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Late-Stage Diversification of Phosphines by C−H Activation: A Robust Strategy for Ligand Design and Preparation

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CONSPECTUS: The advent of the twenty-first century marked a golden era in the realm of synthetic chemistry, exemplified by groundbreaking advancements in the field of C−H activation, which is a concept that quickly transitioned from mere academic fascination to an essential element within the synthetic chemist's toolkit. This methodological breakthrough has given rise to a wealth of opportunities spanning a wide range of chemical disciplines. It has facilitated the late-stage diversification of elaborate organic frameworks, encompassing the spectrum from simple methane to complex polymers, thus refining the lead optimization process and easing the production of diverse molecular analogues. Among these strides forward, the development of phosphorus(III)-directed C−H activation stands out as an increasingly significant and inventive approach for the design and synthesis of ligands, substantially redefining the contours of synthetic methodology.

Phosphines, renowned for their roles as ligands and organocatalysts, have become fundamentally important in modern organic chemistry. Their efficiency as ligands is significantly affected by coordination with transition metals, which is essential for their involvement in catalytic processes, influencing both the catalytic activity and the selectivity. Historically, the fabrication of phosphines predominantly relied on synthesis employing complex, multistep procedures. Addressing this limitation, our research has delved into ligand design and synthesis through innovative catalytic P(III)-directed C−H activation strategies. In this Account, we have explored a spectrum of procedures, including direct arylation using metal catalysis, and ventured further into domains such as C−H alkylation, alkenylation, aminocarbonylation, alkynylation, borylation, and silylation. These advances have enriched the field by providing efficient methods for the late-stage diversification of biaryl-type monophosphines as well as enabled the C−H activation of triphenylphosphine and its derivatives. Moreover, we have successfully constructed libraries of diverse axially chiral binaphthyl phosphine ligands, showcasing their potency in asymmetric catalysis. Through this Account, we aim to illuminate the exciting possibilities presented by P(III)-directed C−H activation in propelling the boundaries of organic synthesis. By highlighting our pioneering work, we hope to inspire further developments in this promising field of chemistry.

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- Wen, J.; Wang, D.; Qian, J.; Wang, D.; Zhu, C.; Zhao, Y.; Shi, Z. Rhodium-catalyzed P^{III}-directed *ortho*-C−H borylation of arylphosphines. *Angew. Chem., Int. Ed.* **2019**, *58*, 2078−2082.[2] *This study introduces a novel rhodium-catalyzed system for the ortho-C−H borylation of triphenylphosphine and its derivatives, which proceeds through the formation of strained metallacycles. We successfully synthesized a series of ortho-boronated phosphines, featuring mono- and diaryl substituents with varied steric and electronic characteristics, and achieved high yields.*
- Lin, L.; Zhang, X.-j.; Xu, X.; Zhao, Y.; Shi, Z. $Ru_3(CO)_{12}$-catalyzed modular assembly of hemilabile ligands by C−H activation of phosphines with isocyanates. *Angew. Chem., Int. Ed.* **2023**, *62*, e202214584.[3] *This study introduces a new method for creating hemilabile phosphine-amide ligands, including axially chiral types, through the ruthenium-catalyzed C−H activation of phosphines directed by P(III) atoms using isocyanates.*

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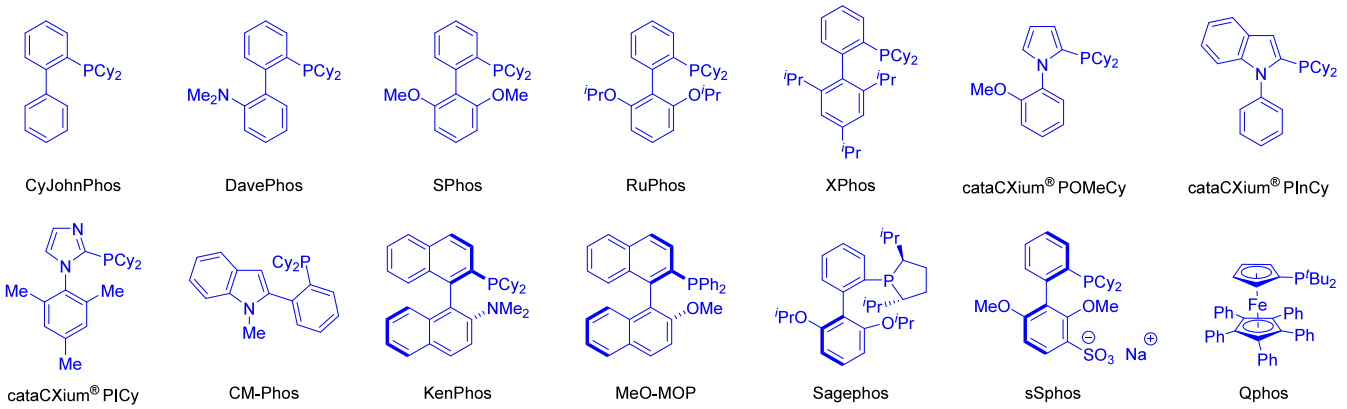

Figure 1. Some widely used and commercially available monophosphine ligands.

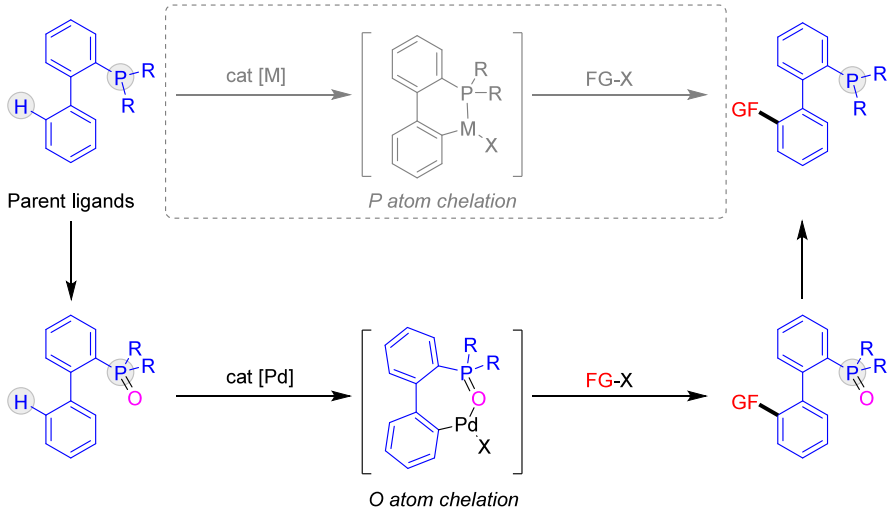

Figure 2. Prior approach to monophosphine ligands by C−H activation.

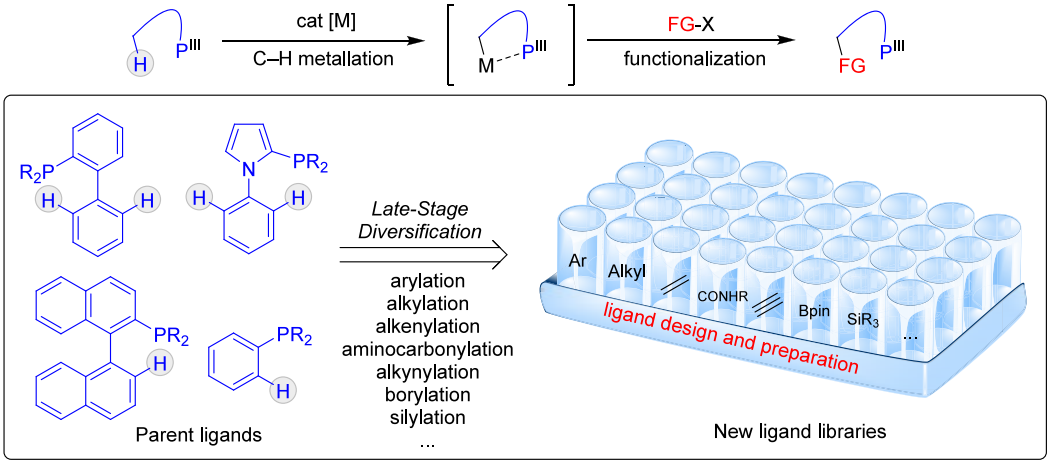

Figure 3. Ligand design and preparation were enabled by P(III)-directed C−H activation.

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1. INTRODUCTION

Transition-metal catalysis has emerged as an indispensable strategy for achieving selective and efficacious chemical transformations in the realm of organic synthesis. The pivotal role of ligands in these catalytic mechanisms is crucial, as they exert a profound impact on both the reactivity and the specificity of the metal catalysts.[5] Phosphine ligands, in particular, are

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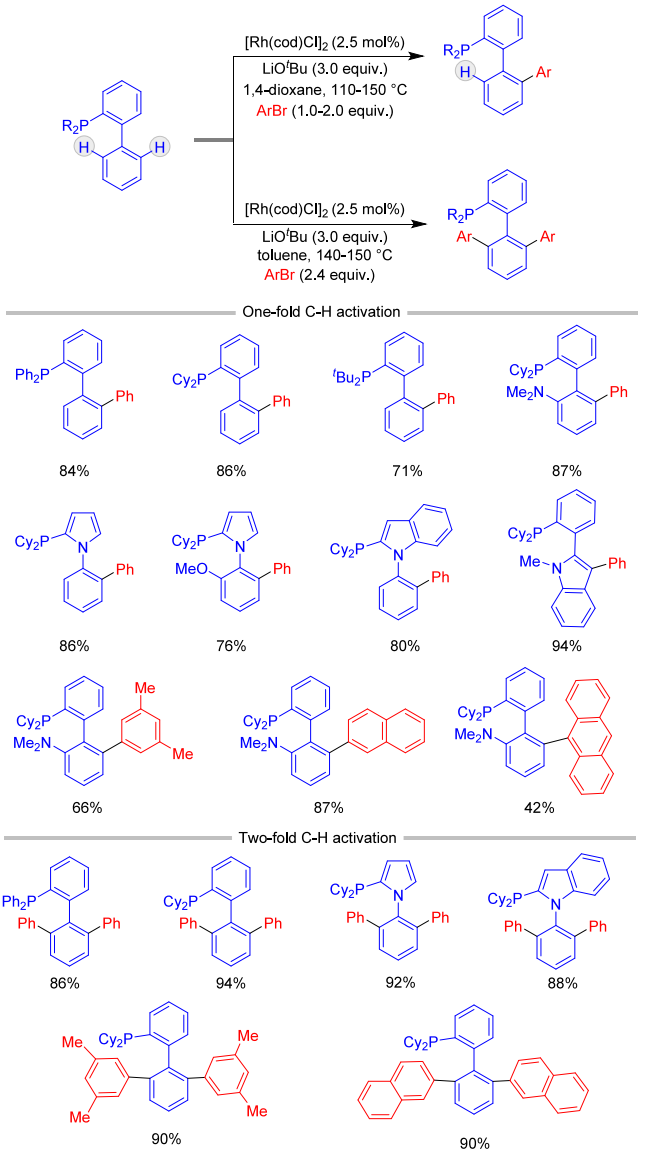

Figure 4. Rh(I)-catalyzed direct arylation of biaryl phosphines with aryl bromides.

esteemed as a class of promising candidates and have garnered significant importance in the landscape of contemporary organic chemistry (Figure 1).[6,7] The relentless quest for innovative phosphine ligands, tailored with unique properties to catalyze specific reactions effectively, continues to be a vibrant and essential domain in the advancement of catalysts.[8−10] Despite the remarkable strides achieved in the field over the past decades, the search for phosphorus ligands that surpass their forerunners in performance is unceasing. The traditional synthetic avenues for phosphine ligand generation have generally relied on multistep processes. This is particularly true for chiral phosphine compounds, which are more challenging to synthesize.[11] Preparations of these intricate molecules often involve the use of chiral auxiliaries and are principally guided by methods of kinetic resolution in practical applications.[12−14] Consequently, there is growing interest in devising more streamlined and proficient methodologies for the synthesis of a diverse array of phosphine ligands, reflecting a dynamic area of development in modern synthetic chemistry.

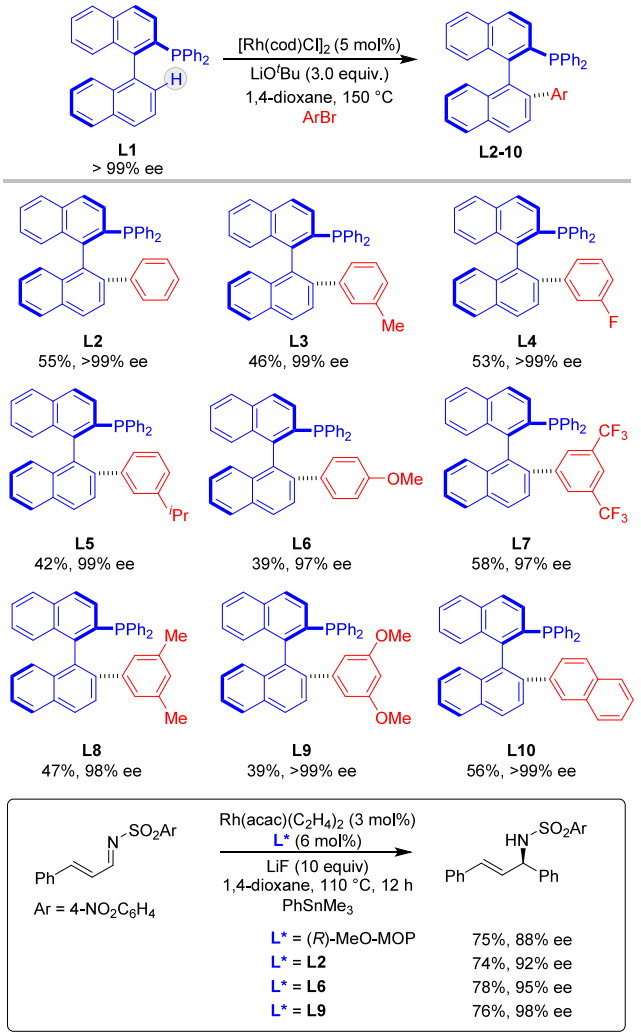

Figure 5. Construction of the axially chiral Ar-MOP family and testing its reactivity.

The strategy of catalytic C−H activation has revolutionized the principles of synthetic chemistry by facilitating the rapid generation of chemical complexity.[15] However, achieving precise control of regioselectivity in C−H activation remains a formidable challenge, given the presence of multiple C−H bonds of comparable strength within complex molecules. The most successful approach to C−H activation involves the utilization of directing groups, either inherent or preinstalled in organic compounds, to position the metal catalyst at a specific C−H bond.[16−21] Promising directing groups include azines, carbonyl groups, and amino derivatives. In this context, there are a series of effective methodologies for the synthesis of biaryl-based phosphine ligands through P═O-directed C−H activation (Figure 2).[22,23] However, this methodology entails an indirect pathway that necessitates the prior preparation of phosphine oxide followed by subsequent reduction to yield the final phosphines. In the realm of ligand design, the utilization of in situ ligand diversification serves as a potent and rare approach, bestowing remarkable reactivity upon newly constructed ligands.

The inception of metallacycle formation involving phosphines through C−H metalation extends over half a century. However, it was not until recent developments in the catalytic mode that P(III)-directed C−H activation within these compounds

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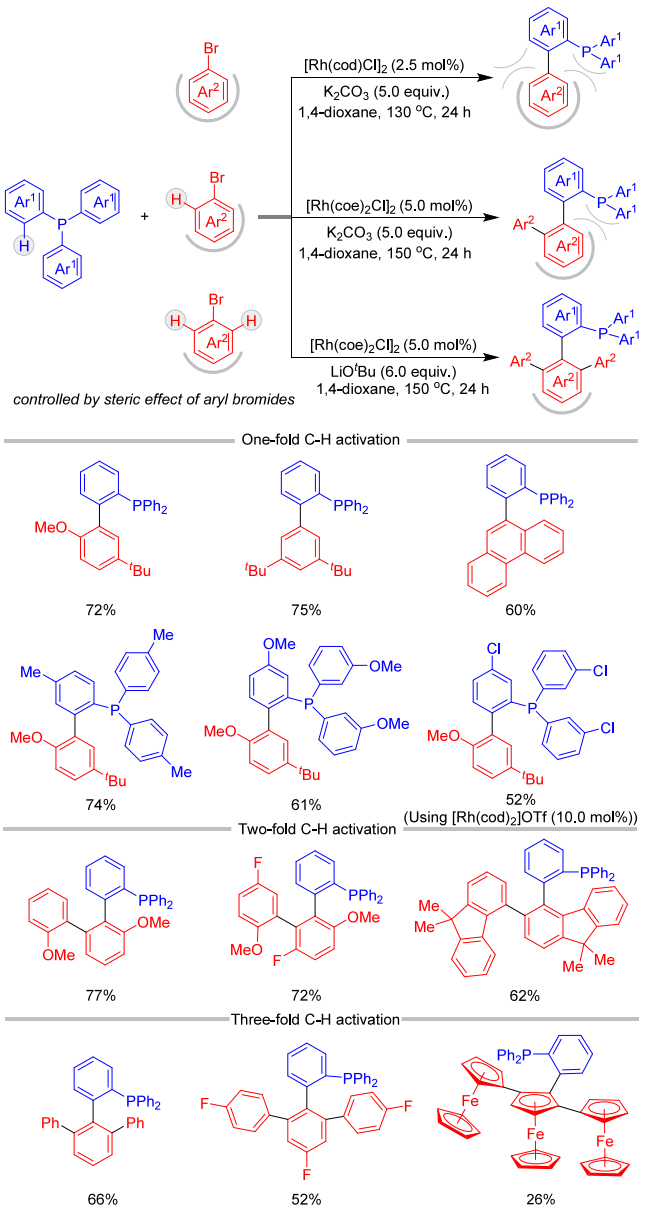

Figure 6. Rh-catalyzed direct arylation of arylphosphines with aryl bromides.

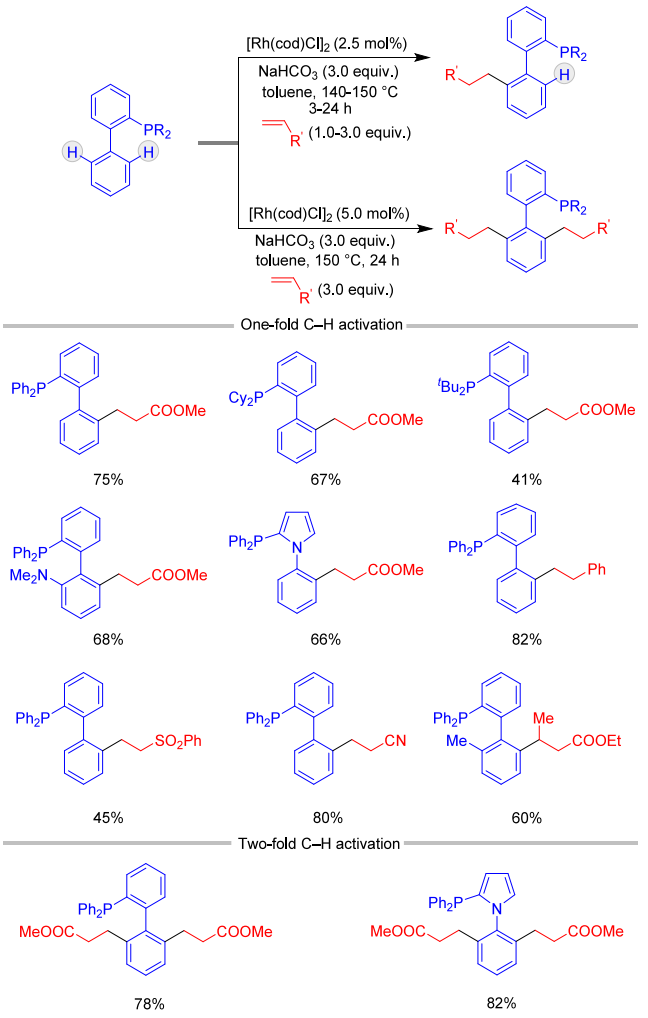

Figure 7. Rh-catalyzed C−H alkylation of biaryl phosphines with olefins.

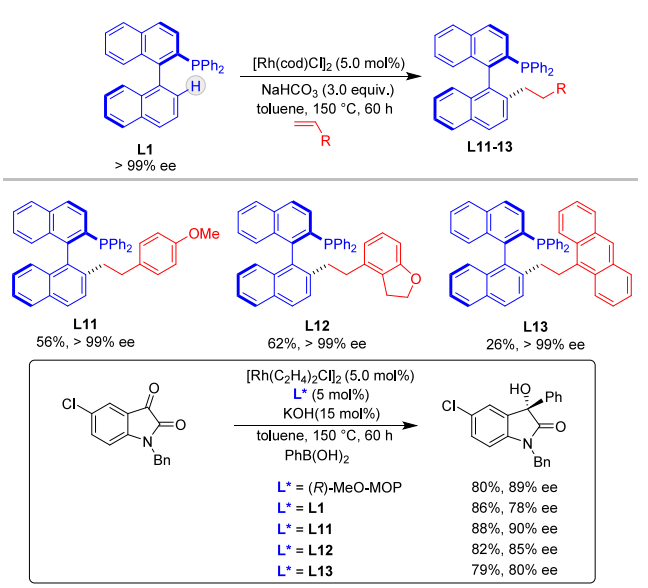

Figure 8. Construction of the axially chiral alkyl-MOP family and testing the developed ligands.

became achievable. In 1999, the Hartwig group fortuitously unearthed a modified phosphine, $Ar_5FcP(^tBu)_2$, generated spontaneously in situ, which unexpectedly took on the role of a supporting ligand in the catalysis of aromatic C−O bond formation, utilizing $Pd(dba)_2$ and $FcP(^tBu)_2$.[24] This serendipitous revelation propelled the development of a widely employed Q-Phos ligand. After 15 years, the Clark research group documented an iridium-catalyzed C−H borylation of phosphines, paving the way for new methodologies.[25] Recently, our team has taken significant strides forward by ingeniously merging phosphines as directing groups with transition-metal catalysis to devise a novel approach for the precise synthesis of phosphine ligands through C−H activation. This cutting-edge chemistry has driven advancements in late-stage diversification strategies, markedly improving both the atom and step efficiency in creating new phosphine families in contrast to conventional synthesis techniques. This Account serves to deliver an exhaustive perspective on this burgeoning field, establishing a solid framework for the design and synthesis of intricate ligands via the late-stage diversification of phosphines through C−H

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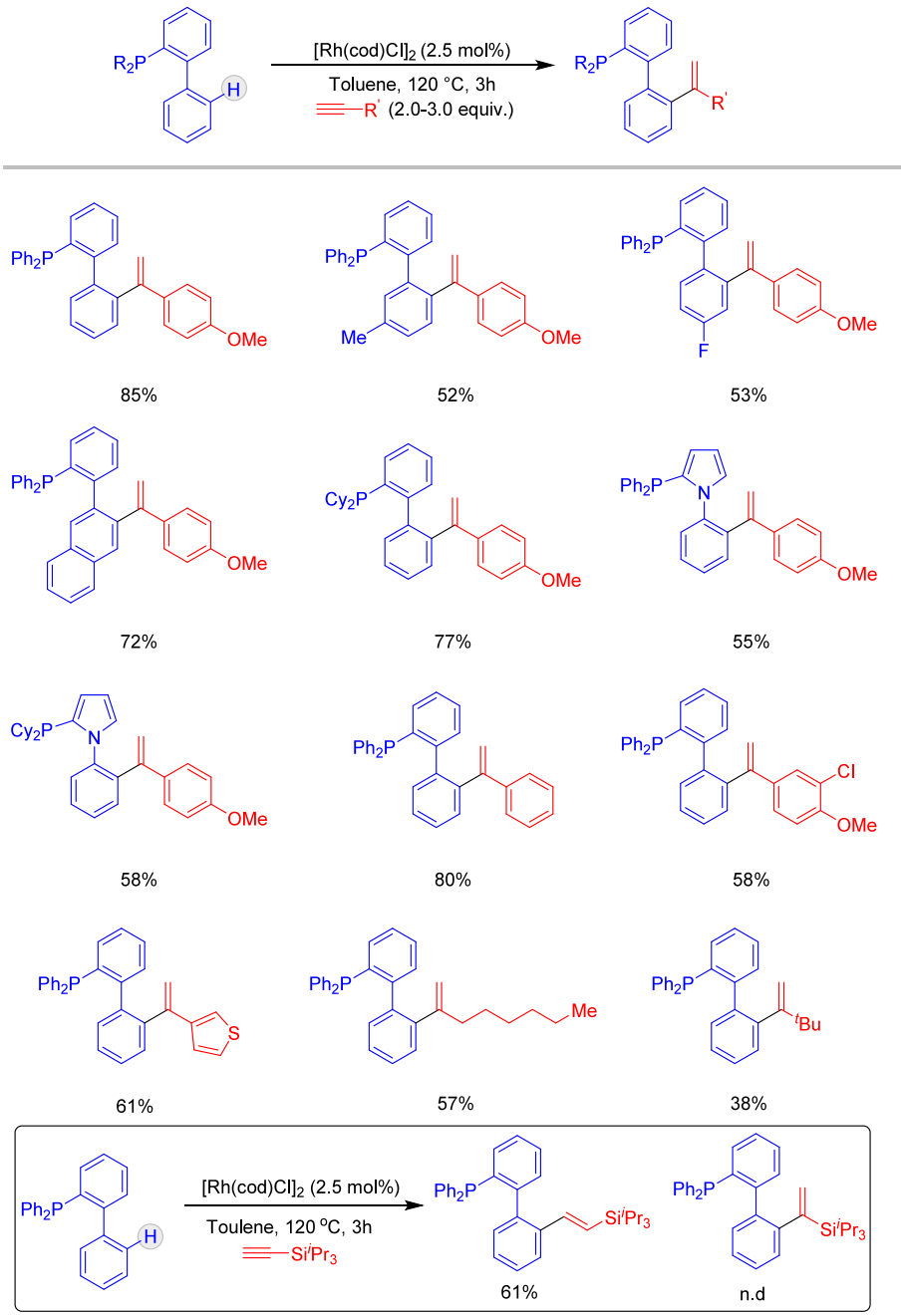

Figure 9. Rh-catalyzed C−H olefination of biaryl phosphines with terminal alkynes.

activation (Figure 3). The topics covered herein are segmented into key areas: 1) C−H arylation, 2) C−H alkylation, 3) C−H alkenylation, 4) C−H aminocarbonylation, 5) C−H alkynylation, 6) C−H borylation, and 7) C−H silylation. Our late-stage diversification strategy enables the generation of an extensive spectrum of ligands, spanning biaryl and cataCXium series structures, axially chiral binaphthyls, ferrocenes, and triaryl phosphines. From readily accessible commercial starting points, we effectively curated a vast and multifaceted library of phosphine compounds. Within this Account, we delve into the origins, progression, and nuances of these methodologies, carefully evaluating the variables that influence these strategies and the roles of the synthesized ligands in metal-catalyzed asymmetric catalysis. The final section is dedicated to discussing the critical advancements that are necessary to further propel this sphere of research, thereby laying the groundwork for future innovation.

1.1. C−H Arylation of Phosphines

The tactic of accomplishing direct arylation via C−H activation has come to the forefront as an exceedingly efficient approach for the synthesis of biaryl compounds, showcasing remarkable atom and step economy.[26] Direct arylation of phosphines is instrumental in establishing a diverse array of C−C bonds, thereby enriching the molecular variety of such ligands.[27−30] We embarked on our exploration of this field in 2017, initially focusing on the C−H arylation of phosphines. In that pivotal year, we introduced a cutting-edge technique for tailoring biaryl-type monophosphines through rhodium-catalyzed C−H arylation (Figure 4).[1] This method utilizes $[Rh(cod)Cl]_2$ as the catalyst, with LiO^tBu serving as the base, and operates

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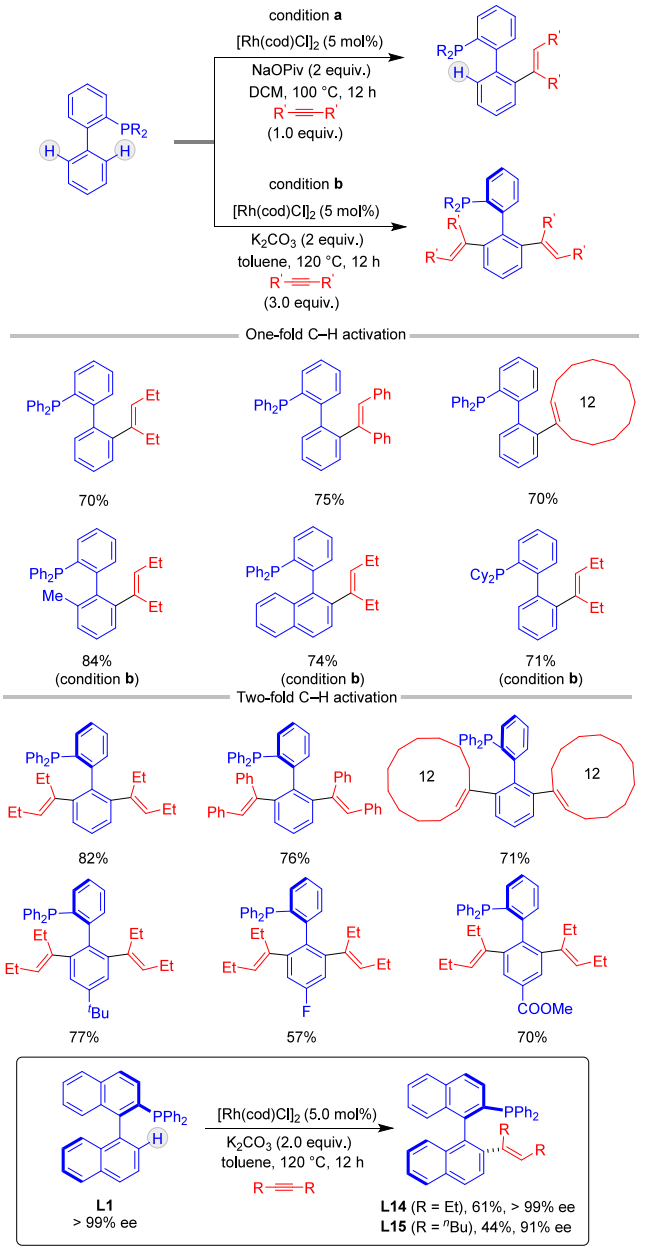

Figure 10. Rh-catalyzed C−H olefination of biaryl phosphines with internal alkynes.

optimally within the temperature range of 110 to 150 °C. It has proven highly successful in yielding an array of arylated phosphines with impressive yields. The variability in substituents on both the aryl and phosphine counterparts is noteworthy, with yields varying from moderate to outstanding. Substituents include but are not limited to the Cy, Ph, and *tert*-Bu groups. This underscores the technique's extensive substrate scope and remarkable functional group compatibility. Altering the amount of bromoarenes to 2.4 equiv and prolonging the reaction duration under designated conditions can facilitate a double C−H arylation, leading to diarylated derivatives. Nonetheless, the sterically bulky JohnPhos, bearing the P^tBu_2 group, was limited to a monoarylation outcome. In a compelling turn of events, CyJohnphos successfully underwent a mono-selective arylation with 4-bromotoluene and, when further treated with a second aryl bromide in one pot, yielded the sought-after products with commendable efficiency. Our investigations have demonstrated that the Rh(I) catalyst, without the need for additional external ligands, is remarkably proficient in promoting the coupling of a vast panorama of aryl bromides with phosphines, delivering precise control over both mono- and bis-arylation selectivity.

Axially chiral monophosphine ligands (MOPs) play a vital role in catalytic asymmetric processes.[31] In our efforts to efficiently synthesize valuable chiral ligands, we have expanded our direct arylation strategy to include the synthesis of a diverse array of Ar-MOP derivatives from enantioenriched phosphine **L1** (Figure 5). We found that a broad spectrum of aryl bromides, featuring electron-donating and -withdrawing groups as well as 2-naphthyl bromide, is amenable to this strategy, yielding the desired ligand family (**L2**−**L10**). These ligands display a variety of steric and electronic properties while preserving their enantiomeric excess (ee) values. To underscore the practicality of our approach, we applied our bespoke chiral Ar-MOP ligand collection to a rhodium-catalyzed asymmetric aryl addition to α,β-unsaturated imine using a phenylstannane reagent. When compared to commercially available MeO-MOP ligands, our in situ-formed ligands exhibited enhanced enantioselectivity.[32] In particular, using ligand **L9**, which features a 3,5-dimethoxyphenyl moiety, we achieved 76% yield and 98% ee for the resulting product. These outcomes highlight the formidable potential of our tailored ligand library in facilitating catalytic reactions with high enantioselectivity.

In the late 1960s, pioneering work demonstrated the *ortho*-C−H metalation of triphenylphosphine within cobalt, iridium, and rhodium complexes, unveiling a four-membered chelate ring structure of $Ph_2P(o\text{-}C_6H_4)M$.[33] Subsequent research has extensively explored the synthesis, reactivity, and structural characterization of various transition-metal complexes featuring *ortho*-metalated arylphosphines ($ArPR_2$). A notable challenge in the field stems from the robust coordination of tertiary phosphine groups to transition metals, which complicates the catalytic versatility of these systems.

In 2022, our group successfully employed a rhodium-catalyzed P(III)-directed C−H activation protocol for arylphosphines in coupling with aryl halides, facilitating the expeditious synthesis of a diverse array of biaryl monophosphines.[34] This methodology is particularly remarkable for its capability to achieve controlled 1-fold, 2-fold, and 3-fold C−H activation by the strategic selection of aryl bromides based on their steric demands. Such selective transformations yield biaryl monophosphine ligands featuring sterically encumbered backbones, along with electronically modulated substituents in a finely tunable manner (Figure 6). The initial C−H arylation event proceeds through the formation of a four-membered chelate ring involving the arylphosphine moiety, while subsequent arylations of the resulting biaryl phosphines proceed via six-membered chelate intermediates. Thus, the utilization of sterically bulky aryl bromides exclusively leads to 1-fold C−H activation. Aryl bromides of moderate steric bulk afford 2-fold C−H activation, whereas aryl bromides bearing solely *para*-substituents facilitate 3-fold C−H activation. It is noteworthy that the integration of bromoferrocene into the phosphine scaffold has been achieved, culminating in the synthesis of a novel compound adorned with three ferrocene units. After we filed our work report, the You research group reported similar work on the phosphine-directed rhodium-catalyzed arylation reaction.[35] Differing from our strategy, they achieved control over the number of C−H arylations by adding various types of phenol ligands.

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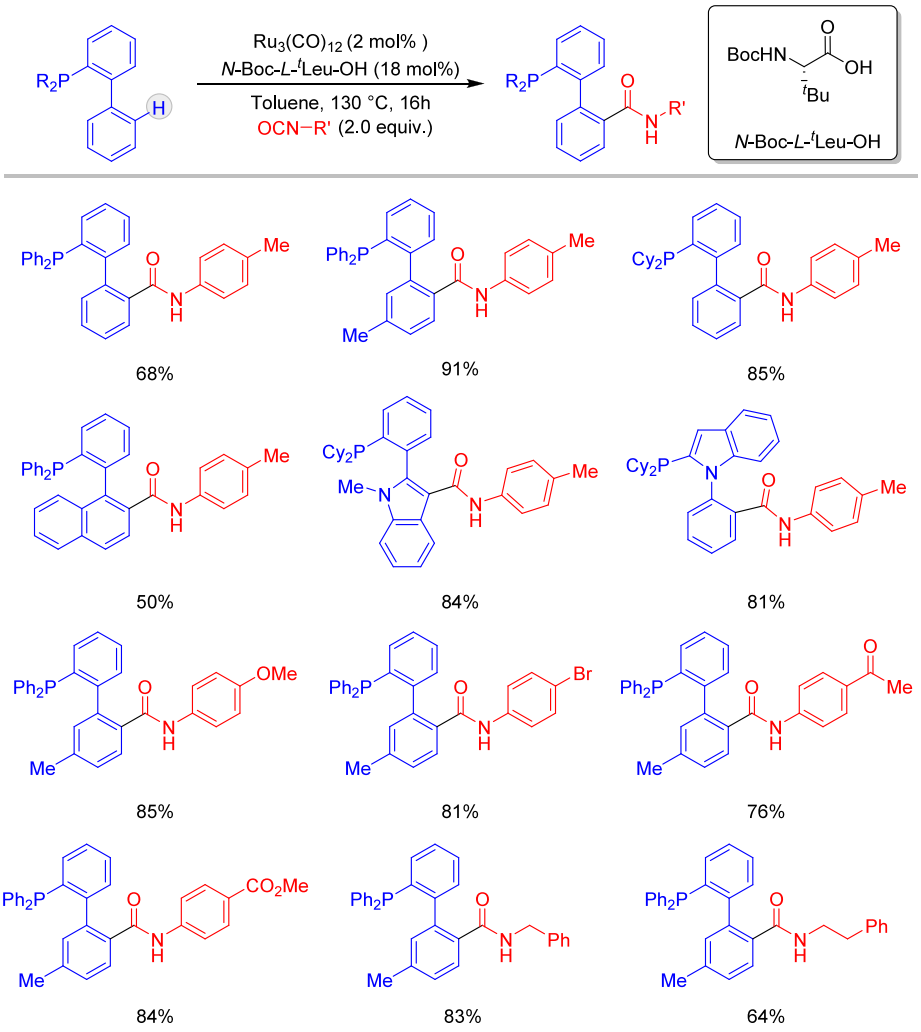

Figure 11. Rh-catalyzed C−H amidation of biaryl phosphines with isocyanates.

1.2. C−H Alkylation of Phosphines

This reaction paradigm for the C−H alkylation of phosphines can occur via hydroarylation with olefins[36] or cross-coupling with alkyl halides,[37−39] directing the P(III) group. In 2019, our team reported a rhodium-catalyzed system that facilitates the direct hydroarylation of alkenes with biaryl phosphines through P(III)-directed C−H activation (Figure 7).[40] By the reaction of phosphines with alkenes in a 1:1 ratio, the desired *ortho*-alkylation products can be synthesized using $[Rh(cod)Cl]_2$ as the catalyst and $NaHCO_3$ as the base in a toluene solvent. By increasing the catalyst loading to 5.0 mol %, elevating the temperature, and adjusting the phosphine-to-olefin ratio to 1:3, we have consistently been able to obtain the dialkylated product in a high yield. This innovative technique offers an on-demand approach for diversifying commercially available phosphine ligands, thereby generating an extensive array of ligand libraries with varied alkyl substituents. This method provides a robust platform for the synthesis of tailor-made ligands, paving the way for advancements in various applications requiring specific ligand properties.

This methodology is also readily adaptable to the fabrication of the axially chiral alkyl-MOP family (Figure 8). By harnessing P(III)-directed C−H alkylation, this technique affords the expeditious and efficient incorporation of alkyl constituents, as epitomized by the creation of ligands **L11**−**L13** from the antecedent **L1** while preserving their enantiomeric purity. The construction of enantiopure alkyl-MOP ligand libraries has showcased a prodigious promise in the domain of catalytic enantioselective transformations. The ligands adorned with methoxyphenyl and anthracene groups have manifested superior stereocontrol in rhodium-catalyzed asymmetric addition processes pairing isatin with phenylboronic acid.[41]

1.3. C−H Alkenylation of Phosphines

Within the dynamic realm of transition-metal catalysis, olefins play an essential role, commonly featured as part of the substrate, a core component of the catalyst system, or a supplementary addition.[42,43] This prominence has spurred a profound need for a universal strategy to synthesize phosphine-π acidic ligands, a landmark development that would unlock a comprehensive array of these pivotal ligands. We articulate the utilization of tertiary phosphines in the hydroarylation of alkynes, facilitated by a P(III)-directed C−H activation approach (Figure 9). Using rhodium(I) catalysis at a moderate temperature of 120 °C, under an argon atmosphere, with toluene as the solvent, the phosphine initiates the assembly of a Markovnikov hydroarylation product using 4-ethynylanisole, resulting in an impressive 85% yield. An extensive survey of the hydroarylation scope confirmed that phosphine ligands—with a spectrum encompassing biaryl constructs to *N*-phenyl pyrrole matrices as well as alkynes tethered to aryl and thiophene units, in addition

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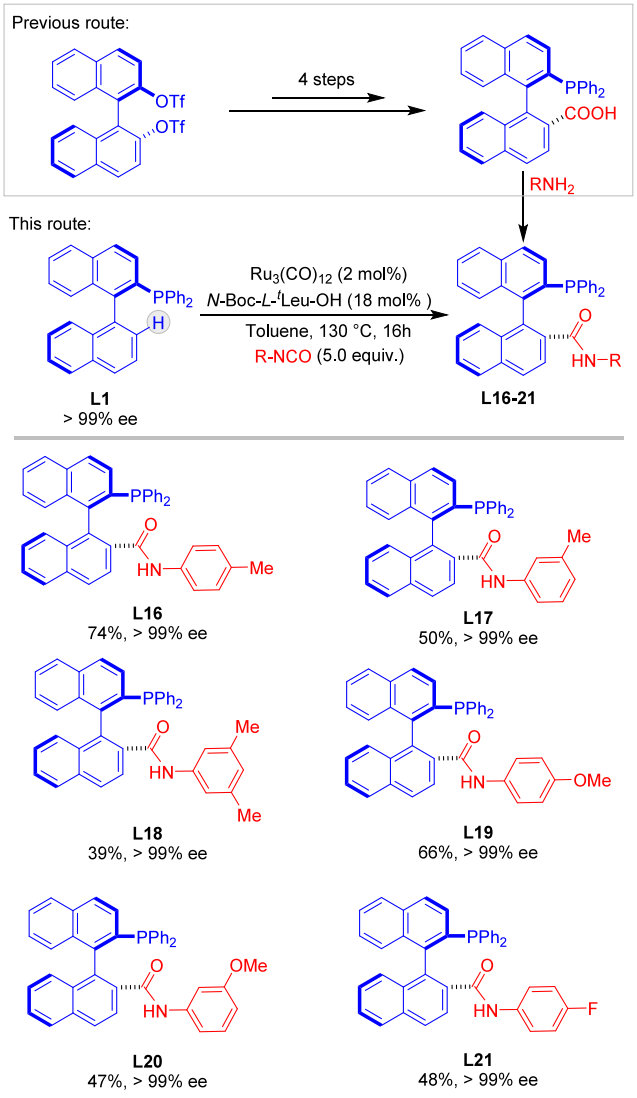

Figure 12. Construction of an axially chiral phosphine-amide family.

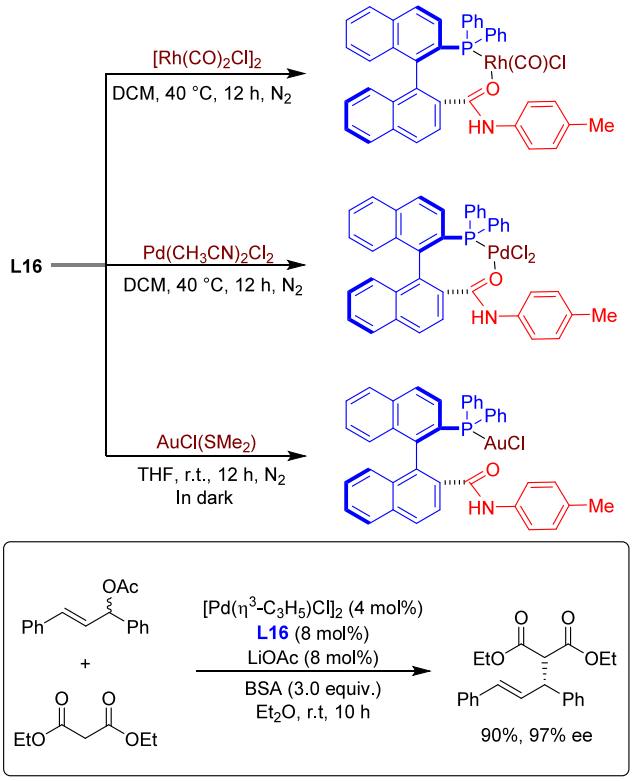

Figure 13. Complexes of **L16** with different transition metals and testing of its reactivity in an asymmetric Tsuji-Trost reaction.

to nonactivated alkyl alkynes—can effectively participate in vinylations, producing a wide array of derivatives. Notably, the utilization of a bulky TIPS-substituted terminal alkyne distinctively led to the genesis of an atypical product that deviates from the Markovnikov norm.

In addition to terminal alkynes, we[44] and Soulé's group[45] developed the hydroarylation of phosphines using internal alkynes. In our discovery, a rhodium-catalyzed P(III)-directed C−H alkenylation showed excellent *E*-selectivity (Figure 10). The process proved successful with both electron-donating and -withdrawing groups and consistently yielded good to moderate results across a spectrum of different substrates. We also successfully extended this reaction to the dialkenylation of diarylphosphines, achieving satisfactory results with notable selectivity. Additionally, an investigation into the alkenylation of chiral monophosphine **L1** was conducted, leading to the desired products **L14** and **L15** with remarkable enantioselectivities.

1.4. C−H Aminocarbonylation of Phosphines

Hemilabile ligands have been widely employed in the realm of transition-metal catalysis, but the synthesis of these molecules typically involves intricate multistep procedures.[46] In the above monodentate P(III)-directed C−H activation, the increased steric hindrance in the formed products can promote ligand exchange with the unreacted phosphines and facilitate the catalyst turnover. However, the preparation of bidentate ligands from monodentate phosphines can be synthetically challenging because the enhanced coordination ability of products may lead to catalyst poisoning. Recently, our study introduced an innovative strategy for the construction of a variety of phosphine-amide ligands against the strong coordination of the formed products. The method utilizes ruthenium-catalyzed C−H activation of phosphines with isocyanates, dircted by P(III) atoms (Figure 11).[3] Utilizing a $Ru_3(CO)_{12}$ catalyst in conjunction with a *mono-N*-protected amino acid (MPAA) results in exceptional reactivity and regioselectivity. Diverse functional substituents located at the aryl motif on isocyanates as well as benzyl- and alkyl-substituted isocyanates were compatible.

The axially chiral hemilabile ligands are challenging to synthesize through traditional routes, typically requiring muti-step synthesis. De novo synthesis of the binaphthalene-based axial chiral phosphine-amides was first described by Hayashi using 2′-(diphenylphosphaneyl)-[1,1′-binaphthalene]-2-carboxylic acid as a key intermediate.[47] Based on the developed approach, we significantly expand the range of available phosphine-amide ligand libraries (Figure 12). When phosphine **L1** (>99% ee) was employed with different isocyanates, a ligand family of axially chiral phosphine-amides **L16**−**L21** with different electric and steric hindrance effects was generated without the erosion of ee under the developed reaction conditions.

The synthesized hemilabile ligands, due to their dynamic coordination behavior, display a markedly increased reactivity, eclipsing that of their monophosphine analogues. Coordination complexes harnessing rhodium and palladium have been

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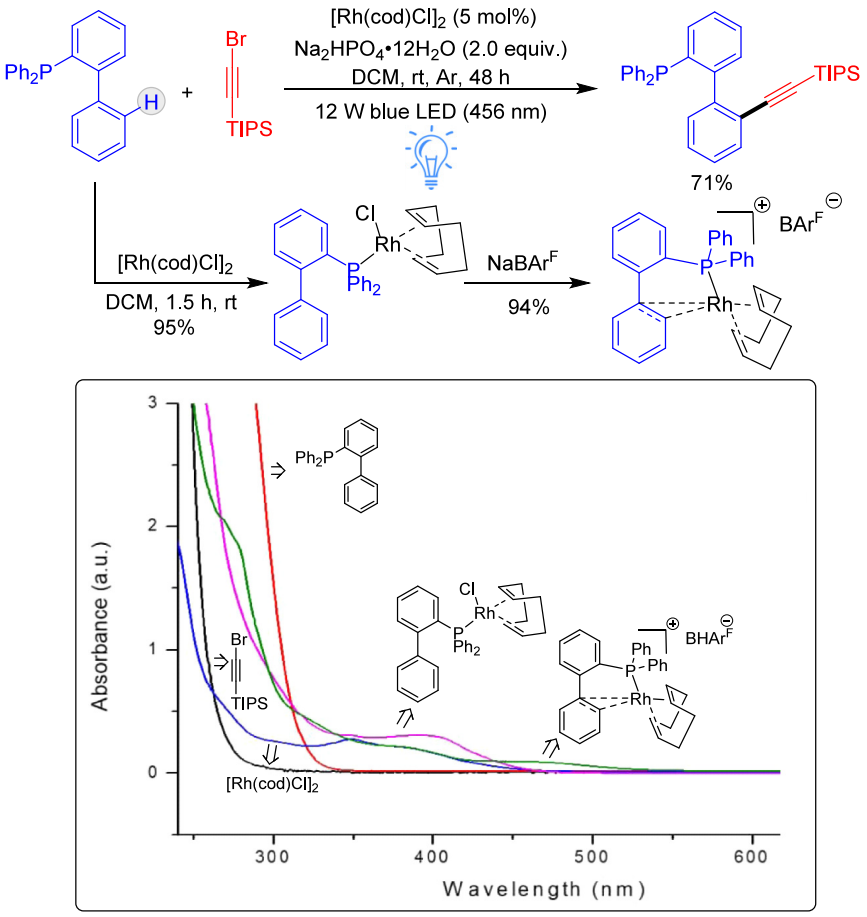

Figure 14. UV/vis study of Rh-catalyzed C−H alkynylation of biaryl monophosphine.

efficaciously synthesized employing ligand **L16**, and their structures elucidated via X-ray crystallography revealed a variety of oxygen atom orientations proximal to the metal nodes. In the case of gold, the complex formation was distinguished by an exclusive chelation mode effected through the phosphorus atom (Figure 13). Such a transformative advancement considerably augments the repertoire of phosphine-amide ligands, the selection of which has been demonstrated to be remarkably efficacious in enantioselective catalysis. For instance, ligand **L16** exhibited excellent reactivity in a palladium-catalyzed enantioselective Tsuji-Trost reaction. Additional chemical transformations, such as the rhodium-catalyzed enantioselective arylation addition to isatins and imines, likewise yielded exceptional results with a curated library of ligands. These instances underscore the expansive capacity of hemilabile ligands within the realm of asymmetric catalysis.

1.5. C−H Alkynylation of Phosphines

The above results have shown our progress in the P(III)-directed C−H activation of phosphines, including arylation, olefination, and alkylation. Typically, these transformations are performed at high temperatures to maintain good activity and a sufficient turnover number. During the past few years, the advent of modern photocatalysis has greatly stimulated the development of innovative approaches for C−H functionalization, harnessing the power of low-energy photons as a precisely controllable energy source.[48,49] Recently, we delved into the potential of this hypothesis and showcased the attainability of a catalytic C−H alkynylation of biaryl monophosphines through the harmonious integration of visible light photocatalysis and P(III)-directed C−H activation (Figure 14).[4] Notably, this process occurs without the requirement for external photosensitizers, offering a unique platform for the ligand design and synthesis. Based on the UV/vis absorption spectra of the reaction components, the phosphine or alkynyl bromide did not exhibit any absorption in the visible light range. In contrast to parent substrates, the rhodium-phosphine complex displayed a displacement of the absorption value toward the visible light range. These observations emphasize that the in situ rhodacycle is the possible light-responsive entity.[50]

A variety of biaryl monophosphines, with different electronic and steric properties, were successfully coupled with alkynyl bromide to produce phosphine-alkyne products (Figure 15). The reaction showed a tolerance for both electron-donating and electron-withdrawing groups on the aromatic ring. Moreover, the reaction efficiency was not significantly affected by the presence of a naphthalene ring structure within the phosphine ligands or variations in the substituents at the phosphorus atom. The use of the cataCXium series ligands in the reaction was demonstrated. Additionally, alkynyl bromides with various silyl substituents participated in the reaction, leading to the desired products. However, the use of (bromoethynyl)benzene encountered issues under the reaction conditions that resulted in a notable homocoupling byproduct. Further experiments were carried out to explore the selective formation of disubstitution products. By the adjustment of the reaction conditions, including the addition of a certain amount of sodium acetate, dual C−H activation was achieved. Moreover, the scope of the research was broadened to include the sequential C−H

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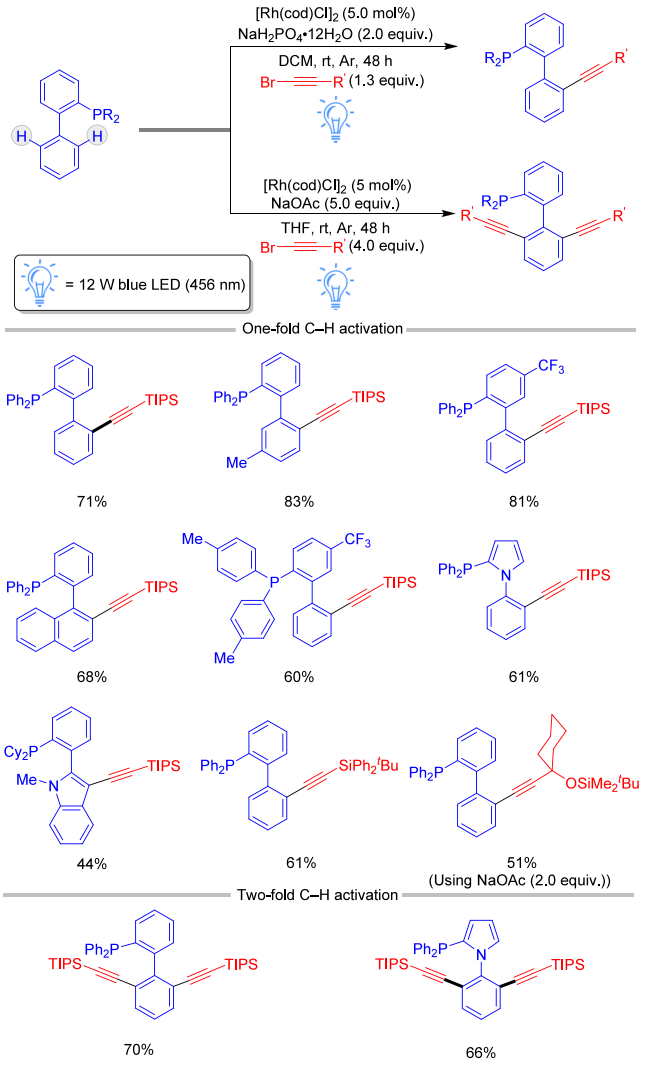

Figure 15. Rh(I)-catalyzed C−H alkynylation of biaryl phosphines.

activation of phosphine ligands with two distinct alkynyl bromides, affording dual alkynylated products after a two-step reaction process that involves initial monoalkynylation followed by an additional coupling step with another alkynyl bromide.

The photocatalytic process could be expanded to create axially chiral ligand **L22** from phosphine **L1**, yielding a product that maintained its high enantiomeric purity under blue LED light irradiation (Figure 16). Further exploration showed that these chiral ligands could effectively coordinate as monodentate ligands with different transition-metal centers, forming complexes with specific configurations. The single-crystal X-ray structure of a complex with iridium revealed the presence of additional π ligands, while reactions with palladium and platinum led to square planar complexes with the phosphorus and the alkyne moieties directly interacting with the metal centers. The structures of these complexes showed elongated C≡C triple-bond distances and distinct bite angles, suggesting that these ligands are versatile and flexible for use in transition-metal-catalyzed reactions.

1.6. C−H Borylation of Phosphines

ortho-Boronated phosphines serve as valuable synthetic building blocks that can be readily further functionalized by using well-established organoboron chemistry. Moreover, they also exhibit properties as a significant class of frustrated Lewis pairs (FLPs),

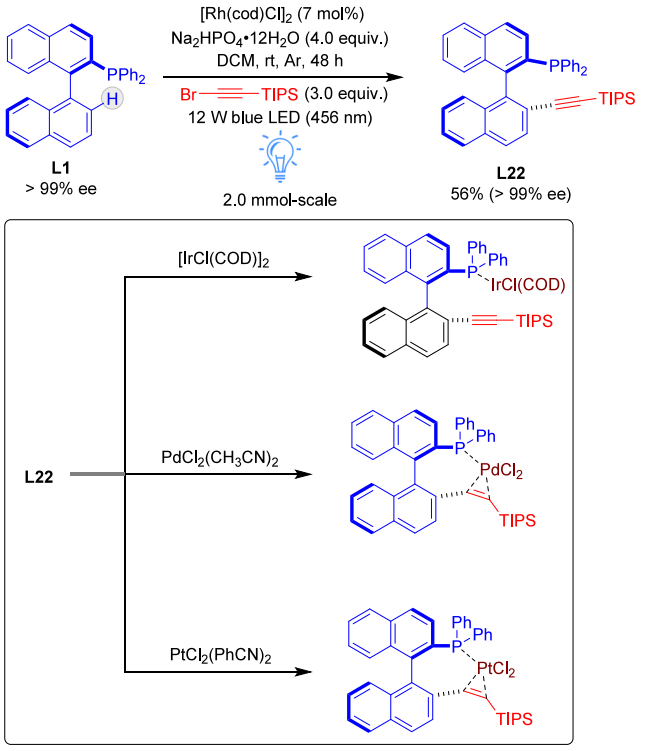

Figure 16. Synthesis of axially chiral ligand **L22** and an investigation of its organometallic reactivity.

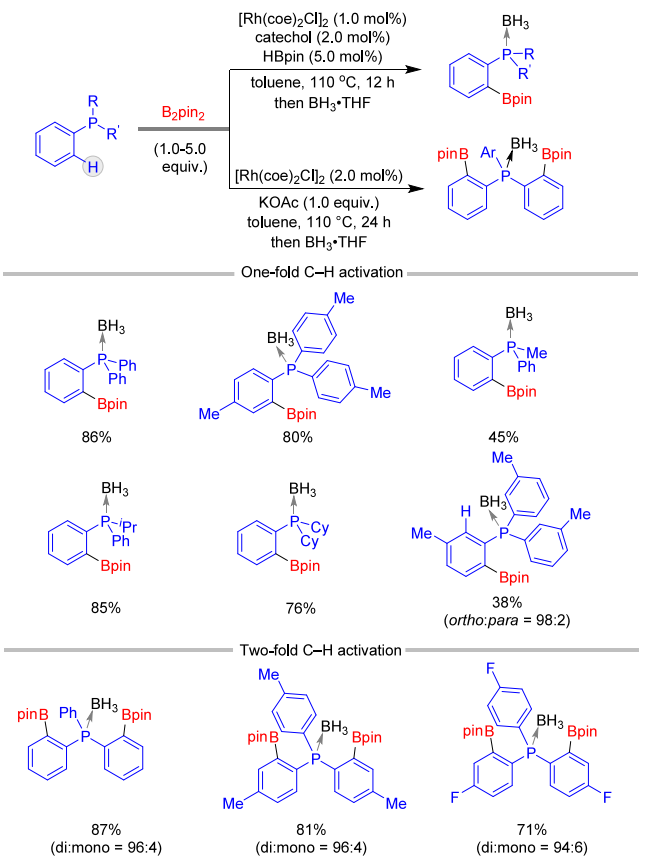

Figure 17. Rh(I)-catalyzed *ortho*-C−H borylation of arylphosphines.

which have been extensively investigated in numerous captivating stoichiometric and catalytic systems for small-

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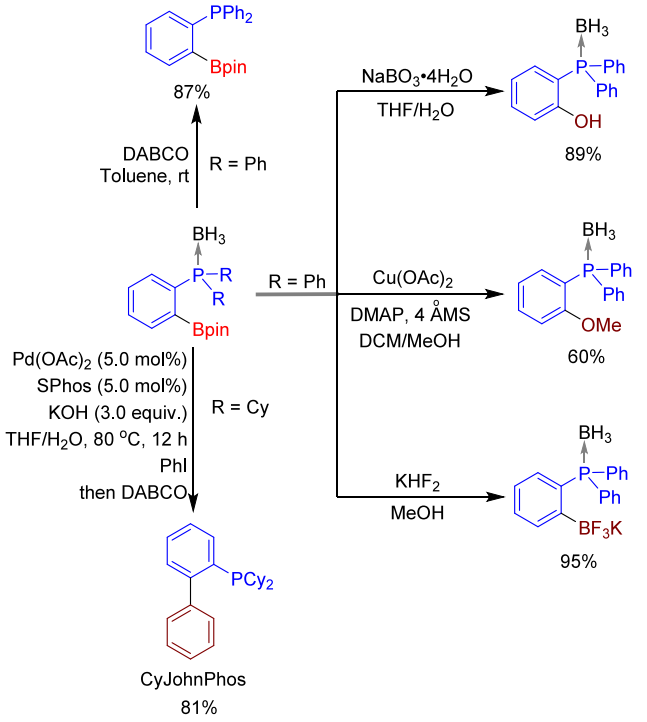

Figure 18. Downstream transformation of the formed boronated phosphines.

molecule activation and reaction.[51] Over the past decade, substantial advancements have been achieved in the realm of C−H borylation reactions[52] in which P(III)-directing groups have been explored to access boronated phosphines.[25,53−58] In this context, our research group uncovered a rhodium-catalyzed, P(III)-chelation-assisted *ortho*-C−H activation of arylphosphines, utilizing catechol as a ligand (Figure 17).[2] To facilitate isolation and purification, further treatment of the mixture with BH_3·THF provided borane complexes. The optimized reaction conditions facilitated P(III)-directed *ortho*-C−H borylation across a wide array of arylphosphines with various electronic and steric properties, leading to the formation of boronate phosphines with varying yields. Arylphosphines with different *para*-substituted groups underwent successful borylation, as did diarylalkylphosphines with both primary and secondary aliphatic groups. Additionally, dialkylarylphosphines with cyclohexyl groups also yielded a good reaction outcome. Highly selective borylation was noted in compounds with multiple potential reaction sites, favoring the less-hindered C−H bonds. After establishing the efficacy of mono C−H borylation, the research further explored and successfully achieved selective diborylation using excess borylating agent, producing diborylation products with high selectivity over the monosubstituted ones for different substrates.

The successful synthesis of boronate phosphines has enabled further research into their application. The newly developed method demonstrated practical utility by easily converting boronate phosphines into a variety of other functional groups (Figure 18). A deprotection step yielded a specific product, which could then be transformed into C−C and C−heteroatom bonds. These compounds could undergo oxidation to produce hydroxylated products or react with copper acetate to yield methoxylated derivatives. Furthermore, boronate phosphines could be converted into potassium trifluoroborate salts, showcasing their capacity as effective bidentate ligands in

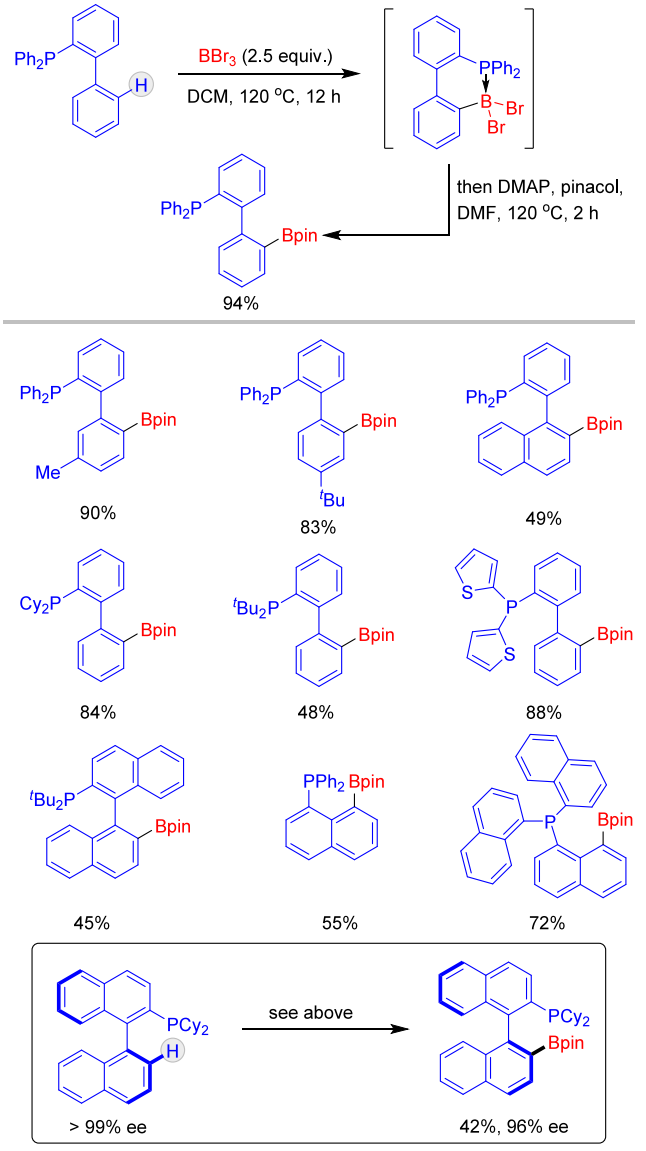

Figure 19. Metal-free P(III)-directed C−H borylation.

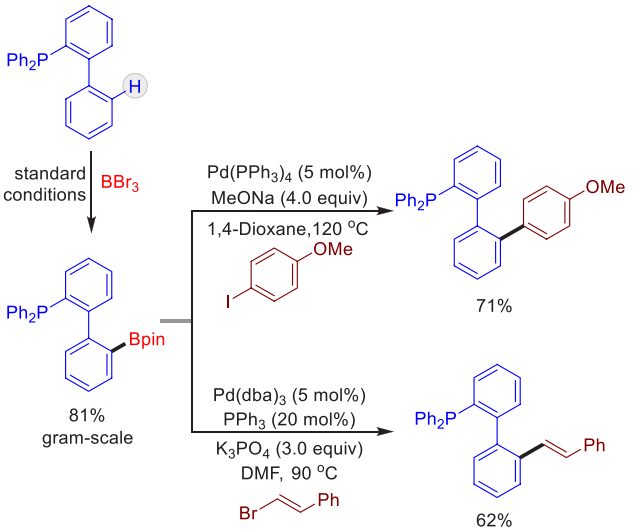

Figure 20. Downstream transformation of phosphine boronate esters.

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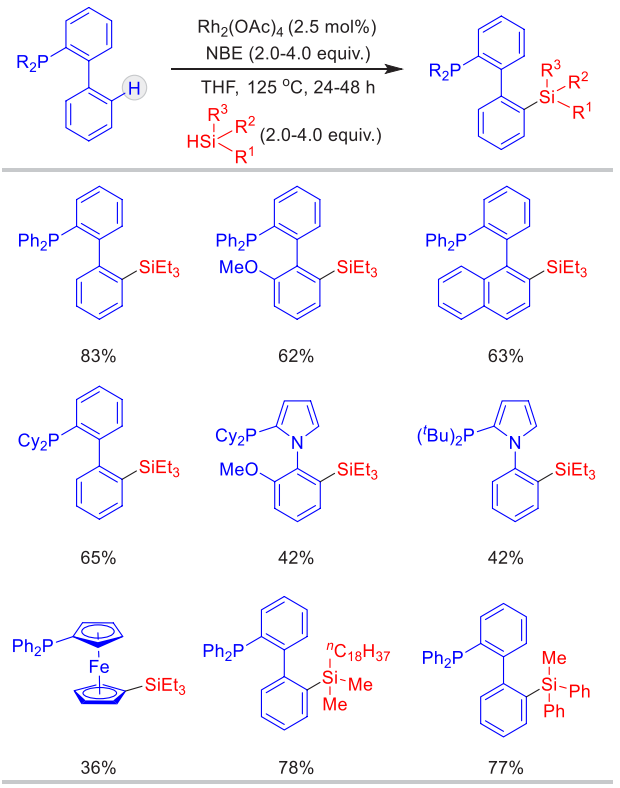

Figure 21. Rh-catalyzed C−H silylation of biaryl phosphines.

palladium-catalyzed reactions. Notably, the boronated phosphines have proven to be versatile intermediates for a cascade Suzuki cross-coupling and subsequent deprotection process, enabling the rapid construction of Buchwald-type phosphine ligands.

In pursuing sustainable and ecofriendly approaches for chemical synthesis, significant progress has been made in the field of metal-free C−H borylation.[59−62] Our previous research successfully employed boron-based Lewis acids, specifically BBr_3, serving the dual role of catalyst and reactant.[63] This methodology enabled efficient borylation across a variety of substrates, including amides, indoles, and pyrroles, showcasing broad functional group tolerance and the requirement for only mild conditions, facilitated by the use of specific directing groups. Building on this foundation, we further developed a metal-free strategy for the C−H borylation of phosphines, with the assistance of chelation from the P(III) atom. This novel approach effectively creates a broad array of phosphine boronate esters without employing any metal (Figure 19).[64] It has successfully borylated a wide spectrum of phosphine substrates furnished with diverse substituents, ranging from alkyl and aryl groups to even those with significant steric bulk, demonstrating its versatility. Furthermore, substrates containing naphthalenyl moieties and thiophene units proved to be compatible with this metal-free C−H borylation technique. The method exhibits distinct *peri*-selectivity for certain polycyclic phosphine substrates, resulting in the formation of a five-membered ring structure within the product. This innovative strategy is instrumental in the streamlined production of precious boryl-functionalized axial chiral ligands, which are pivotal for catalyzing asymmetric reactions. A notable feature of the process is its preservation of enantiomeric integrity, which is vital for synthesizing high-fidelity chiral molecules. While the technique

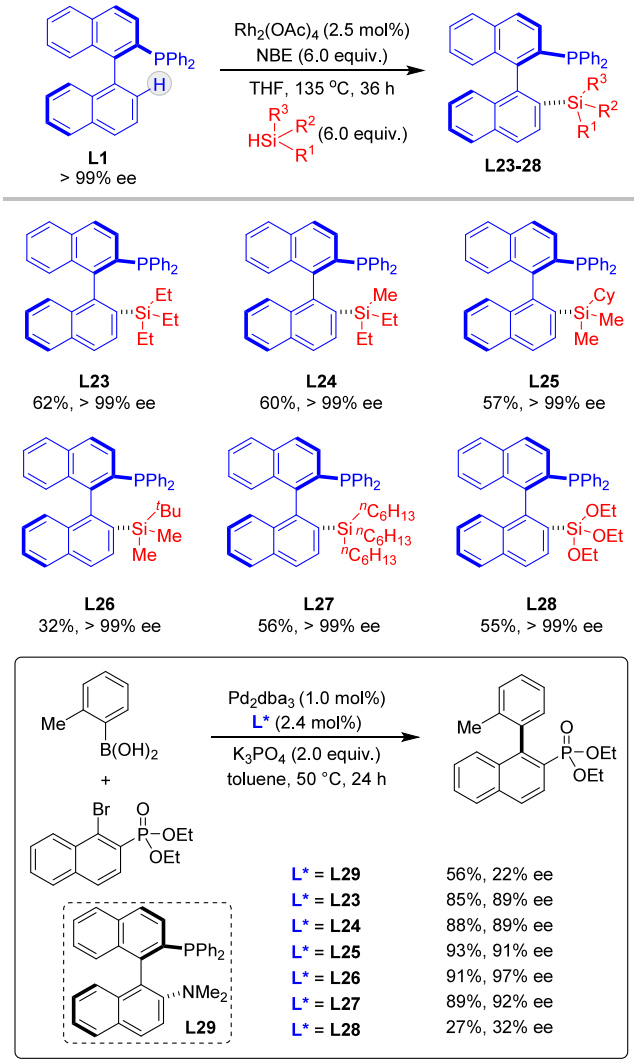

Figure 22. Construction of the axially chiral sily-MOP family and testing its reactivity.

is broadly effective, it is noteworthy that certain phosphines, specifically benzyldiphenylphosphine and triarylphosphine, did not undergo borylation under the established conditions, suggesting opportunities for further inquiry and refinement. Concurrently, the Bourissou research group also disclosed a related investigation of metal-free, phosphine-directed C−H borylation reactions, contributing additional insights to the field.[65]

The metal-free P(III)-directed C−H borylation protocol has been successfully scaled up to gram-level synthesis, demonstrating its practicality for large-scale applications (Figure 20). The phosphine boronate esters that are produced can be further transformed to a variety of organophosphorus compounds. This includes the ability to undergo palladium-catalyzed Suzuki-Miyaura couplings with organohalides to yield arylation and olefination products effectively.

1.7. C−H Silylation of Phosphines

Organosilane chemistry has received significant attention because of the important roles that silyl-substituted arenes play in various fields, including material science, biomedical applications, and synthetic chemistry, where they are utilized as reagents, catalysts, and ligands.[66,67] Unlike conventional silylation techniques that require a preformed metalated

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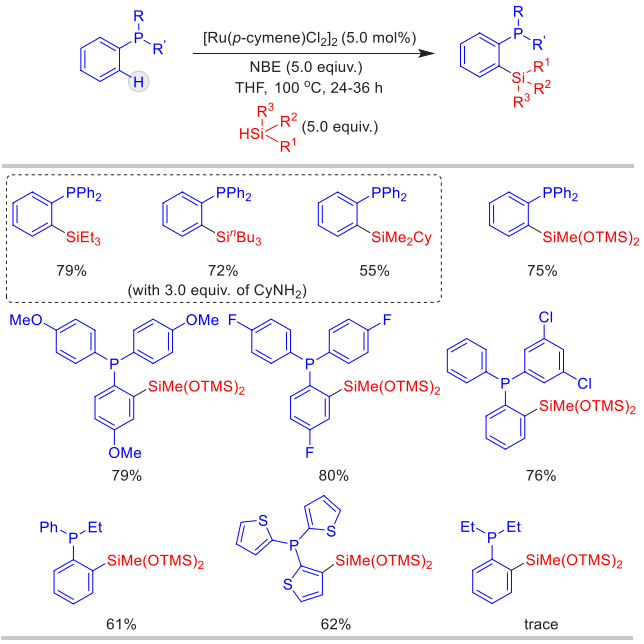

Figure 23. Ru-catalyzed aromatic C−H silylation.

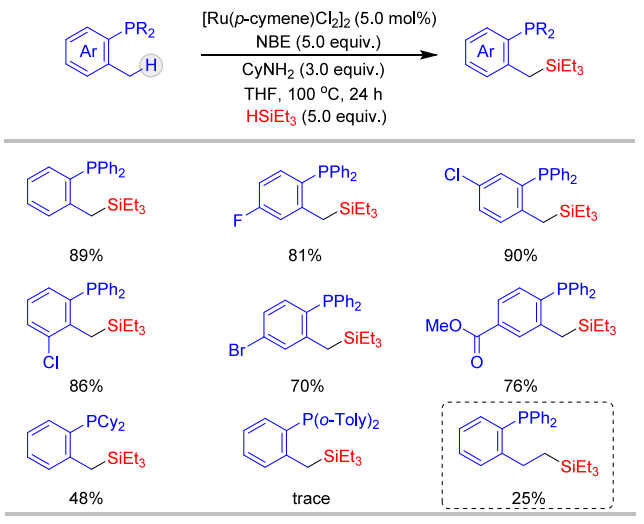

Figure 24. Ru-catalyzed benzylic C−H silylation.

substrate, modern strategies have been developed to functionalize C−H bonds directly with silane reagents. A cornerstone in this area was laid by the research reported in 1995 by Tanaka et al., with their work on Pt-catalyzed intermolecular *ortho*-C−H silylation using an imine as the directing group.[68] Building upon this, various research groups have contributed to chelation-assisted silylations of aromatic C−H bonds, although historically these were limited to aromatic compounds with N and O coordinating groups. Recognizing the challenges associated with controlling regioselectivity when using P atom coordination, current efforts have led to the development of an operationally simple and efficient protocol for synthesizing silyl-substituted phosphines.

This advancement has been realized by our group through a Rh-catalyzed, P(III)-directed C−H silylation process that transforms monophosphines into their silylated counterparts using hydrosilanes (Figure 21).[69] Utilizing 2.5 mol % $Rh_2(OAc)_4$ as the catalyst and 2 equiv of norbornene (NBE)

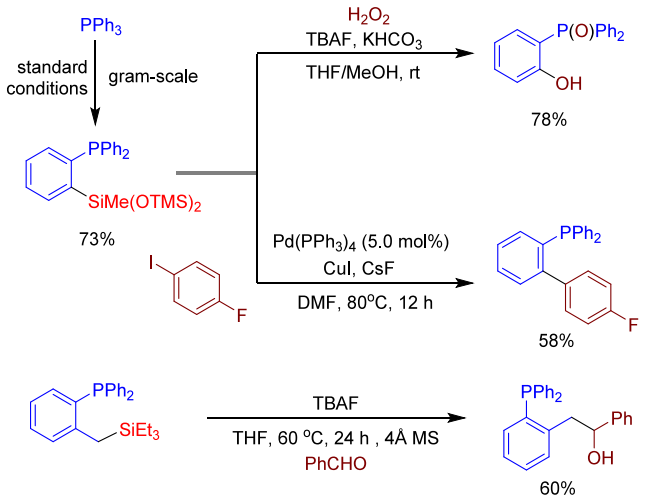

Figure 25. Follow-up transformation of the formed products.

as a hydrogen acceptor at 125 °C under an argon atmosphere in THF, a series of silyl-substituted phosphines can be well constructed. The versatility of this technique has been demonstrated with substrates such as biaryl-, heteroaryl-, ferrocene-, and binaphthalene-based phosphines, offering a method for late-stage modification of compounds that is both atom- and step-economical in comparison to the traditional lithiation/silylation methods previously employed to install silyl groups onto phosphine ligands. The reaction conditions developed have been fine-tuned to accommodate a diverse set of Buchwald phosphine ligands, producing silylation products efficiently. The silyl groups introduced enable the modulation of the steric properties of phosphine ligands, an important consideration for ligand design, which often requires the adjustment of the steric profile around the ligating atoms. The reaction scope has been thoroughly explored, revealing high yields and selectivities across a variety of hydrosilanes, including those with varying sterics and electronics. Even substrates with significant steric hindrance that challenge other catalyst systems have been successfully modified using this P(III)-directed silylation approach, which showcases the robustness of the method.

Building on the importance of binaphthalene-based chiral monophosphine ligands for catalytic asymmetric reactions, a methodology was developed to create a family of sily-MOP (Figure 22). This approach utilized direct C−H silylation without affecting the ee of the substrate. A variety of hydrosilanes with different alkyl groups were found to be effective coupling partners, yielding products with good yields and maintaining high stereochemical integrity. Further exploration with this ligand library was pursued in palladium-catalyzed asymmetric Suzuki-Miyaura cross-coupling reactions. A notable enhancement in both yield and enantioselectivity was achieved using one of the silyl-substituted ligands in place of KenPhos, historically known to produce good results.[70] This highlighted the improved performance and potential of the silyl-substituted ligands in catalysis.

Silicon-substituted arylphosphines possess intriguing characteristics, which have found extensive applications in ligand design and diverse chemical transformations.[71,72] Despite the rapid advancements in modern organic synthesis, only two viable approaches for the synthesis of these compounds have been explored thus far. One involves the substitution of silicon

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electrophiles with lithiated arylphosphines formed in situ, following a classic pathway. The other, a more recent method, utilizes the lithium-di-1-adamantylamide-mediated aryne insertion into Si−P reagents.[73] Notably, a breakthrough in this field has been achieved through the development of the first aromatic C−H silylation between arylphosphines and hydrosilanes, facilitated by a ruthenium complex (Figure 23).[74] The exceptional *ortho*-selectivity observed is attributed to the involvement of a four-membered metallacyclic intermediate that incorporates phosphorus chelation. Various silylated arylphosphines are generated, showcasing broad compatibility with different functional groups. Beyond triphenylphosphine, substituting one phenyl group with an alkyl group and replacing all three aryl groups with thiophene units also yielded the corresponding silylated products in moderate yields.

The developed catalytic system demonstrated notable reactivity not only for aromatic C−H bonds but also for sp^3 C−H bonds, realizing efficient benzylic C−H silylation (Figure 24). The use of substrates with different substituents resulted in high yields for the benzylic C−H silylation products, with selectivity favoring monosilylated outcomes even when bulky groups were present. The reaction proved to be versatile, accommodating substrates with various functional groups, such as halogens and esters, with ease. However, substrates with steric hindrance, such as those with multiple *ortho*-substituent groups, were less reactive, resulting in lower yields of the desired silylation product. As the carbon chain extends to the ethyl group, the silylation reaction occurs only at the terminal methyl group and not at the methylene group. These findings underline the efficiency of the catalytic system for benzylic C−H functionalization across a broad substrate scope. Successful reaction outcomes depended on the degree of substitution on the benzyl group, suggesting a level of steric influence on the reaction pathway.

The practicality of the C−H silylation process was demonstrated through a series of investigations (Figure 25). The reaction was scaled up successfully, yielding products similar to those seen in small-scale experiments. Furthermore, the versatility of the synthesized silylated phosphines was showcased through various subsequent synthetic transformations. For example, exposure to an oxidant led to the formation of a hydroxylated product. The silylated phosphines also engaged in palladium-catalyzed Hiyama cross-coupling, producing Buchwald-type phosphine derivatives. In addition, the silyl group in the benzylic position allowed for further functionalization under mild conditions, generating alcohol derivatives when the mixture was treated with aldehyde and a fluoride source. These findings illustrate the wide-reaching potential of the developed silylation strategy in synthetic chemistry applications.

2. CONCLUSIONS AND OUTLOOK

Throughout our Account, we have detailed significant advancements in the realm of C−H functionalization of phosphine ligands, employing innovative P(III)-directed activation techniques. These methods address the challenge of achieving regioselective control in the presence of multiple C−H bonds. Our groundbreaking work in this area has paved the way for the efficient synthesis of a diverse array of phosphine ligands, enhancing both the atom and step economies of these processes.

Looking ahead, there are still several avenues to explore and challenges to overcome in this field. For instance, expanding the scope of substrates and further refining the selectivity and efficiency of these methodologies will be crucial. Moreover, developing environmentally benign and cost-effective catalytic systems remains a significant objective. The potential for asymmetric C−H functionalization of phosphine ligands, which is relatively uncharted territory, also presents exciting opportunities for future research. In addition, our findings lay the groundwork for the potential use of these novel phosphine ligands in catalytic applications, particularly in asymmetric synthesis. We anticipate that these advancements will open new doors for the synthesis of complex molecules and inspire further innovations in the fields of organic synthesis and catalysis.

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Notes

The authors declare no competing financial interest.

Biographies

Zexian Li was born in Henan province, People's Republic of China, in 1992. He received his B.S. and M.S. degrees in chemistry and organic chemistry from Zhengzhou University in 2015 and 2017. Then, he moved to Nanjing University and completed his Ph.D. in organic chemistry with Prof. Zhuangzhi Shi. In 2021, he joined the group of Prof. Zhuangzhi Shi at Nanjing University as a research fellow. His current research efforts are focused on synthetic methodology, including C−H activation and asymmetric catalysis.

Zhuangzhi Shi was born in Jiangsu province, People's Republic of China, in 1983. He received his B.S. and M.S. degrees in chemistry and organic chemistry from Yangzhou University in 2005 and 2008. Then, he moved to Peking University and completed his Ph.D. in medicinal chemistry with Prof. Ning Jiao. In 2011, he joined the group of Prof. Frank Glorius at Westfalische Wilhelms-Universitat Münster (Germany) as an Alexander von Humboldt Research Fellow. In 2014, he joined the Department of Chemistry at Nanjing University as a full professor. His current research efforts are focused on synthetic methodology, including the activation of inert chemical bonds, radical chemistry, boron chemistry, and asymmetric catalysis.

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