，現代社会になくてはならない存在となっている。

もうひとつ，常圧で安定なケイ素の同素体として，アモルファスシリコンがある。これはケイ素同士が無秩序に三次元網目状構造を成したもので，見た目は茶色い粉末状だ。やはり半導体材料となるが，結晶ケイ素に比べてエネルギーギャップが大きく，成膜しやすいなどの特徴があるため，薄膜トランジスタや太陽電池などへの応用がなされている。ただしアモルファスシリコンは，ケイ素の骨格にところどころ水素が結合していると考えられ，正確な意味での同素体とは言いがたい。

その他，結晶ケイ素に高圧をかけて行くと，βスズ構造などいくつかの結晶構造へと相転移することが知られているが，これらの用途はまだ十分に拓かれていない。

新たな3次元ケージ

しかし最近になり，3次元網目状ケイ素の新顔が登場した（*Nat. Mater.* **2015**, *14*, 169.）。カーネギー研究所のT. A. Strobelらは，まず高温高圧下でナトリウムとケイ素を反応させ，ケイ素のケージの中にナトリウムが閉じ込められた形の$NaSi_6$という組成の化合物を得た。これを真空下で400 Kに加熱すると，徐々にナトリウムが抜け，ケイ素のケージがほぼそのままの形で残るのだ。

こうして得られた新しいケイ素の同素体は，5，6，8員環から成るネットワークを持ち，単位格子は24個のケイ素原子からできている。空気中でも750 K付近まで安定に存在でき，バンドギャップも1.3 eV程度と，太陽電池などへ応用するのに適した性質を備えている。また，この方法の応用で，さらに新しい構造のケイ素同素体が得られてくる可能性もあり，今後の展開が期待される。

シリセン登場

炭素材料におけるナノカーボン類に相当する構造は，ケイ素では得られないのだろうか？フラーレン同様の構造をとるSi_{60}分子については，いくつかの理論計算が行なわれているものの，いまだ合成はされていない。炭素と異なり，ケイ素原子同士のπ共役系が弱いことが要因と考えられる。グラファイトに相当するケイ素同素体も，まだ知られていない。

しかし最近，ケイ素版グラフェンというべき，シリセンという新材料が注目を浴びている。グラフェン同様，ケイ素がハニカム状に広がった構造だ。シリセンは以前より興味が持たれ，理論面か

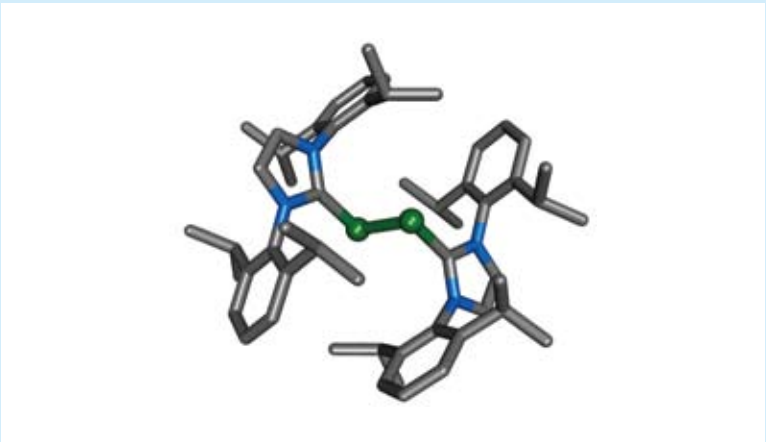
らの研究が行なわれてきたが，銀の表面にケイ素を蒸着させることで，初めてシリセンが作り出されたのは 2010 年のことだった（*Appl. Phys. Lett.* **2010**, *97*, 223109.）。

ただしケイ素は，炭素のような sp^2 混成軌道が安定でないため，完全な平面ではなく凸凹しており，また空気に不安定という欠点もある。しかし，グラフェンでは実現不可能な機能を持たせうるなど期待も大きく，2015 年には早くもシリセンを用いたトランジスタが作り出されている。超高速コンピュータの実現へ向けて，夢が広がる新素材だ。

NHC でケイ素を挟む

また 2008 年には，２つの N- ヘテロサイクリックカルベン（NHC）に 2 原子のケイ素が挟まれた形の化合物が，Robinson らによって合成された（*Science* **2008**, *321*, 1069.）。NHC が配位した四塩化ケイ素を，KC_8 で還元することによって生成する。C-Si-Si の角度は約 93° と，ほぼ直角に近い折れ曲がり方をしている。

これまで Si_2 という分子は，極低温でスペクトル的に存在が確認されていただけだったが，カルベンによって安定化され，結晶として取り出すことが可能になった。カルベンはあくまで配位子であり，中央の Si_2 は新たなケイ素同素体とみなすことができる。元素科学の金字塔と評される研究だ。



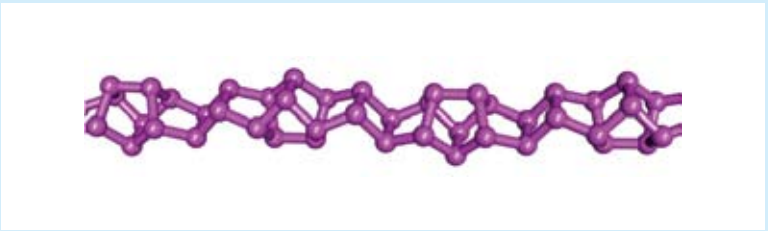
NHC に挟まれて安定化された Si_2（中央の緑色）

複雑なリンの同素体

高校の教科書を見ると，リンの同素体には黄リン・赤リンなどがあるとされている。黄リンは P_4 という分子から成る発火性の淡黄色固体，赤リンは赤褐色の粉末で比較的反応性に乏しく，マッチなどに用いられるとの記述がある。

しかし近年では，黄リンという純物質は存在せず，赤リンなどの不純物をわずかに含んだ白リンがその正体と考えられるようになった。その他，黒リン・紫リン・紅リンなどの「同素体」が記載されている本もあるが，これらにも正確な意味での同素体とはいえないものがあることがわかってきた。たとえば紅リン（scarlet phosphorus）と呼ばれるものは，実のところ赤リンの微細な結晶と見られている。というわけで，リンの同素体の世界はなかなか複雑だ。

1 次元ポリマー状のリン同素体が発見されたのは，21 世紀に入ってからのことだ。A. Pfitzner, H. Eckert らのグループは，赤リンとヨウ化銅 (I) から得られる付加体を，シアン化カリウム水溶液で洗浄することで銅を除き，ほぼ純粋なリンから成る赤茶色の固体を得た。これを分析したところ，12 原子のリンからできた単位構造を繰り返した形のポリマーであることがわかった（*Angew. Chem. Int. Ed.* **2004**, *43*, 4228.）。うちひとつの構造を図に示す。製法の工夫次第で，さらに新しい同素体ができる可能性もまだまだありそうだ。



リン原子から成る 1 次元ポリマー

NHC による安定化

周期表でひとつ上に位置する，窒素は二原子分子 N_2 が最も安定だ。リンでも，これに相当する P_2 という分子が知られている。リン原子同士は三重結合で結びついており，結合距離は約 189.5 pm と，通常の P-P 単結合（220 pm 前後）よりはるかに短い。この「二リン」は，白リンを 1100 K まで加熱することで生成するが，極めて不安定で取り扱いは難しい。近年，ジエンと反応してヘテロ Diels–Alder 反応を起こすことが判明し，リン化合物の新たな合成法として応用が拓ける可能性がある。

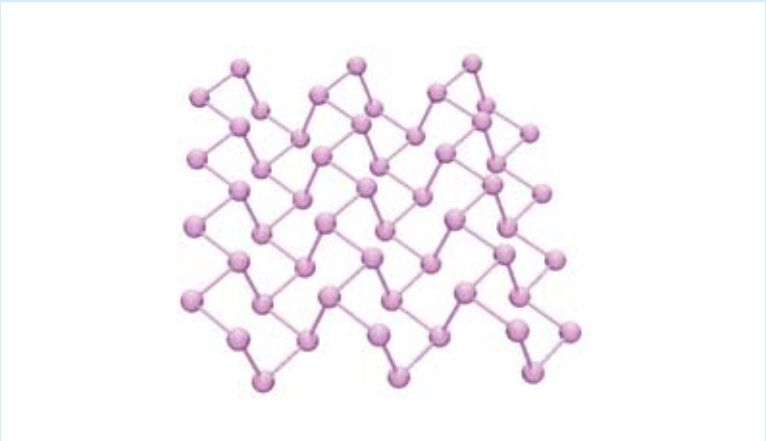
ではこの二リンも，ケイ素のように NHC の配位によって安定化させられないのだろうか？実は Robinson らのグループが，ケイ素の場合とほぼ同様の手法によって，安定化された二リン分子を作り出している（*J. Am. Chem. Soc.* **2008**, *130*, 14970.）。NHC が化学の世界にもたらした，大きな変化の一例に挙げられよう。

リンのシート

黒リンは古くから知られているリンの同素体のひとつで，白リンを 12,000 気圧下で加熱することで生成する。リン原子から成るハニカム構造のシートが積み重なったもので，炭素でできたグラファイトに似た構造といえる。

現在盛んに研究が行われているグラフェンは，グラファイトから一層だけを剥がし取ることで初めて作り出された。同じように，黒リンから一層だけを剥ぎ取れば，ユニークな性質を持った物質が得られるのではないか？これが P. D. Ye らによって実現したのは，2014 年のことだ（*ACS Nano* **2014**, *8*, 4033.）。

フォスフォレンと名付けられたこの 2 次元材料は，グラフェンと異なって波打った構造をとる。また，グラフェンが良導体であるのに対し，フォスフォレンは半導体として振る舞う。この新物質はすでに大きな注目を集めており，前述の論文の引用数はすでに 800 を超えている。安価なリンから優れた電子デバイスが誕生する可能性を秘めており，先行きが期待される材料のひとつだ。



フォスフォレンの構造（Wikipedia より）

ケイ素とリン，なじみ深い二つの元素にも，これだけ新たな発見が相次いでいる。化学の可能性の広さを，改めて思い知らされる気がする。

執筆者紹介

佐藤　健太郎（Kentaro　Sato）

[ご経歴]　1970 年生まれ，茨城県出身。東京工業大学大学院にて有機合成を専攻。製薬会社にて創薬研究に従事する傍ら，ホームページ「有機化学美術館」（http://www.org-chem.org/yuuki/yuuki.html，ブログ版は http://blog.livedoor.jp/route408/）を開設，化学に関する情報を発信してきた。東京大学大学院理学系研究科特任助教（広報担当）を経て，現在はサイエンスライターとして活動中。著書に「有機化学美術館へようこそ」（技術評論社），「医薬品クライシス」（新潮社），「『ゼロリスク社会』の罠」（光文社），「炭素文明論」（新潮社），「世界史を変えた薬」（講談社）など。

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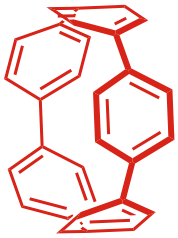
最小の“カーボンナノリング”：[5]シクロパラフェニレン（[5]CPP）

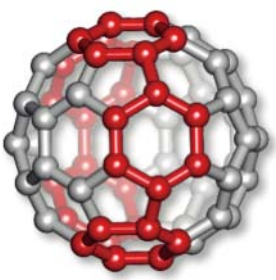
C2931　[5]Cycloparaphenylene (= [5]CPP)（1）　　20mg 39,000円　100mg 118,000円



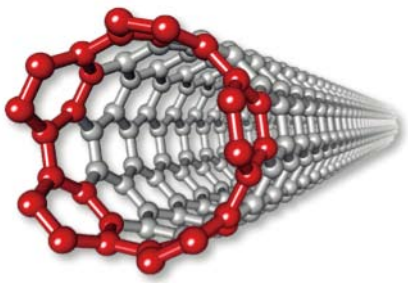
[5]CPP (**1**)

シクロパラフェニレン（CPP）はベンゼン環をパラ位で環状につなげた化合物で，カーボンナノリングとも呼ばれます。この構造はカーボンナノチューブ（CNT）の最小構成単位に相当し，基礎化学のみならず材料科学などの応用分野からも注目されています。実際，伊丹らはこのCPPをテンプレートとし，炭素骨格をつなげていくことで，均一な直径を持つCNTをボトムアップ合成できることを見出しました[1]。特定のサイズのCPPがフラーレンを包摂することも報告されており，ホスト分子材料としても注目されています[2]。

最近では，より大きな歪みを持った小さいサイズのCPPが合成されています。山子[3,4]およびJasti[5]らのグループは，これまで合成されたCPPの中で最も小さな環サイズを持つ[5]CPP（**1**）の合成手法をそれぞれ独自に報告しています。**1**をテンプレートとすることで，最小の直径を有するCNTをボトムアップ合成できると期待されます。**1**はフラーレン（C_{60}）の部分構造で，かつ同じ直径（0.7 nm）を有しており，C_{60}に匹敵する狭いHOMO-LUMOギャップを持ちます。また，有機溶媒への高い溶解性を示します。



C_{60}



[5,5]CNT

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P. J. Evans, E. R. Darzi, R. Jasti, *Nat. Chem.* **2014**, *6*, 404.

異性体を含まないアントラジチオフェン誘導体

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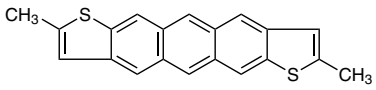
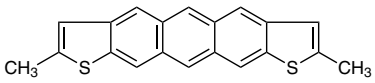


anti-DMADT (**1**)



syn-DMADT (**2**)

ペンタセンは優れたp型有機半導体ですが，その高いHOMOレベルに起因する酸化への不安定性のため，デバイス作成時の性能のバラつきや長期的安定性に問題があります。それに対して，低いHOMOレベルを有するアントラジチオフェンは酸化に対してより安定であり，ペンタセン同様の優れたp型半導体特性を示します。しかしながら，多くのアントラジチオフェン誘導体は，チオフェン環の向きによる*syn*-，*anti*-異性体の混合物であるため，デバイス作成時にそれぞれの異性体が性能に与える影響が不明確でした。

ジメチルアントラジチオフェン（DMADT）は，時任・侭田らによって開発されたアントラジチオフェン誘導体であり，*anti*-体と*syn*-体を単一異性体としてそれぞれ合成しています[1)]。これにより，DMADTは*syn/anti*それぞれの物性が報告されており，光学特性やエネルギーレベルは類似するも，ホール移動度はより対称性の高い*anti*-DMADT（μ = 0.41 cm^2/Vs）が，*syn*-DMADT（μ = 0.084 cm^2/Vs）よりも5倍ほど優れた値を示します。この結果はアントラジチオフェンを使ったデバイス作製において，単一異性体を使用する重要性を示しています。

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1) M. Mamada, T. Minamiki, H. Katagiri, S. Tokito, *Org. Lett.* **2012**, *14*, 4062.

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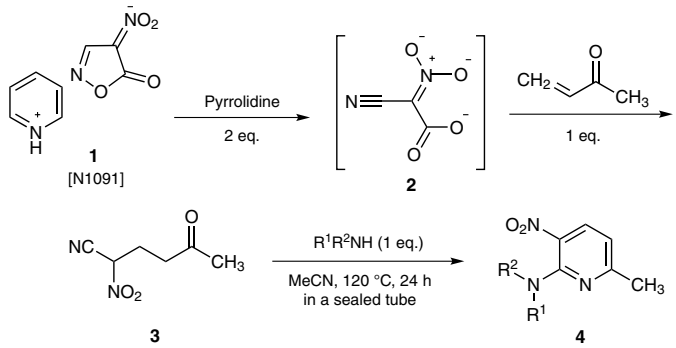
ニトロアセトニトリル（NAN）は，反応性の高いシアノ基とニトロ基を有するとともに，中間のメチレン基が高い酸性度を示すため，シアノニトロメチル化剤として合成化学的に有用です。しかしながら，NAN は爆発性を有することから，安全に使用できる代替試薬が求められています。

西脇らにより開発された 4-ニトロ-5(2*H*)-イソオキサゾロンピリジニウム塩（**1**）は，2 分子の有機塩基を作用させることで開環反応が速やかに進行し，NAN の合成等価体として働くシアノアシニトロ酢酸塩 **2** に誘導されます [1]。生成した **2** は，非極性，極性を問わず有機溶媒への溶解性が高いことから，安全で取り扱いの容易なシアノニトロメチル化剤として多岐にわたる多官能性化合物の合成に有用です。

例えば，発生させた **2** とビニルケトンの反応で得られたマイケル付加体 **3** に，アミンを作用させることで，ニトロ基とアミノ基を隣接位に有する二官能性ピリジン誘導体 **4** を得ることができます [2]。イソオキサゾリンやイソオキサゾール，ジヒドロピリジン，ナフチリジンなどの多官能性複素環の合成も報告されています [2-4]。



1
[N1091]

2

3

4

さらに，**1** から誘導されるシアノアシニトロ酢酸塩 **2** を利用して得られる生成物は，シアノ基，ニトロ基を有するため，種々多様な骨格へと導くことが可能です。

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新しい Julia 型メチレン化試薬

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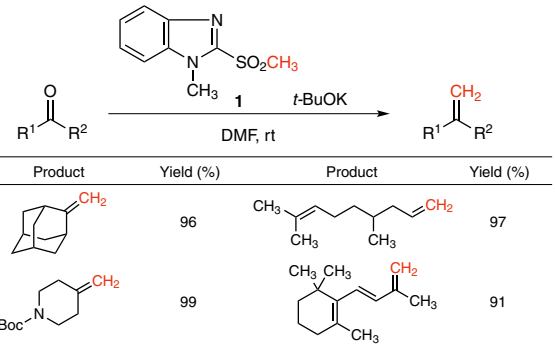
安藤らは，1- メチル -2-(メチルスルホニル)ベンゾイミダゾール（**1**）をメチレン源に用いる Julia–Kocienski 反応型のメチレン化反応を報告しています。**1** は塩基存在下，室温でケトンやアルデヒドをメチレン化合物に変換し，α,β-不飽和ケトンやかさ高いケトンなど，幅広い基質に適用可能です。さらに，反応の副生成物であるベンゾイミダゾール誘導体は，分液操作により除去が可能なため，容易に精製が行えます。



Product	Yield (%)	Product	Yield (%)
	96		97
	99		91

文献
1) K. Ando, T. Kobayashi, N. Uchida, *Org. Lett.* **2015**, *17*, 2554.

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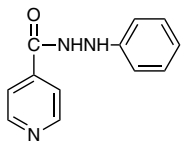

1

iPSCs（induced pluripotent stem cells）と ESCs（embryonic stem cells）の研究の進展によって，それらの種々の細胞への分化が再生医学へ応用されることが期待されています[1-3]。しかしながら，自己再生と分化という特性が，それらの細胞を腫瘍原性にしています[4-7]。この腫瘍形成は残存する未分化の多能性細胞に正の相関があることが見出されています[6]。

PluriSIn 1（**1**）は stearoyl-CoA desaturase の阻害剤で，オレイン酸の合成を阻害し，残存する未分化のヒト多能性幹細胞（hPSCs）を選択的に除去します[8]。Ben-David らは，この阻害は小胞体ストレス，その応答，翻訳の減少を hPSCs 内で引き起こし，結果としてアポトーシスに至るという機構を提唱しています[8]。

本製品は試薬であり，試験・研究用のみにご利用ください。

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