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Precise Synthesis of Chiral Phosphorus Compounds: From Robust Pincer Complexes to Chiral Brønsted Acid/Amide-Directed C−H Activation

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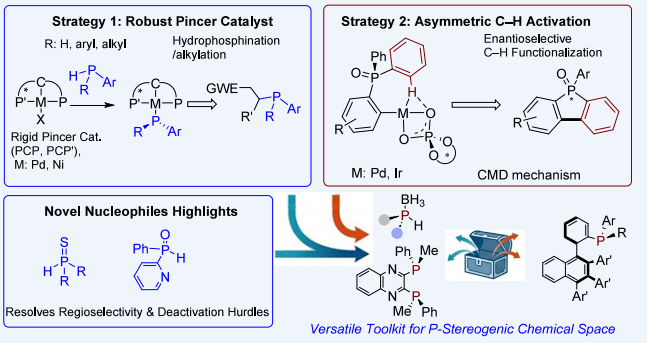
CONSPECTUS: Chiral phosphines represent a cornerstone of molecular sciences, serving as the "privileged engines" that drive modern asymmetric catalysis. Despite their utility, the catalytic construction of chiral phosphorus compounds remains a formidable challenge, primarily because trivalent phosphorus nucleophiles tend to poison metal centers—a phenomenon we term the "Coordination Paradox". Our laboratory has systematically addressed this bottleneck by pioneering two distinct catalytic manifolds governed by fundamentally different chemical principles. The first strategy centers on a "Logic of Robustness" designed to thwart the deactivation pathways triggered by phosphorus nucleophiles. By engineering rigid, tridentate PCP and PCP′ pincer complexes, we created a coordinatively protected environment for transition metals. This robust platform facilitated the first highly enantioselective 1,4- and 1,6-additions to diverse Michael acceptors, ultimately enabling the challenging asymmetric alkylation of primary phosphines. The second strategy pursues a logic of high atom-efficiency through direct synthesis. We introduced chiral phosphoric acids (CPAs) and carboxylic amides as stereocontrol elements in Pd- and Ir-catalyzed C−H bond activation. This approach does not merely supplement existing methods; it offers a direct route to structurally complex motifs—such as benzophosphole oxides and axially chiral biaryl phosphine. By participating in the concerted metalation-deprotonation (CMD) manifold, the CPA/amide directs the cleavage of enantiotopic C−H bonds with high fidelity. Furthermore, the development of novel nucleophiles, such as secondary phosphine sulfides and 2-pyridyl phosphine oxides, has resolved long-standing issues regarding regioselectivity and catalyst deactivation in allylic substitution and cross-coupling. Collectively, these advancements shift the field from labor-intensive stoichiometric methods toward an era of modular, atom-economical catalytic synthesis, providing a versatile toolkit for the chiral phosphorus community.



KEY REFERENCES

- Feng, J.-J.; Chen, X.-F.; Shi, M.; Duan, W.-L. Palladium-Catalyzed Asymmetric Addition of Diarylphosphines to Enones toward the Synthesis of Chiral Phosphines. *J. Am. Chem. Soc.* **2010**, *132*, 5562−5563.[1] *This foundational study introduced the "Survivor Logic," demonstrating that rigid tridentate pincer frameworks can effectively prevent catalyst poisoning by phosphorus nucleophiles, thereby enabling high enantioselectivity.*
- Wang, C.; Huang, K.; Ye, J.; Duan, W.-L. Asymmetric Synthesis of P-Stereogenic Secondary Phosphine-Boranes by an Unsymmetric Bisphosphine Pincer-Nickel Complex. *J. Am. Chem. Soc.* **2021**, *143*, 5685−5690.[2] *This work describes the use of unsymmetric PCP′-pincer nickel complexes to overcome stereocontrol challenges associated with primary phosphines, offering efficient access to configurationally stable secondary phosphine-boranes.*
- Zhang, C.-W.; Hu, X.-Q.; Dai, Y.-H.; Yin, P.; Wang, C.; Duan, W.-L. Asymmetric C−H Activation for the Synthesis of *P*- and Axially Chiral Biaryl Phosphine Oxides by an Achiral Cp*Ir Catalyst with Chiral Carboxylic Amide. *ACS Catal.* **2022**, *12*, 193−199.[3] *This study reports a new strategy that employs a chiral carboxylic amide ligand in combination with an achiral Cp*Ir catalyst. It enables the simultaneous construction of P-central and axial chirality via asymmetric C−H activation, affording biaryl phosphine oxides with high stereoselectivity.*

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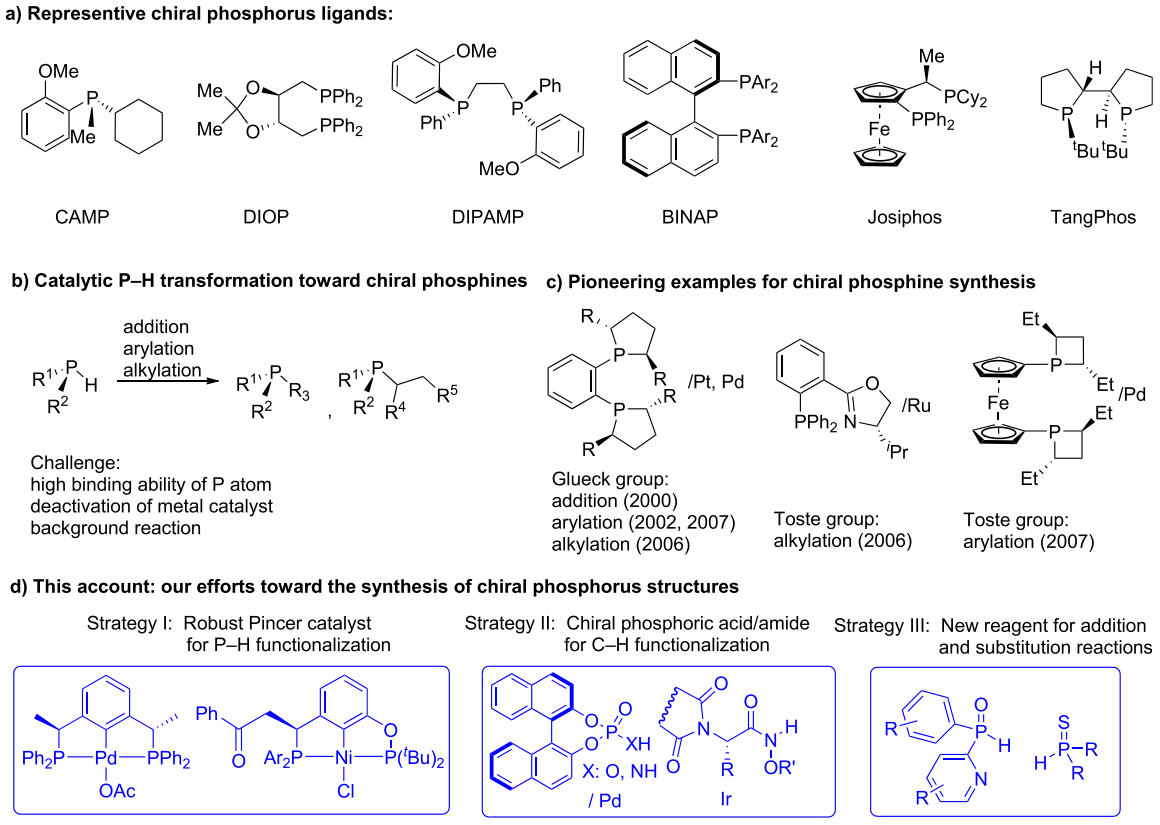
Scheme 1. Catalytic Asymmetric Synthesis of Phosphines



- Wu, Z.-H.; Wang, H.-Y.; Yang, H.-L.; Wei, L.-H.; Hayashi, T.; Duan, W.-L. Secondary Phosphine Sulfide-Enabled Iridium-Catalyzed Asymmetric Allylic Substitution. *Angew. Chem. Int. Ed.* **2022**, *61*, e202213904.[4] *This paper introduces secondary phosphine sulfides as superior nucleophiles in iridium-catalyzed asymmetric allylic substitution (AAS), achieving exceptional regio- and enantioselectivity (up to 99.9% ee) for the synthesis of branched allylic phosphines.*

1. INTRODUCTION

Chiral phosphorus compounds,[5] particularly those bearing *P*-stereogenic centers, constitute a class of "privileged" motifs indispensable to both modern asymmetric catalysis and the discovery of novel bioactive molecules. The seminal development of highly effective chiral phosphine ligands—such as the *P*-stereogenic ligand DIPAMP[6] developed by Knowles, the carbon-chiral backbone of the DIOP ligand[7] reported by Kagan, and the axially chiral diphosphine BINAP[8] pioneered by Noyori—revolutionized the field of homogeneous asymmetric catalysis (Scheme 1a). These privileged scaffolds provide precisely defined chiral environments that enable transition metals to catalyze a vast array of asymmetric transformations with exquisite stereocontrol. Despite their tremendous utility, the synthesis of optically pure chiral phosphines has historically been a formidable endeavor.[9] Conventional methodologies often rely on chiral pool materials, stoichiometric auxiliaries, or the tedious resolution of racemates—approaches that typically lack step- and atom-economy and severely impede the rapid screening of ligand libraries.

To circumvent the limitations of traditional stoichiometric methods, the catalytic asymmetric synthesis of chiral phosphines emerged as a highly attractive alternative.[10] As summarized in a 2008 review by Glueck,[10a] early breakthroughs in this domain predominantly focused on transition-metal-catalyzed asymmetric P−C bond-forming reactions with trivalent phosphines as the nucleophile (Scheme 1b).[10,11] Notable progress before 2010 included the palladium- and platinum-catalyzed asymmetric arylation[11b,e,f] and alkylation[11d] of secondary phosphines, as well as ruthenium-catalyzed phosphinations[11c,g] proceeding via nucleophilic phosphido intermediates (Scheme 1c). While these pioneering studies successfully demonstrated the feasibility of generating *P*-stereogenic centers catalytically, the field progressed relatively slowly. Many of these early methods were plagued by restricted substrate scopes, low catalytic turnover, and difficulties in maintaining high levels of enantiocontrol over diverse architectures.

A fundamental bottleneck in this domain is what we term the "Coordination Paradox". Trivalent phosphorus (P(III)) compounds are essential nucleophiles for forging P−C bonds. However, the strong coordinating affinity of the P(III) lone pair to transition metals frequently acts as a powerful "catalyst poison".[12] This aggressive coordination often leads to irreversible catalyst deactivation or the competitive displacement of delicately designed chiral ligands from the metal center, thereby abruptly terminating the catalytic cycle and eroding enantioselectivity. Over the past decade, our research group has focused on addressing this intrinsic paradox. We recognized that surmounting the toxic effects of P(III) nucleophiles required fundamentally new catalytic strategies. Consequently, our laboratory has systematically established two parallel, conceptually divergent, and noninterchangeable catalytic tracks. The first relies on the "Logic of Robustness", wherein we designed highly rigid tridentate pincer-metal (Pd, Ni) complexes that act

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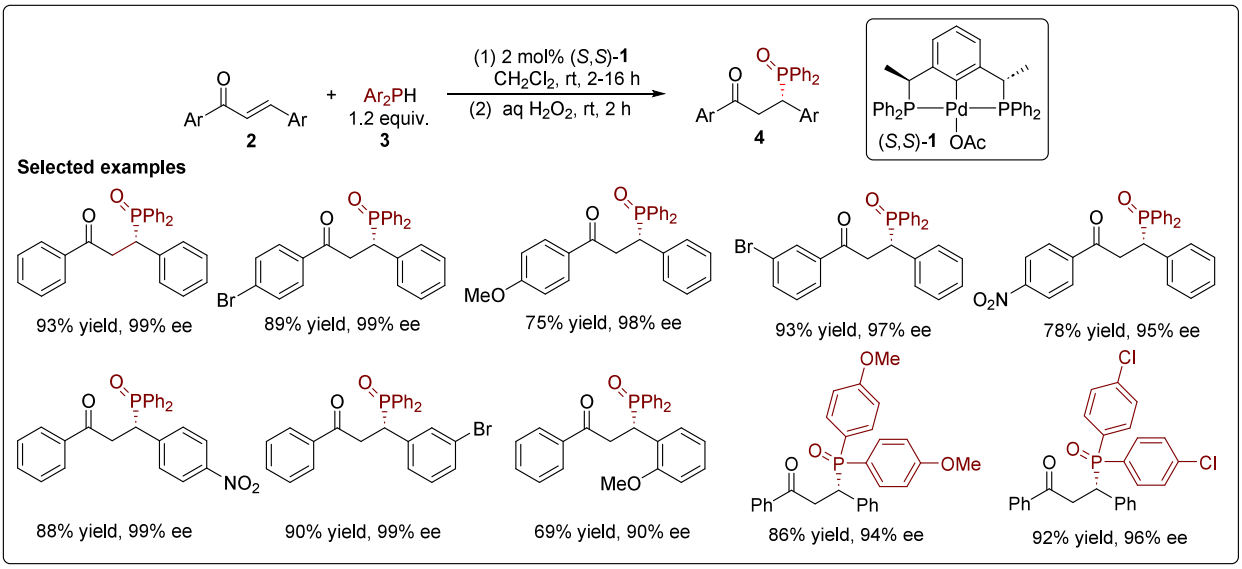
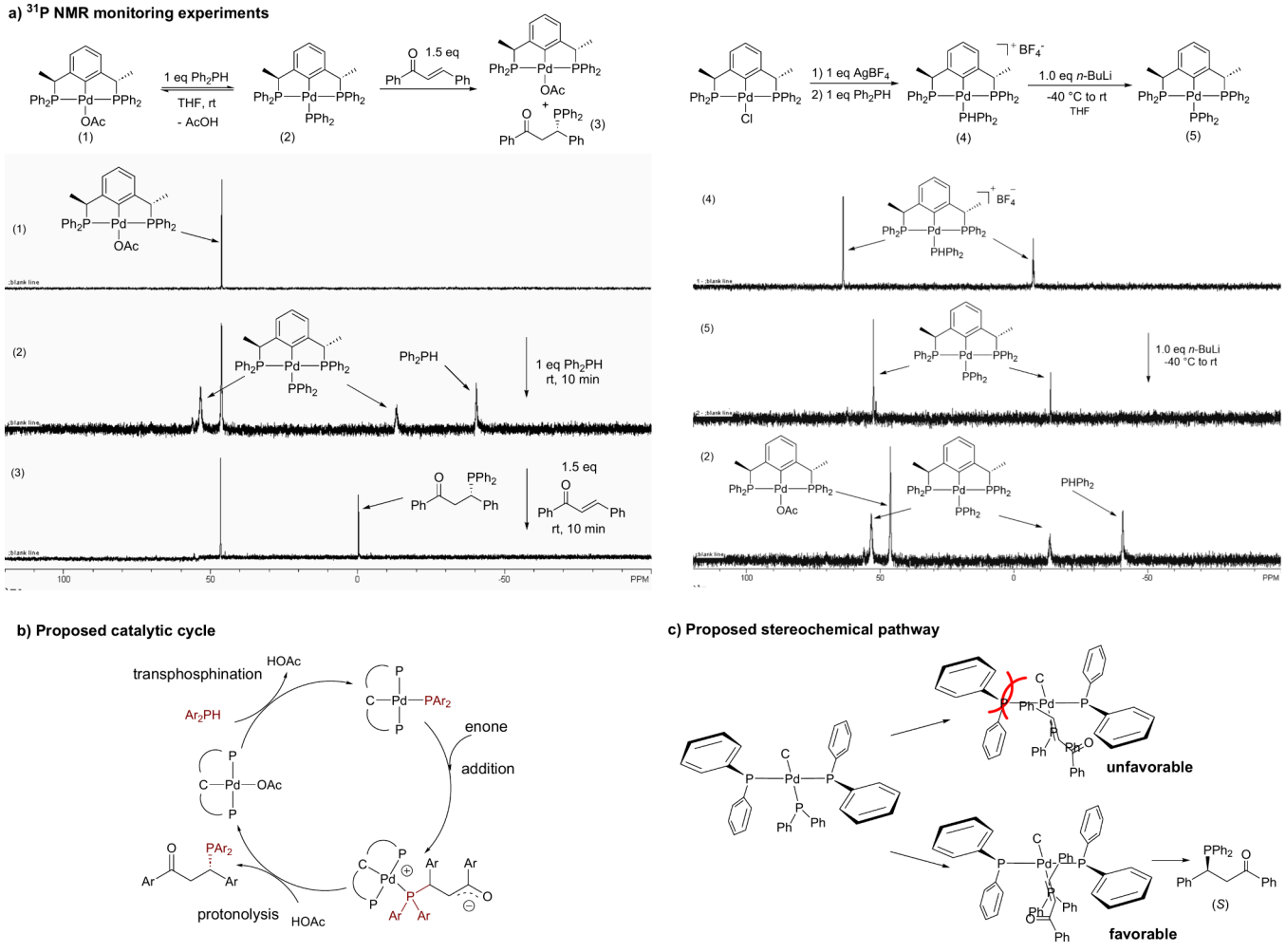
Scheme 2. Pincer-Pd Catalyzed Asymmetric Addition of Diarylphosphines to Enones



Scheme 3. ^{31}P NMR Monitoring Experiments and Catalytic Cycle



as "catalytic survivors", successfully resisting ligand displacement and enabling highly enantioselective additions and substitutions. The second is founded on the "C−H Bond Activation", wherein we pioneered the use of chiral phosphoric acids and amides to direct asymmetric C−H activation, completely bypassing the coordination poisoning by utilizing P(V) precursors and achieving stereocontrol without traditional chiral phosphine ligands. Besides, two types of phosphorus

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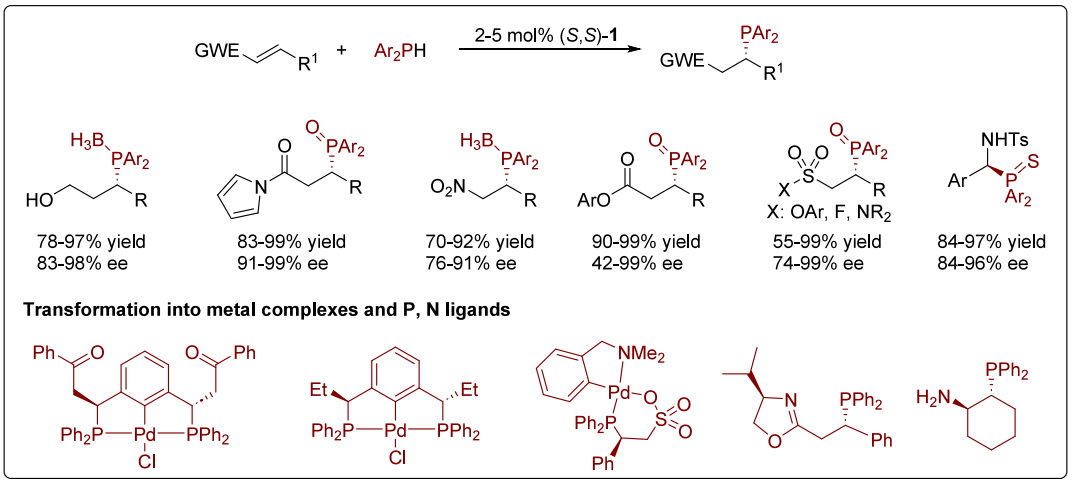
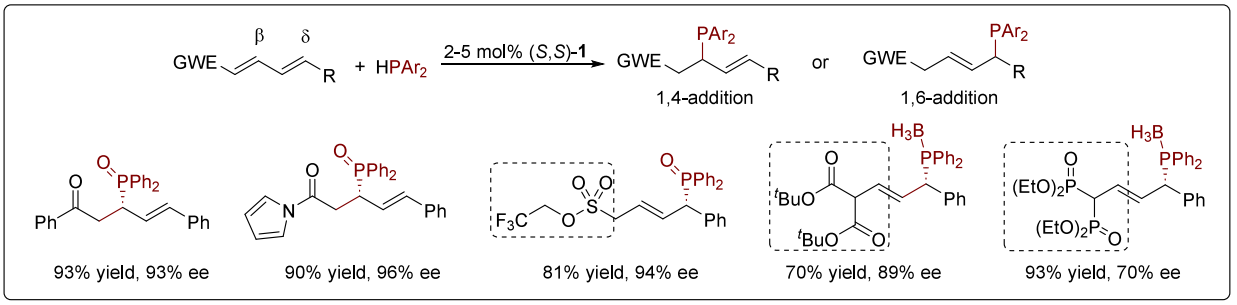
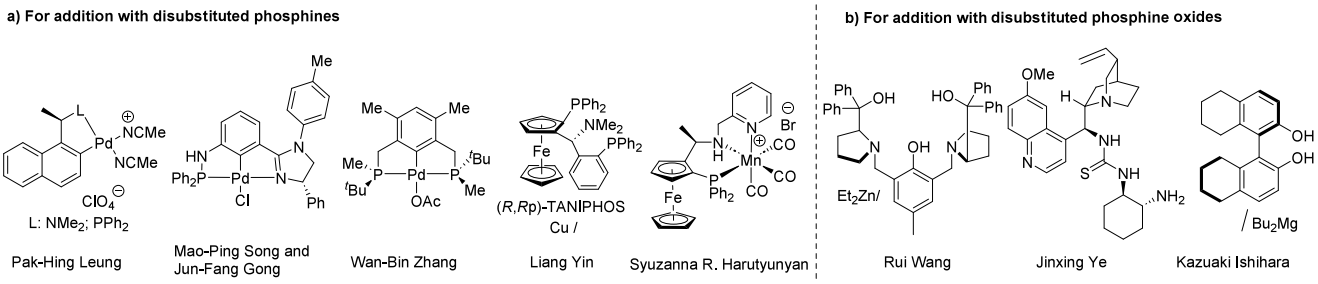
Scheme 4. Evaluation on the Scope of Electrophiles



Scheme 5. EWG-Enabled Asymmetric 1,6-Phosphorus Addition



Scheme 6. Reported Catalysts for Asymmetric Phosphorus Addition in the Past Decade



reagents have been designed to overcome the long-standing problem and realize the highly selective transformation. This Account chronicles our systematic exploration (Scheme 1d) and mechanistic discoveries within these frameworks, offering a comprehensive roadmap for the precise, modular construction of chiral phosphorus compounds.

2. THE LOGIC OF ROBUSTNESS—PINCER SCAFFOLDS AS "SURVIVORS"

2.1. Design Concept and the "Survivor" Catalyst

The most fundamental obstacle in transition-metal-catalyzed asymmetric P−C bond formation is the aggressive coordinating nature of trivalent phosphorus nucleophiles. In classical catalytic systems, these P(III) species frequently outcompete and displace delicate chiral ligands, leading to irreversible catalyst deactivation or the proliferation of nonselective background reactions.[12] To conquer this "coordination paradox," we hypothesized that a tridentate pincer-metal framework would firmly anchor the transition metal and resist ligand displacement even in a phosphorus-rich environment. Specifically, we employed a C_2-symmetric bis(phosphine) (PCP) pincer-palladium complex.[13] The rigid carbon backbone of this scaffold, equipped with stereogenic methyl groups at the benzylic positions, strictly dictates the spatial arrangement of the phenyl substituents on the coordinating phosphorus atoms. This structural rigidity effectively creates a deep, well-defined chiral pocket that selectively shields one enantioface of the incoming electrophile, thereby ensuring precise stereocontrol.

2.2. The First Breakthrough in Enones and Mechanistic Insights

Our initial validation of the pincer-palladium platform focused on the hydrophosphination of α,β-unsaturated ketones (Scheme 2).[1] Utilizing merely 2 mol% of C_2-symmetric PCP pincer-palladium acetate complex (*S*,*S*)-**1**, we achieved the first highly enantioselective addition of diarylphosphines to enones without the need for external base additives, securing the corresponding

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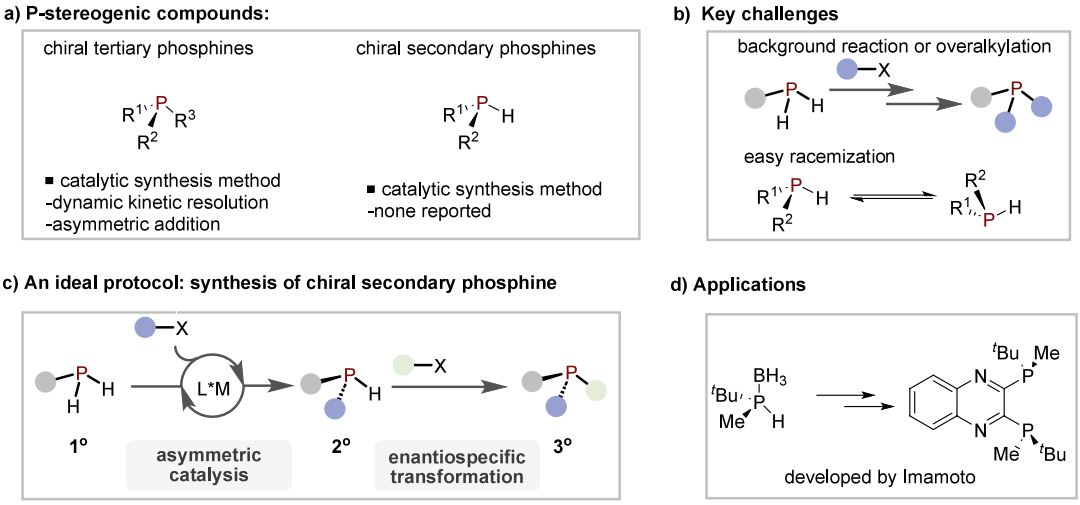
Scheme 7. Catalytic Asymmetric Synthesis of Secondary Phosphines



chiral phosphine oxides in up to 99% ee. The ^{31}P NMR monitoring experiments were conducted to understand the reaction (Scheme 3a). Mixing the Pd catalyst **1** with $HPPh_2$ generated a new species bearing two ^{31}P new peaks. This intermediate was identified as the pincer Pd-PPh_2 based on the deprotonation of Pincer $[Pd\text{-}PHPh_2]BF_4$. The catalytic cycle (Scheme 3b) commences with a transphosphination that abstracts a proton, generating a nucleophilic palladium-phosphido intermediate and acetic acid. Following nucleophilic attack, the intermediate is protonolyzed by the acetic acid, liberating the product and regenerating the active catalyst. The chiral space induced by the methyl group on the benzyl position of (*S*,*S*)-**1** favors the approach of the enone with its *Si*-face, thus generating the adduct with (*S*)-configuration (Scheme 3c).

2.3. Broadening the Synthetic Horizon

Encouraged by this mechanistic clarity, we systematically expanded the substrate scope of the PCP pincer-PdOAc catalyst (Scheme 4).[14] The highly reversible nature of hydrophosphination to *α*,*β*-unsaturated aldehydes (enals) resulted in poor enantioselectivities. We circumvented this equilibrium issue by performing the reaction in *tert*-amyl alcohol, where the adduct precipitates, thereby ensuring high conversion. Following in situ reduction with borane, the initial adducts were rapidly trapped to afford configurationally stable chiral secondary phosphine-boranes with up to 98% ee.[14a] The robust nature of the pincer catalyst subsequently enabled high-precision additions to a diverse array of acceptors, including *N*-acylpyrroles,[14b] nitroalkenes,[14c] and *N*-tosylimines.[14d] Furthermore, we demonstrated that *α*,*β*-unsaturated sulfonic esters[14f] and even sulfonyl fluorides[14j] were excellent substrates, granting modular access to highly valuable chiral phosphine-sulfonate ligands and their derivatives. This catalytic protocol is also efficient for preparing valuable chiral metal-phosphine complexes or ligand precursors.

2.4. Mastering Regiocontrol: The Asymmetric 1,6-Addition

Transitioning from simple 1,4-additions to conjugated diene systems presented a formidable regiochemical challenge. Intrinsically, the *α*,*β*-position of a conjugated diene is far more electrophilic than the remote *δ*-position, heavily biasing the reaction toward 1,4-addition. To overcome this inherent electronic preference, we devised a "steric steering" approach. We postulated that appending exceptionally bulky electron-withdrawing groups (EWGs) to the diene terminus would incite severe steric repulsion against the bulky phenyl rings of the palladium-phosphido intermediate. Indeed, while standard dienones exclusively afforded 1,4-adducts, equipping the diene with massive EWGs—such as trifluoroethyl sulfonic esters or tetraethyl bis(phosphonates)—completely inverted the regioselectivity.[15] The profound steric clash steered the nucleophilic attack toward the less hindered *δ*-position, culminating in the first highly enantioselective 1,6-addition of diarylphosphines and delivering chiral allylic phosphines with exceptional precision (Scheme 5).

2.5. Parallel Strategies in the Chemical Community

It is important to contextualize our findings within the broader renaissance of asymmetric hydrophosphination that was occurring simultaneously. While our laboratory concentrated on structurally symmetric PCP scaffolds, other research groups developed highly complementary approaches to navigate the coordination paradox (Scheme 6). For instance, Mao-Ping Song and Jun-Fang Gong et al elegantly designed unsymmetric PCN pincer complexes featuring both imidazoline and phosphinite/phosphine donors, achieving excellent stereocontrol in additions to enones and alkenoylpyridines.[16] Wanbin Zhang's laboratory took a distinctly different structural approach by embedding *P*-stereogenic centers directly into the pincer ligand backbone itself, a modification that proved highly effective for the addition to nitroalkenes.[17] Beyond pincer architectures, Pak-Hing Leung and co-workers demonstrated the profound utility of chiral palladacycles to achieve highly enantioselective P−C bond formations.[18] Furthermore, Liang Yin's group expanded the frontier into earth-abundant base-metal catalysis, utilizing copper(I) systems to successfully activate traditionally unreactive substrates such as *α*,*β*-unsaturated amides and phosphine sulfides.[19] Recently, remarkable progress has also been made in manganese catalysis. Highly enantioselective syntheses of chiral phosphorus compounds have been achieved using a PNP Mn catalyst, offering a cost-effective and sustainable alternative to noble metals.[20] In addition, several groups made significant progress with phosphine oxides as the nucleophile based on concise catalyst development (Scheme 6b).[21−23] These collective efforts underscore that overcoming the catalyst poisoning effect of phosphorus nucleophiles requires meticulously engineered, robust catalytic environments.

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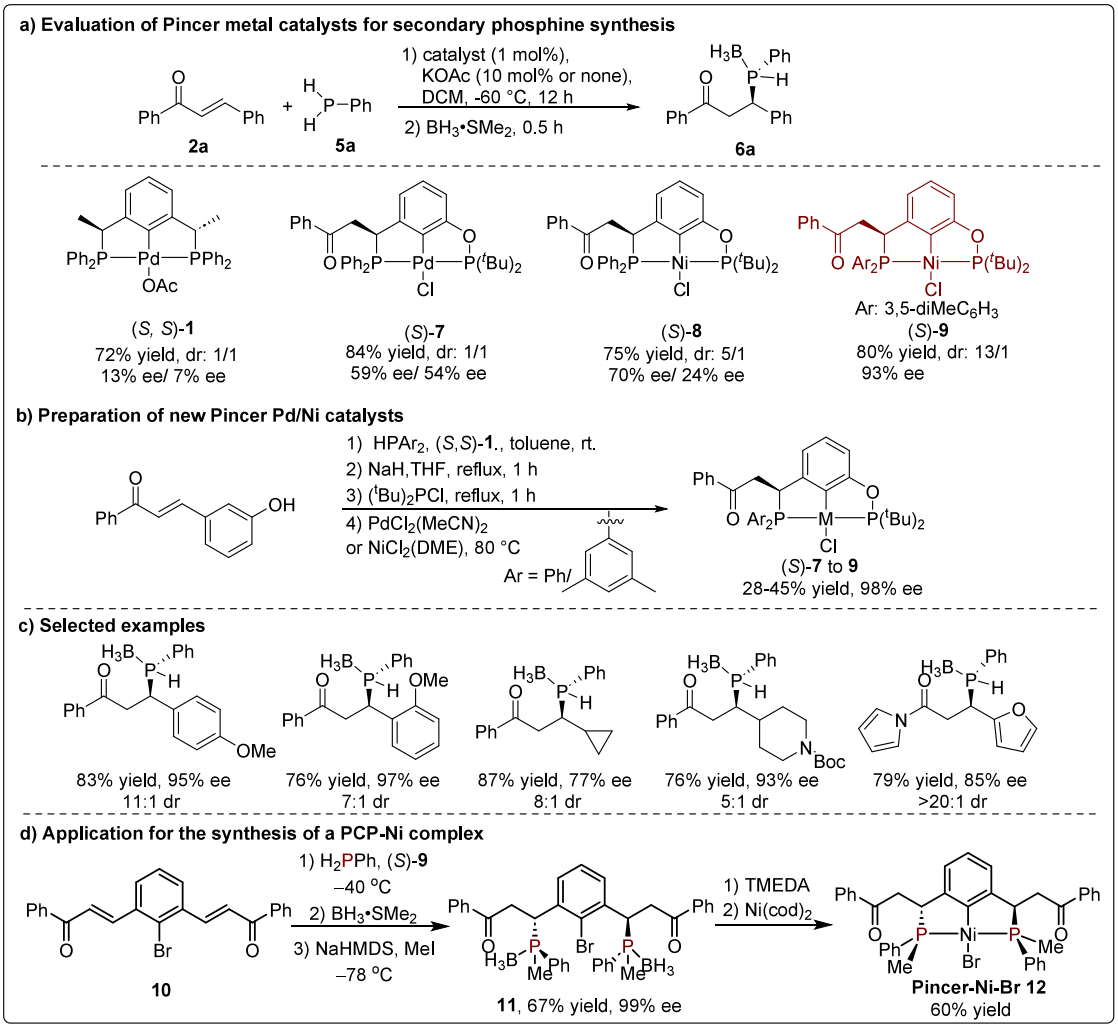
Scheme 8. Development of New Unsymmetric PCP Catalysts for Secondary Phosphine Synthesis



3. CATALYTIC SYNTHESIS OF *P*-STEREOGENIC SECONDARY PHOSPHINES

3.1. The Inherent Challenges of Primary Phosphine Reactivity

Moving beyond the construction of tertiary phosphines, our laboratory set its sights on a significantly more formidable challenge: the catalytic asymmetric synthesis of *P*-stereogenic secondary phosphines (Scheme 7). These molecules are the ultimate "holy grail" building blocks in phosphorus chemistry because their highly reactive P−H bonds allow for divergent, modular synthesis of complex ligand architectures. However, their direct catalytic synthesis from primary phosphines has historically been elusive due to several intrinsic chemical hurdles. First, due to the presence of a P−H bond, chiral secondary phosphine compounds are more prone to racemization than tertiary phosphine compounds via acid- or base-catalyzed pathways.[24] Second, the relatively small steric profile of primary phosphines often leads to nonstereoselective background alkylations, overalkylation events, and the displacement of delicate chiral ligands from the catalyst.[12]

3.2. Overcoming the Limitations of Symmetric Scaffolds: Design of the Unsymmetric PCP′-Nickel Catalyst

Our initial attempts to solve this problem relied on the "survivor logic" of well-established C_2-symmetric PCP-palladium platform. We attempted the asymmetric conjugate addition of phenylphosphine to enones using this robust catalyst (*S*,*S*)-**1** (Scheme 8a). To our disappointment, while the P−C bond formation proceeded, the enantioselectivity was exceptionally poor, yielding nearly racemic mixtures alongside very low diastereomeric ratios. We deduced that the spatial orientation of the small primary phosphine substrate was insufficiently restricted; unlike bulky diarylphosphines, the compact primary phosphine could freely rotate around the palladium-phosphorus bond within the symmetrical chiral pocket, completely undermining stereocontrol.

To circumvent this, we redesigned our catalyst framework. We hypothesized that an unsymmetric coordination sphere would be required to enforce a rigid spatial arrangement on the small phosphido intermediate. Thus, we engineered a novel unsymmetric PCP′ pincer ligand featuring a standard diarylphosphino (PAr_2) donor on one arm and a significantly bulkier di-*tert*-butylphosphinite ($OPtBu_2$) donor on the other.[2] This severe steric disparity effectively broke the symmetry of the catalytic pocket. Furthermore, by transitioning the metal center from palladium to nickel, we discovered the ideal balance between reactivity and spatial confinement (Scheme 8b). This unsymmetric PCP′-nickel complex successfully catalyzed the highly enantioselective addition of primary phosphines to various electron-deficient alkenes, yielding configurationally

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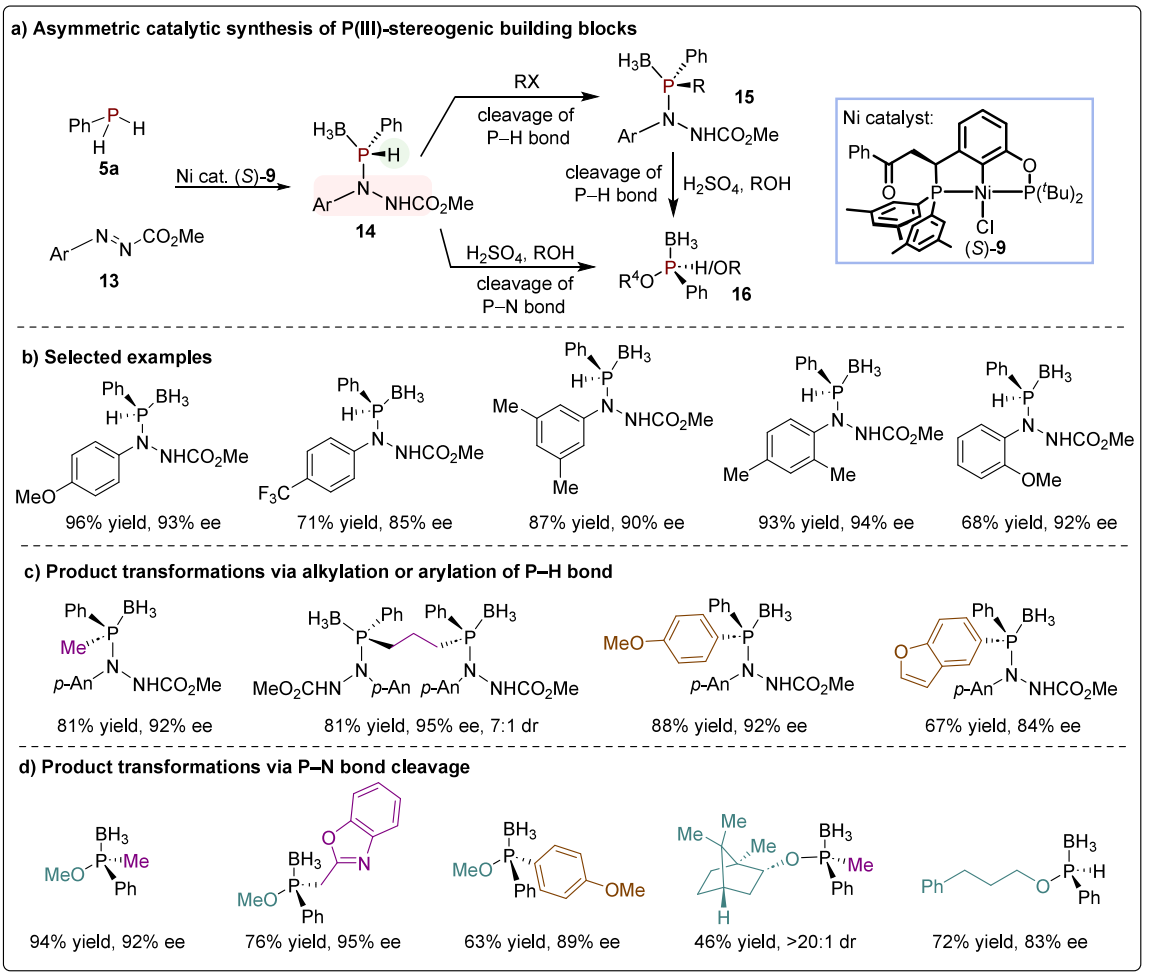
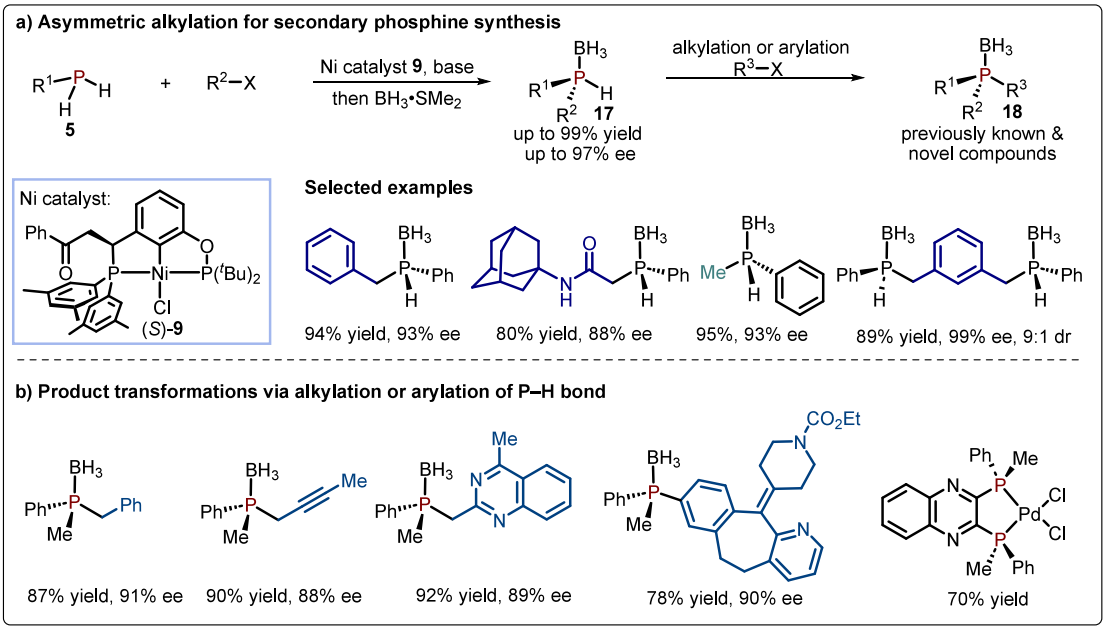
Scheme 9. Asymmetric Addition of Primary Phosphine to Azo Compounds



Scheme 10. Asymmetric Alkylation for the Synthesis of Secondary P(III)-Stereogenic Phosphines



stable *P*-stereogenic secondary phosphine-boranes (after *in situ* protection) with exceptional precision (Scheme 8c).

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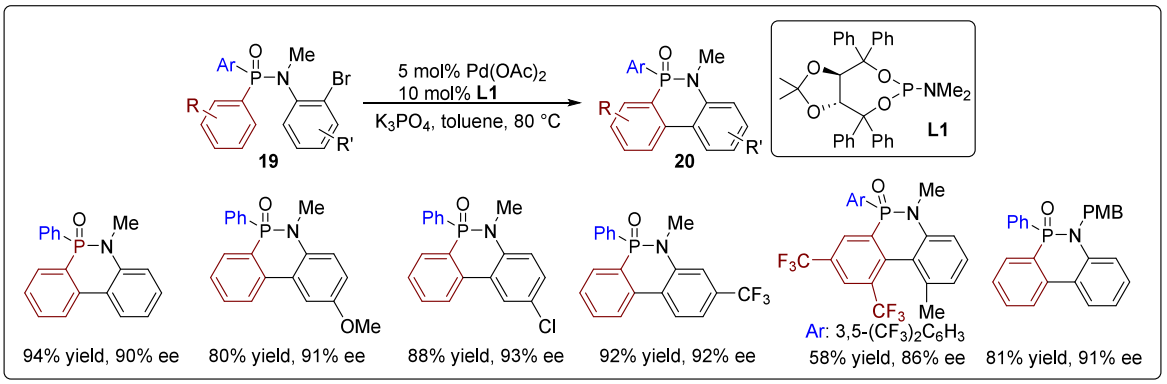
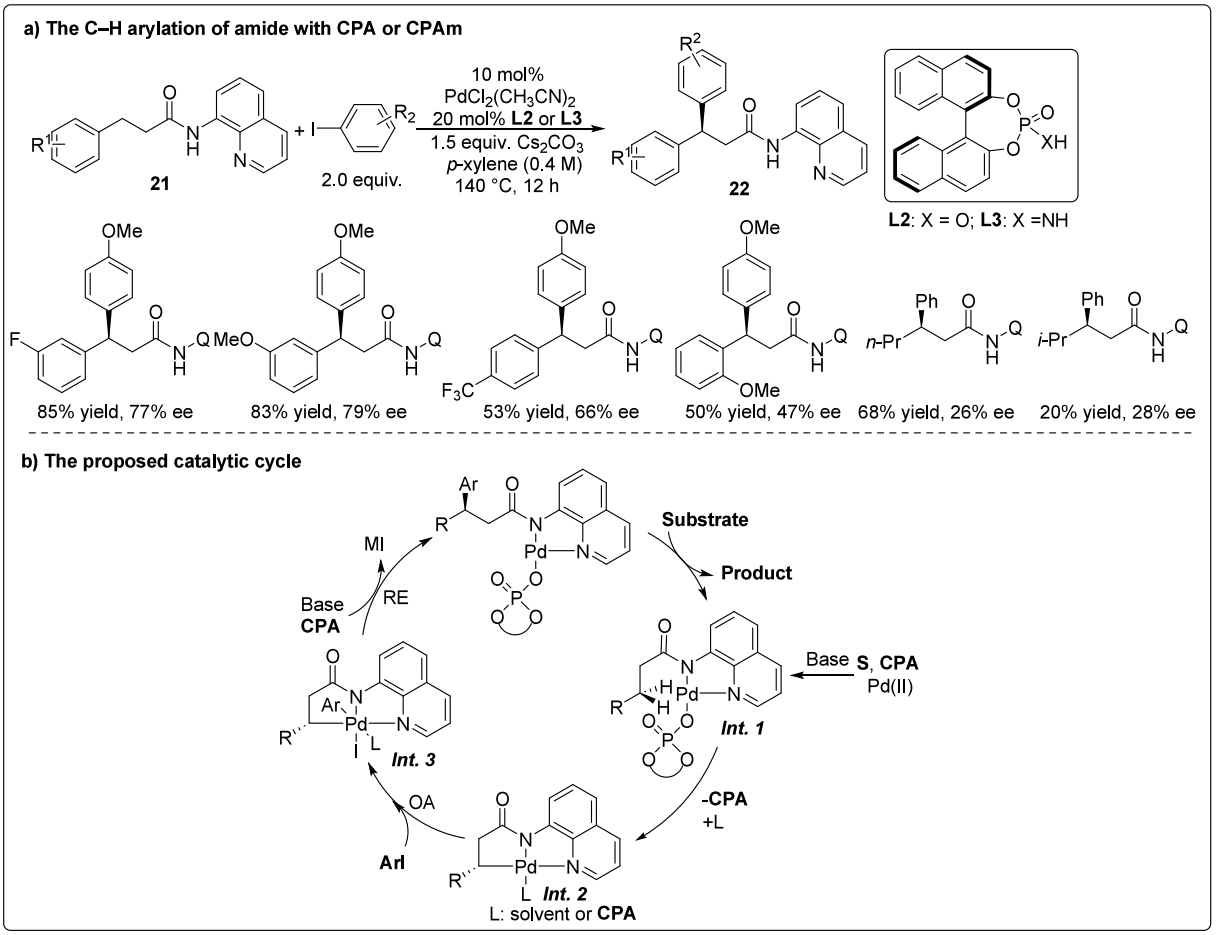
Scheme 11. Asymmetric C−H Arylation for the Synthesis of *P*-chiral Phosphinamides



Scheme 12. First Example of Application of CPA into Asymmetric C−H Activation



3.3. Expanding the Scope: Azo Addition for Phosphanyl Hydrazine Building Blocks

Recognizing the power of this unsymmetric pincer-nickel platform, we sought to expand its utility beyond carbon electrophiles to forge P−N bonds. We successfully applied this catalyst to the asymmetric addition of primary phosphines to electron-deficient azo compounds, specifically diazenecarboxamides (Scheme 9).[25] This reaction represents an important advance, generating novel P-stereogenic secondary aminophosphine-boranes. These unique molecules serve as chiral phosphanyl-hydrazine building blocks. Their significant synthetic utility stems from the presence of both a reactive P−H bond and a selectively cleavable P−N bond, providing two orthogonal handles for subsequent stereospecific functionalization.

3.4. The Ultimate Test: Enantioselective Alkylation of Primary Phosphines

The true testament to the robustness of this PCP′-nickel platform was achieving the direct asymmetric alkylation of primary phosphines with alkyl halides—a reaction historically plagued by rapid, racemic background S_N2 substitutions.[26] We discovered that by utilizing diisopropylethylamine (iPr_2NEt) as a base and operating at cryogenic temperatures (−78 °C), we could entirely suppress the nonselective background reaction.

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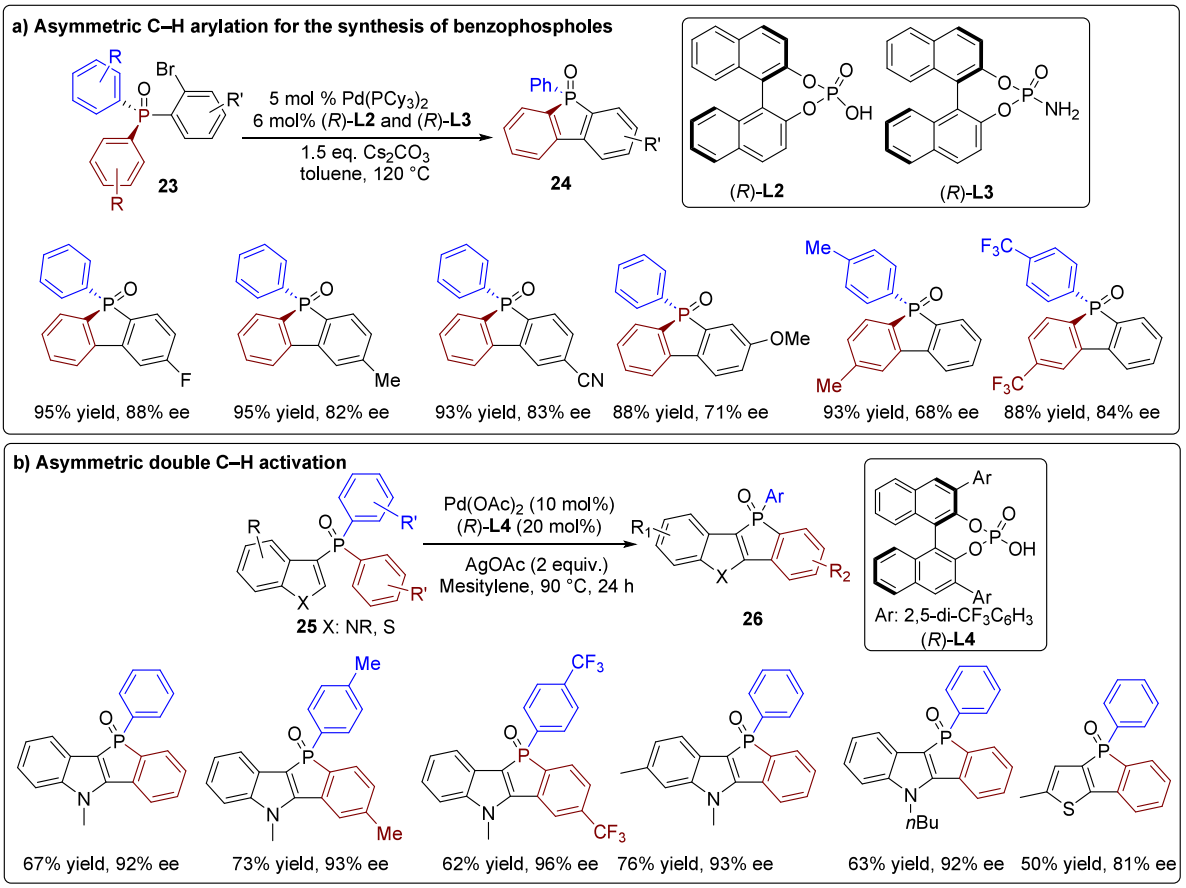
Scheme 13. Application of CPA for the Synthesis *P*-Chiral Heterocycles



Under these conditions, the nickel catalyst effectively intercepts the primary phosphine (Scheme 10).[27] Detailed mechanistic and computational studies (DFT) revealed that the reaction operates under a classic Curtin–Hammett scenario: the base generates two rapidly interconverting nickel-phosphido diastereomers,[28] and the unsymmetric chiral pocket dictates that the nucleophilic attack on the alkyl halide proceeds almost exclusively through the lowest-energy transition state of one specific diastereomer. This enantioselective process enabled us to couple a wide array of benzyl, allyl, and propargyl halides with primary phosphines, affording an extensive library of highly enantioenriched secondary phosphine-boranes (Scheme 10).

3.5. Diversity-Oriented Synthesis and Derivatization Potential

The chiral secondary phosphine-boranes synthesized via these addition and alkylation methodologies are not merely academic curiosities; they are remarkably versatile "hubs" for diversity-oriented synthesis. Because the borane group preserves the delicate phosphorus stereocenter, the remaining P–H bond can undergo a variety of stereospecific transformations (Schemes 8–10). We demonstrated that these intermediates readily undergo base-mediated alkylation or palladium/copper-cocatalyzed cross-coupling with aryl iodides, yielding complex tertiary phosphines with complete retention of chirality (Schemes 9c and 10b). Similarly, the P–N bond of phosphanyl hydrazine adducts can undergo acid-mediated, stereoinvertive nucleophilic substitution with alcohols to efficiently generate chiral phosphinites (Scheme 9d). Through these modular derivatization strategies, we have bypassed the need for stoichiometric chiral auxiliaries. We successfully applied this platform to the rapid, gram-scale synthesis of advanced chiral ligands, including the direct catalytic construction of frameworks that mimic the privileged PCP and QuinoxP* architectures (Schemes 8d and 10b). This methodology firmly establishes our catalytic platforms as powerful tools for accessing *P*-stereogenic chemical space.

4. PILLAR II: CPA AND AMIDE-DIRECTED ASYMMETRIC C–H ACTIVATION

4.1. The Conceptual Shift to Asymmetric C–H Functionalization

Transition-metal-catalyzed C–H bond functionalization represents the pinnacle of step- and atom-economic synthesis, offering direct access to complex molecular architectures from unfunctionalized precursors.[29] Historically, achieving high enantioselectivity in these transformations has relied heavily on two main strategies: the use of chiral transition metal complexes to facilitate enantio-determining C–H bond cleavage, or the unbiased scission of C–H bonds followed by stereoselective coupling with external partners. In the context of organophosphorus chemistry, we recognized that C–H activation could offer a brilliant work around to the "coordination paradox" that plagues the synthesis of *P*-stereogenic compounds. By utilizing pentavalent phosphorus (P(V)) oxides and amides as stable starting materials, we could entirely circumvent the catalyst poisoning typically caused by trivalent phosphorus nucleophiles. Concurrently, several other research groups have also elegantly leveraged asymmetric C–H

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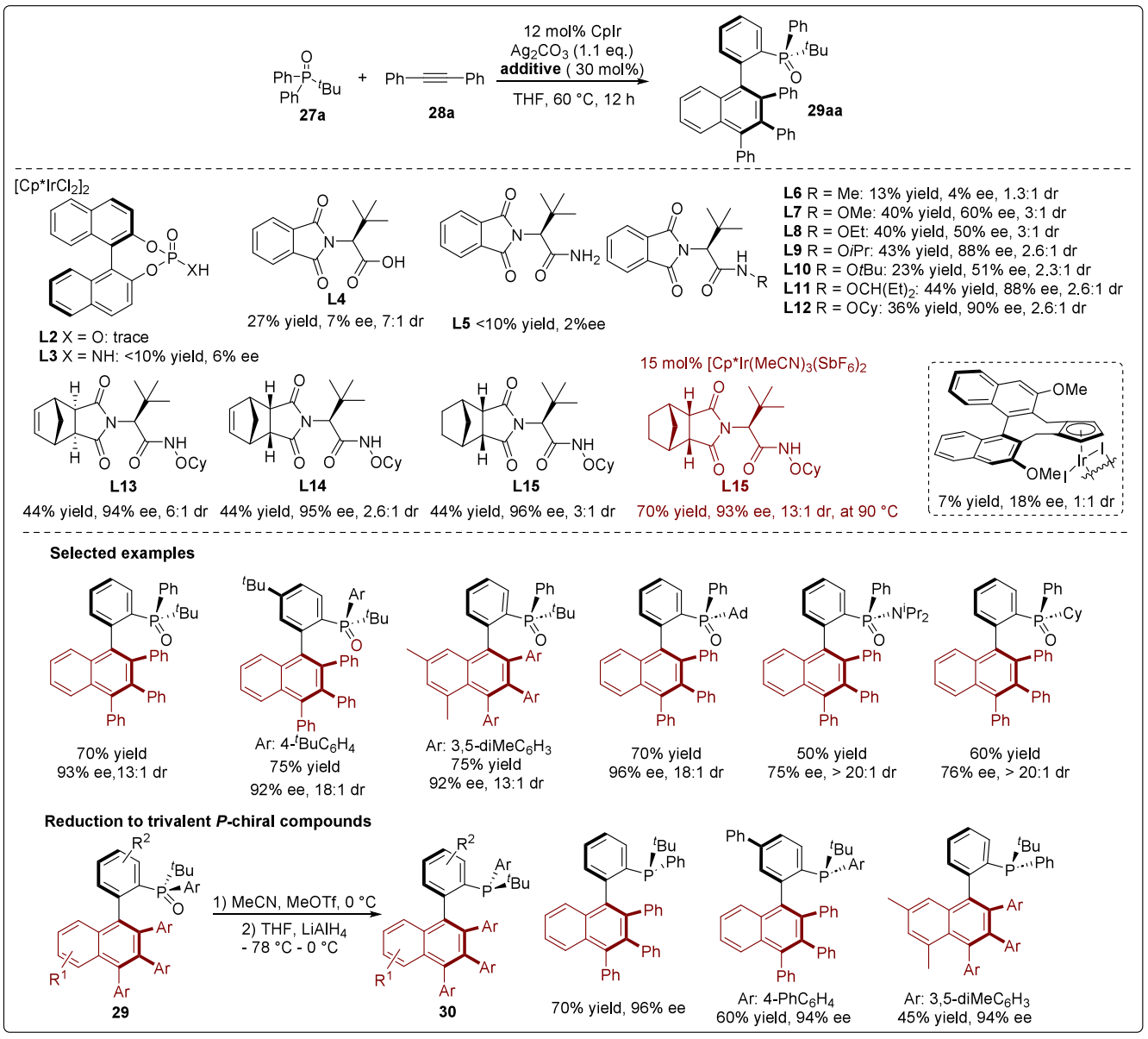
Scheme 14. Chiral Amide-Enabled Cp*Ir-Catalyzed Asymmetric C−H Activation



activation strategies to access *P*-stereogenic molecules, significantly broadening the structural diversity of chiral phosphines.[30]

Our laboratory's initial breakthrough in this arena was achieved through a palladium-catalyzed intramolecular C−H arylation, which we reported in 2015.[31] By employing a TADDOL-derived chiral phosphoramidite ligand,[32] we successfully developed the desymmetrization of *N*-(*o*-bromoaryl)-diarylphosphinic amides (Scheme 11). This methodology enabled the highly enantioselective construction of *P*-chiral biphenyl phosphinic amides, providing a direct and robust route to valuable precursors for biaryl monophosphine ligands.

4.2. A New Paradigm: Bifunctional Control via Chiral Phosphoric Acids

While the use of classical chiral phosphorus ligands was successful, we sought to develop a fundamentally new stereocontrol strategy that did not rely on permanent coordination to the metal center. We hypothesized that the Concerted Metalation-Deprotonation (CMD)[33] pathway—a key mechanistic step in many C−H activations—could be leveraged for external stereocontrol. Recognizing the high basicity of the phosphoryl group and the excellent chiral environment provided by BINOL scaffolds, we pioneered the use of chiral phosphoric acids (CPAs) and phosphoric amides as bifunctional "directors". In this unique catalytic mode, the CPA does not merely sit in the outer coordination sphere; it actively participates in the CMD transition state, specifically abstracting a proton to stereoselectively cleave enantiotopic C−H bonds (Scheme 12).[34]

We successfully applied this protocol to the synthesis of rigid, *P*-stereogenic heterocycles. We demonstrated that a Pd/CPA catalytic system could efficiently desymmetrize diaryl(2-bromoaryl)phosphine oxides, affording *P*-stereogenic dibenzophospholes with excellent enantiomeric ratios (up to 5:95 er) (Scheme 13a).[35] Pushing this strategy even further, we recently disclosed a palladium-catalyzed asymmetric intramolecular oxidative double C−H activation. By pairing palladium with a sterically demanding BINOL-based CPA, we achieved the direct cross-coupling of two arenes—an indole ring and a phenyl group

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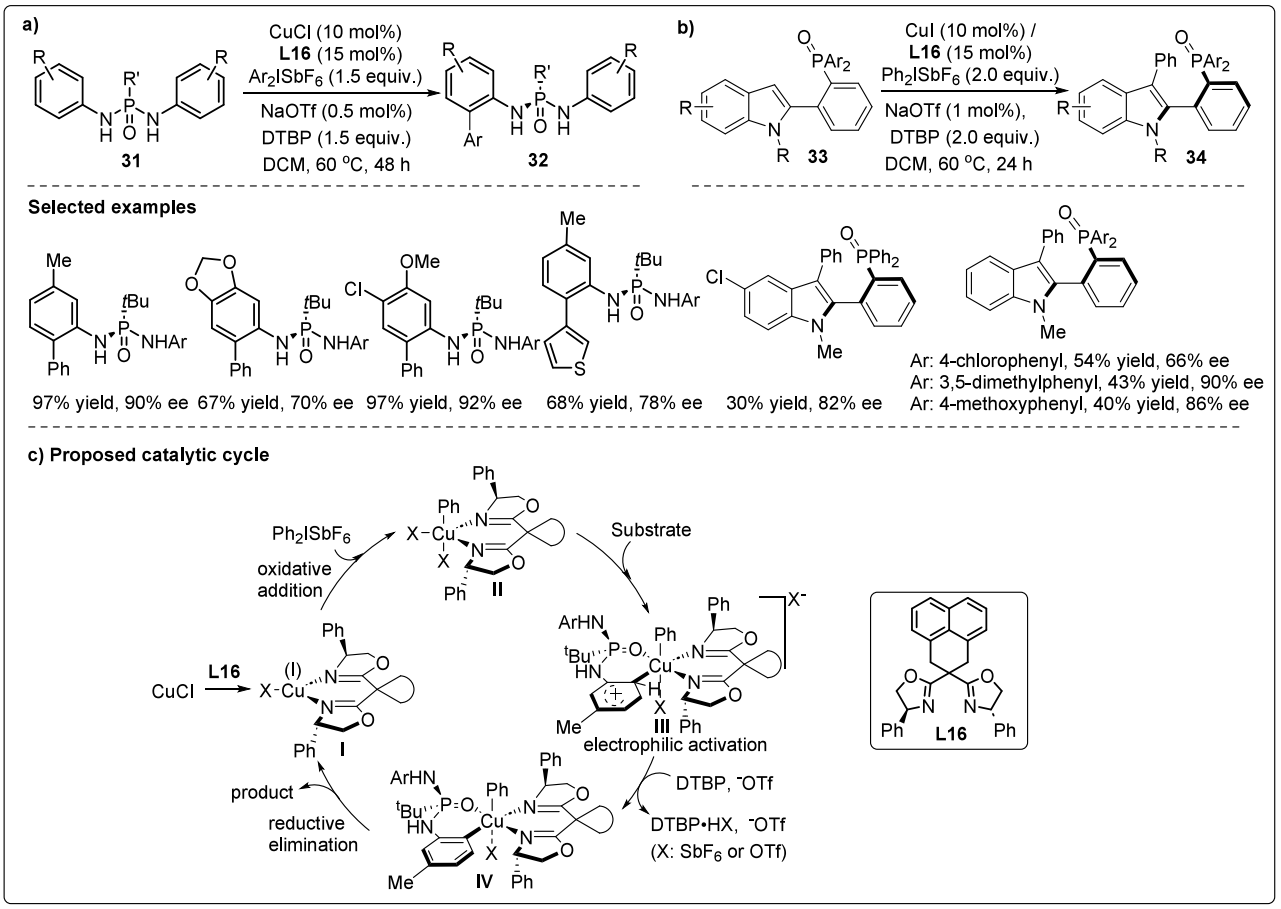
Scheme 15. Cu-Catalyzed Asymmetric C−H Activation



attached to the phosphorus center (Scheme 13b).[36] This transformation yielded structurally complex, luminescent *P*-stereogenic benzophosphole oxides with exceptional enantioselectivity. Crucially, mechanistic investigations and kinetic isotope effect studies confirmed that the CPA-assisted C−H cleavage on the phenyl ring is both the rate-determining and enantio-determining step, firmly validating our bifunctional CMD design rationale.

4.3. Expanding the Toolbox: Iridium-Catalyzed Dual Induction

Transitioning beyond palladium, we explored the intermolecular C−H coupling of tertiary phosphine oxides with alkynes using iridium catalysis. While chiral cyclopentadienyl (Cp^X) ligands have driven massive progress in group 9 metal-catalyzed C−H activations, their synthesis and structural tuning can be quite laborious.[37] We envisioned a more modular and accessible approach: pairing a simple, commercially available achiral Cp*Ir catalyst with an external chiral carboxylic amide. The design rationale for this system hinged on manipulating the amide's conformational flexibility. By installing specific bulky *N*-alkoxy substituents, we intentionally induced severe steric repulsion between the amide and the Cp* ring on the iridium center. This steric clash restricted the free rotation of the Ir−N bond, effectively locking the catalyst into a highly rigid and defined chiral pocket during the C−H activation event. This synergistic strategy enabled the simultaneous, highly stereoselective construction of both *P*-central and axial chirality, delivering biaryl phosphine oxides with up to 96% ee and excellent diastereoselectivities (Scheme 14).[3]

4.4. Sustainable Frontiers: Base-Metal Catalyzed C−H Arylation

Ultimately, the future of catalytic C−H functionalization lies in transitioning from precious noble metals to earth-abundant, cost-effective 3d metals like copper and cobalt. However, the development of base-metal-catalyzed asymmetric C(sp^2)−H arylation has historically lagged far behind its 4d and 5d counterparts.[29f] To bridge this gap, our laboratory developed a copper-catalyzed protocol that utilizes diaryliodonium salts as arylating agents in conjunction with chiral bisoxazoline (BOX) ligands. This system achieved the highly enantioselective *ortho*-arylation of phosphonic diamides, forging *P*-chiral centers with up to 92% ee (Scheme 15a).[38] Furthermore, this Cu/BOX platform was successfully extended to the enantioselective C-3 arylation of diarylphosphine oxide indoles, demonstrating its ability to dictate stereocontrol for the construction of axially chiral phosphorus scaffolds (Scheme 15b). KIE experiments ($k_H/k_D = 1.0$) indicated that the cleavage of the *ortho* C−H bond is not a rate-determining step, and the reaction was proposed via a Cu-catalyzed electrophilic arylation pathway (Scheme 15c).

5. INNOVATION THROUGH NUCLEOPHILIC DEVELOPMENT

5.1. Overcoming Deactivation in Asymmetric Allylic Substitution via Secondary Phosphine Sulfides

The transition-metal-catalyzed asymmetric allylic substitution (AAS) is a cornerstone methodology for the direct construction of complex chiral frameworks, yet the successful incorporation

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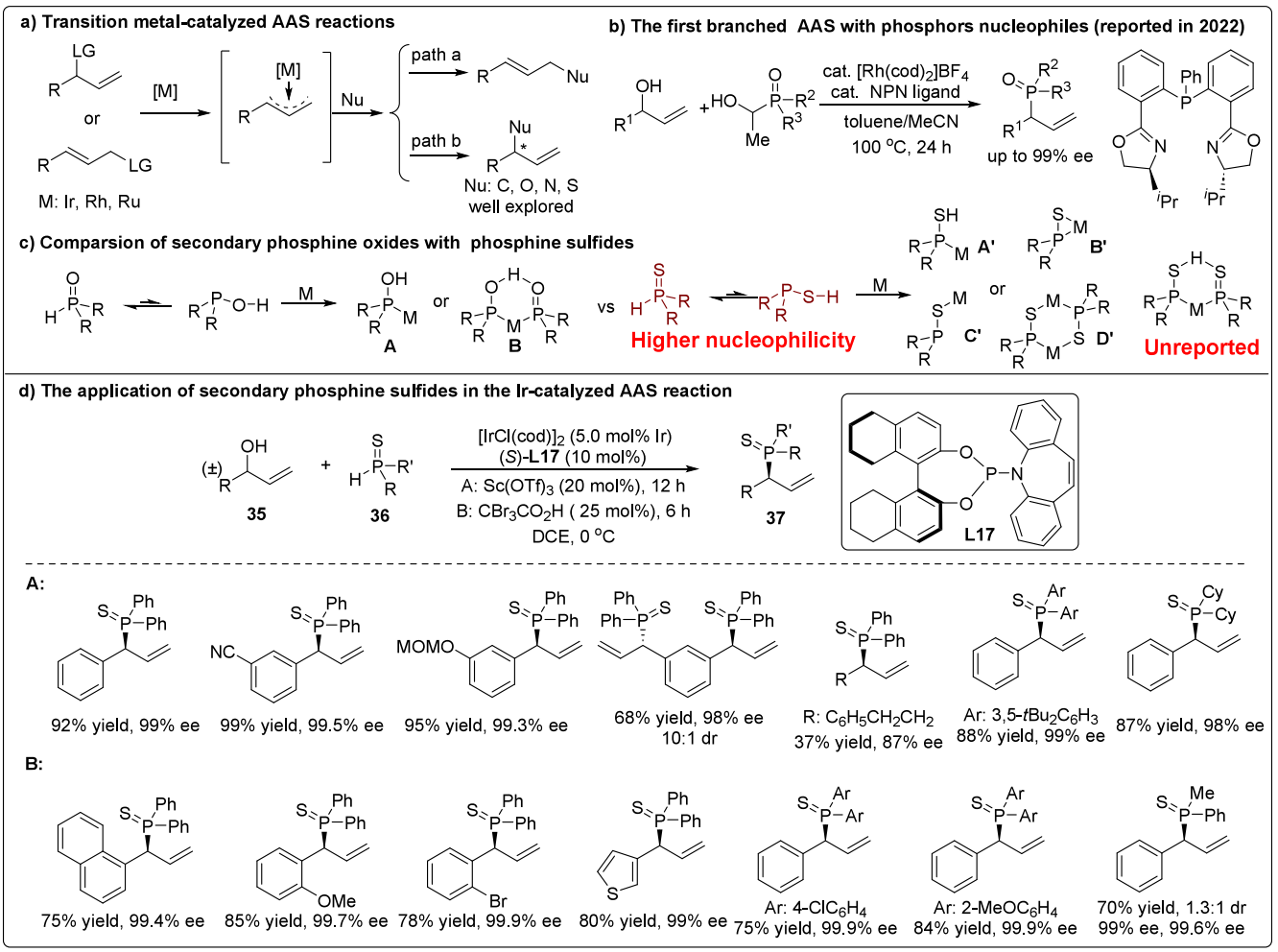
Scheme 16. Secondary Phosphine Oxide-Enabled Ir-Catalyzed Asymmetric Allylic Substitution



of phosphorus nucleophiles into this transformation has historically been challenging.[39,40] The primary obstacle lies in the coordination ability of phosphorus reagents, which inevitably leads to the rapid poisoning of the metal catalyst (Scheme 16a). Consequently, achieving precise control over both regio- and stereoselectivity to forge branched, *P*-chiral allylic compounds remained elusive. For instance, widely utilized chiral phosphoramidite ligands bind relatively weakly to the metal center and are easily displaced by phosphorus nucleophiles. During our investigations, we found that even secondary phosphine oxides (SPOs)—which are considered less toxic to catalysts—failed to undergo iridium-catalyzed AAS. We deduced that SPOs tend to form a bidentate H-bonded chelate with loss of a proton, which irreversibly deactivates the metal catalyst.[12] Notably, Changkun Li's group recently reported the use of protected secondary phosphine oxides for the AAS reaction in the presence of Rh/NPN tridentate catalyst, generating branched phosphination product in excellent enantioselectivity (Scheme 16b).[41]

To overcome this coordination hurdle, our laboratory developed a strategy that uses secondary phosphine sulfides as alternative nucleophiles. Our design rationale hinged on the distinct coordination chemistry of sulfur; unlike their oxygen analogs, phosphine sulfides coordinate to transition metals via weaker modes and do not form the problematic bidentate complexes that might cause catalyst deactivation (Scheme 16c).[12c] Importantly, these sulfide reagents maintain a high degree of nucleophilicity necessary for the reaction to proceed. This nucleophilic switch proved to be highly effective. By utilizing an iridium catalyst, a readily available Carreira-type P-olefin ligand,[42] and a Lewis or Brønsted acid promoter, we successfully achieved highly regio- and enantioselective AAS, using phosphorus nucleophiles to form branched products. The protocol operated under mild conditions, delivering an array of branched allylic phosphine sulfides with excellent stereocontrol (Scheme 17d: up to 99.9% ee).[4] This approach circumvented the long-standing catalyst deactivation dilemma, opening a new avenue for the precise synthesis of functionalized allylic phosphorus architectures.

5.2. Precision Stereocontrol via 2-Pyridyl-Directed Nucleophiles

Beyond catalyst poisoning, another intrinsic challenge in asymmetric phosphorus synthesis is the difficulty of discriminating between two structurally similar aryl groups on a phosphorus atom during desymmetrization (Scheme 17a).[43] To address this subtle stereochemical challenge, we pioneered the use of 2-pyridinyl secondary phosphine oxides as structurally engineered nucleophiles. The core design principle behind this strategy leverages the inherent chelating capability of the 2-pyridyl group. We hypothesized that the nitrogen atom on the pyridine ring would function as an internal directing group, coordinating to the transition metal alongside the phosphorus

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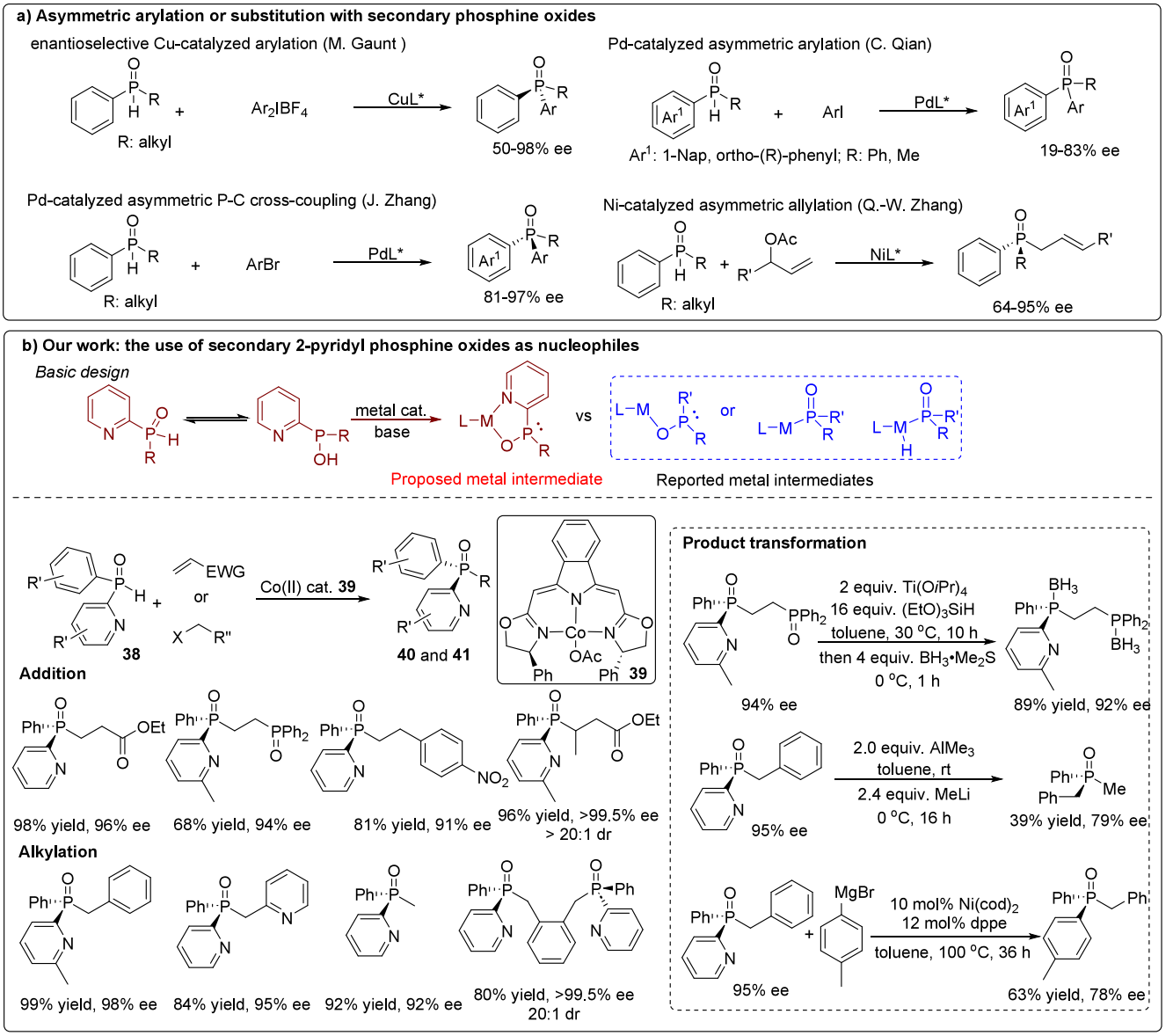
Scheme 17. Co-catalyzed Addition and Substitution of 2-Pyridyl Phosphine Oxides



moiety to form a rigid, bidentate chelate. This dual-coordination mode effectively restricts the conformational freedom of the phosphorus substrate, thereby magnifying the local environment and enabling the catalyst to readily differentiate between the two similar aromatic rings at the phosphorus center (Scheme 17b).

This directing-group strategy was validated in our development of a cobalt-catalyzed asymmetric addition and alkylation platform. Using a cobalt complex of an NNN ligand developed by the Gade group,[44] the chelation-assisted protocol efficiently converted racemic secondary phosphine oxides into highly enantioenriched tertiary phosphine oxides, achieving outstanding yields and enantioselectivities up to 99.5% ee.[45] The impact of this innovation extends well beyond methodology; it provides a route for synthesizing optically active pyridyl-substituted phosphorus compounds. These P, N-bidentate structures are highly prized as privileged ligands in catalysis, having demonstrated exceptional utility and selectivity in industrially relevant transformations, such as the stereoselective alkoxycarbonylation of diynes.[46]

6. CONCLUSION AND OUTLOOK

By systematically dismantling the historical "coordination paradox," our laboratory has delineated a dual-track roadmap for the precise catalytic synthesis of chiral phosphorus compounds. While the "Logic of Robustness" and the CMD-enabled C−H activation platforms have resolved critical deactivation and stereocontrol bottlenecks.

Despite these significant methodological leaps, several challenges persist within the field. The catalytic construction of molecules bearing multiple contiguous stereocenters—particularly those requiring the simultaneous installation of *P*-stereogenic, C-stereogenic, and axially chiral elements—remains synthetically demanding and often suffers from poor diastereocontrol. Furthermore, the paradigm of *P*-stereogenic synthesis must pivot toward sustainable, earth-abundant base-metal catalysis. The distinct single-electron transfer regimes and radical-mediated pathways inherent to first-row transition metals (e.g., Ni, Co, Cu) present underexplored avenues for achieving highly selective synthesis of *P*-chiral compounds. Our recent developments utilizing cobalt-catalyzed directed addi-

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tions and copper-mediated C(sp^2)−H arylations underscore the transformative potential of 3d metals in this domain. Continued innovation in synergistic metal catalysis and the strategic deployment of structurally engineered nucleophiles will be imperative for expanding the frontiers of asymmetric organophosphorus chemistry.

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Notes

The authors declare no competing financial interest.

Biographies

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Wei-Liang Duan received his Ph.D. from Kyoto University in 2007. Following postdoctoral research at the University of Illinois at Urbana−Champaign, he joined the faculty at Shanghai Institute of Organic Chemistry, CAS in 2008 to begin his independent research. He moved to Yangzhou University in 2016 and to Shaanxi Normal University in 2021. Recently, he joined the College of Chemistry and Chemical Engineering at Inner Mongolia University in 2023. His research interests mainly focused on chiral phosphorus chemistry and asymmetric C−H activation.

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REFERENCES

(1) Feng, J.-J.; Chen, X.-F.; Shi, M.; Duan, W.-L. Palladium-Catalyzed Asymmetric Addition of Diarylphosphines to Enones toward the Synthesis of Chiral Phosphines. *J. Am. Chem. Soc.* **2010**, *132*, 5562−5563.

(2) Wang, C.; Huang, K.; Ye, J.; Duan, W.-L. Asymmetric Synthesis of P-Stereogenic Secondary Phosphine-Boranes by an Unsymmetric Bisphosphine Pincer-Nickel Complex. *J. Am. Chem. Soc.* **2021**, *143*, 5685−5690.

(3) Zhang, C.-W.; Hu, X.-Q.; Dai, Y.-H.; Yin, P.; Wang, C.; Duan, W.-L. Asymmetric C−H Activation for the Synthesis of *P*- and Axially Chiral Biaryl Phosphine Oxides by an Achiral Cp*Ir Catalyst with Chiral Carboxylic Amide. *ACS Catal.* **2022**, *12*, 193−199.

(4) Wu, Z.-H.; Wang, H.-Y.; Yang, H.-L.; Wei, L.-H.; Hayashi, T.; Duan, W.-L. Secondary Phosphine Sulfide-Enabled Iridium-Catalyzed Asymmetric Allylic Substitution. *Angew. Chem., Int. Ed.* **2022**, *61*, No. e202213904.

(5) (a) Knowles, W. S.; Sabacky, M. J. Catalytic Asymmetric Hydrogenation Employing a Soluble Optically Active Rhodium Complex. *Chem. Commun.* **1968**, 1445−1446. (b) Horner, L.; Siegel, H.; Büthe, H. Asymmetric Catalytic Hydrogenation with an Optically Active Phosphine Rhodium Complex in Homogeneous Solution. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 942−942.

(6) Knowles, W. S.; Sabacky, M. J.; Vineyard, B. D.; Weinkauff, D. J. Asymmetric Hydrogenation with a Complex of Rhodium and a Chiral Bisphosphine. *J. Am. Chem. Soc.* **1975**, *97*, 2567−2568.

(7) Dang, T. P.; Kagan, H. B. The asymmetric synthesis of hydratropic acid and amino-acids by homogeneous catalytic hydrogenation. *J. Chem. Soc. D* **1971**, 481−481.

(8) Miyashita, A.; Yasuda, A.; Takaya, H.; Toriumi, K.; Ito, T.; Souchi, T.; Noyori, T. Synthesis of 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP), an atropisomeric chiral bis(triaryl)phosphine, and its use in the rhodium(I)-catalyzed asymmetric hydrogenation of alpha-(acylamino)acrylic acids. *J. Am. Chem. Soc.* **1980**, *102*, 7932−7934.

(9) (a) Pietrusiewicz, K. M.; Zablocka, M. Preparation of Scalemic P Chiral Phosphines and Their Derivatives. *Chem. Rev.* **1994**, *94*, 1375−1411. (b) Tang, W.; Zhang, X. New Chiral Phosphorus Ligands for Enantioselective Hydrogenation. *Chem. Rev.* **2003**, *103*, 3029−3070. (c) Xu, G.; Senanayake, C. H.; Tang, W. P-Chiral Phosphorus Ligands Based on a 2,3-Dihydrobenzo[d][1,3]oxaphosphole Motif for Asymmetric Catalysis. *Acc. Chem. Res.* **2019**, *52*, 1101−1112. (d) Imamoto, T. P-Stereogenic Phosphorus Ligands in Asymmetric Catalysis. *Chem. Rev.* **2024**, *124*, 8657−8739.

(10) (a) Glueck, D. S. Catalytic Asymmetric Synthesis of Chiral Phosphanes. *Chem.—Eur. J.* **2008**, *14*, 7108−7117. (b) Harvey, J. S.; Gouverneur, V. Catalytic enantioselective synthesis of P-stereogenic compounds. *Chem. Commun.* **2010**, *46*, 7477−7485. (c) Liu, B.-X.; Feng, F.; Long, J.; Gu, S.-X. Recent Advances in Transition Metal-Catalyzed Asymmetric Synthesis of P-chiral Organophosphorus Compounds (2020−Present). *Chin. J. Chem.* **2025**, *43*, 2228−2244.

(11) (a) Kovacik, I.; Wicht, D. K.; Grewal, N. S.; Glueck, D. S.; Incarvito, C. D.; Guzei, I. A.; Rheingold, A. L. Pt(Me-Duphos)-Catalyzed Asymmetric Hydrophosphination of Activated Olefins: Enantioselective Synthesis of Chiral Phosphines. *Organometallics* **2000**, *19*, 950−953. (b) Moncarz, J. R.; Laritcheva, N. F.; Glueck, D. S. Palladium-Catalyzed Asymmetric Phosphination: Enantioselective Synthesis of a *P*-Chirogenic Phosphine. *J. Am. Chem. Soc.* **2002**, *124*, 13356−13357. (c) Chan, V. S.; Stewart, I. C.; Bergman, R. G.; Toste, F. D. Asymmetric Catalytic Synthesis of *P*-Stereogenic Phosphines via a Nucleophilic Ruthenium Phosphido Complex. *J. Am. Chem. Soc.* **2006**, *128*, 2786−2787. (d) Scriban, C.; Glueck, D. S. Platinum-Catalyzed Asymmetric Alkylation of Secondary Phosphines: Enantioselective Synthesis of *P*-Stereogenic Phosphines. *J. Am. Chem. Soc.* **2006**, *128*, 2788−2789. (e) Blank, N. F.; Moncarz, J. R.; Brunker, T. J.; Scriban, C.; Anderson, B. J.; Amir, O.; Glueck, D. S.; Zakharov, L. N.; Golen, J. A.; Incarvito, C. D.; Rheingold, A. L. Palladium-Catalyzed Asymmetric Phosphination. Scope, Mechanism, and Origin of Enantioselectivity. *J. Am. Chem. Soc.* **2007**, *129*, 6847−6858. (f) Chan, V. S.; Bergman, R. G.; Toste, F. D. Pd-catalyzed dynamic kinetic enantioselective arylation of silylphosphines. *J. Am. Chem. Soc.* **2007**, *129*, 15122−15123. (g) Chan, V. S.; Chiu, M.; Bergman, R. G.; Toste, F. D. Development of Ruthenium Catalysts for the Enantioselective Synthesis of *P*-Stereogenic Phosphines via Nucleophilic Phosphido Intermediates. *J. Am. Chem. Soc.* **2009**, *131*, 6021−6032.

(12) (a) Tolman, C. A. Steric Effects of Phosphorus Ligands in Organometallic Chemistry and Homogeneous Catalysis. *Chem. Rev.*

1977, *77*, 313−348. (b) Crabtree, R. H. Deactivation in Homogeneous Transition Metal Catalysis: Causes, Avoidance, and Cure. *Chem. Rev.* **2015**, *115*, 127−150. (c) Francos, J.; Elorriaga, D.; Crochet, P.; Cadierno, V. The Chemistry of Group 8 Metal Complexes with Phosphinous Acids and Related P-OH Ligands. *Coord. Chem. Rev.* **2019**, *387*, 199−234. (d) Li, Y.-B.; Tian, H.; Yin, L. Copper(I)-Catalyzed Asymmetric 1,4-Conjugate Hydrophosphination of α,β-Unsaturate Amides. *J. Am. Chem. Soc.* **2020**, *142*, 20098−20106. (e) Chen, Z.; Wang, H.; Du, P.; Zhao, J.; Zhang, X.; Qian, H.; Zhang, J.; Ma, S. DACH-ZYC-Phos/Pd-Catalyzed Enantioselective Allenylation of Secondary Phosphine Oxides via Ligand Relay. *J. Am. Chem. Soc.* **2025**, *147*, 24958−24968.

(13) (a) Longmire, J. M.; Zhang, X. Synthesis of chiral phosphine ligands with aromatic backbones and their applications in asymmetric catalysis. *Tetrahedron Lett.* **1997**, *38*, 1725−1728. (b) Longmire, J. M.; Zhang, X.; Shang, M. Synthesis and X-ray Crystal Structures of Palladium(II) and Platinum(II) Complexes of the PCP-Type Chiral Tridentate Ligand (1R,1′R)-1,3-Bis[1-(diphenylphosphino)ethyl]-benzene. Use in the Asymmetric Aldol Reaction of Methyl Isocyanoacetate and Aldehydes. *Organometallics* **1998**, *17*, 4374−4379.

(14) (a) Chen, Y.-R.; Duan, W.-L. Palladium-Catalyzed 1,4-Addition of Diarylphosphines to α,β-Unsaturated Aldehydes. *Org. Lett.* **2011**, *13*, 5824−5826. (b) Du, D.; Duan, W.-L. Palladium-catalyzed 1,4-addition of diarylphosphines to α,β-unsaturated *N*-acylpyrroles. *Chem. Commun.* **2011**, *47*, 11101−11103. (c) Feng, J.-J.; Huang, M.; Lin, Z.-Q.; Duan, W.-L. Palladium-Catalyzed Asymmetric 1,4-Addition of Diarylphosphines to Nitroalkenes for the Synthesis of Chiral P,N-Compounds. *Adv. Synth. Catal.* **2012**, *354*, 3122−3126. (d) Huang, M.; Li, C.; Huang, J.; Duan, W.-L.; Xu, S. Palladium-catalyzed asymmetric addition of diarylphosphines to *N*-tosylimines. *Chem. Commun.* **2012**, *48*, 11148−11150. (e) Du, D.; Lin, Z.-Q.; Lu, J.-Z.; Li, C.; Duan, W.-L. Palladium-Catalyzed Addition of Diarylphosphines to α,β-Unsaturated Carboxylic Esters. *Asian J. Org. Chem.* **2013**, *2*, 392−394. (f) Lu, J.; Ye, J.; Duan, W.-L. Palladium-Catalyzed Asymmetric Addition of Diarylphosphines to α,β-Unsaturated Sulfonic Esters for the Synthesis of Chiral Phosphine Sulfonate Compounds. *Org. Lett.* **2013**, *15*, 5016−5019. (g) Li, C.; Bian, Q.-L.; Xu, S.; Duan, W.-L. Palladium-catalyzed 1,4-addition of secondary alkylphenylphosphines to α,β-unsaturated carbonyl compounds for the synthesis of phosphorus- and carbon-stereogenic compounds. *Org. Chem. Front.* **2014**, *1*, 541−545. (h) Dai, G.-F.; Song, Y.-C.; Xiao, F.; Duan, W.-L. Palladium-Catalyzed Asymmetric 1,4-Addition of Diarylphosphines to α,β-Unsaturated Sulfonamides. *Synthesis* **2018**, *50*, 3506−3512. (i) Cheng, A.-Q.; Wu, Z.-H.; Yang, H.-L.; Duan, W.-L. Palladium-Catalyzed Asymmetric 1,4-Addition of Diarylphosphines to α,β-Unsaturated Sulfonyl Fluorides. *Synthesis* **2023**, *55*, 2773−2778.

(15) (a) Lu, J.; Ye, J.; Duan, W.-L. Palladium-catalyzed asymmetric 1,6-addition of diarylphosphines to $\alpha,\beta,\gamma,\delta$-unsaturated sulfonic esters: controlling regioselectivity by rational selection of electron-withdrawing groups. *Chem. Commun.* **2014**, *50*, 698−700. (b) Huang, J.; Zhao, M.-X.; Duan, W.-L. Palladium-catalyzed asymmetric 1,6-addition of diphenylphosphine to (4-aryl-1,3-butadienylidene)bis-(phosphonates) for the synthesis of chiral phosphines. *Tetrahedron Lett.* **2014**, *55*, 629−631. (c) Wei, X.; Lu, J.; Duan, W.-L. Palladium-Catalyzed Asymmetric 1,6-Addition of Diarylphosphines to Allylidenemalonates for Chiral Phosphine Synthesis. *Synthesis* **2016**, *48*, 4155−4160.

(16) (a) Yang, M.-J.; Liu, Y.-J.; Gong, J.-F.; Song, M.-P. Unsymmetrical Chiral PCN Pincer Palladium(II) and Nickel(II) Complexes with Aryl-Based Aminophosphine−Imidazoline Ligands: Synthesis via Aryl C−H Activation and Asymmetric Addition of Diarylphosphines to Enones. *Organometallics* **2011**, *30*, 3793−3803. (b) Hao, X.-Q.; Zhao, Y.-W.; Yang, J.-J.; Niu, J.-L.; Gong, J.-F.; Song, M.-P. Enantioselective Hydrophosphination of Enones with Diphenylphosphine Catalyzed by Bis(imidazoline) NCN Pincer Palladium(II) Complexes. *Organometallics* **2014**, *33*, 1801−1811. (c) Hao, X.-Q.; Huang, J.-J.; Wang, T.; Lv, J.; Gong, J.-F.; Song, M.-P. PCN Pincer Palladium(II) Complex Catalyzed Enantioselective Hydrophosphination of Enones: Synthesis of Pyridine-Functionalized Chiral Phosphine Oxides as $NC_{sp3}O$ Pincer Preligands. *J. Org. Chem.* **2014**, *79*, 9512−9530.

(17) (a) Ding, B.; Zhang, Z.; Xu, Y.; Liu, Y.; Sugiya, M.; Imamoto, T.; Zhang, W. P-Stereogenic PCP Pincer-Pd Complexes: Synthesis and Application in Asymmetric Addition of Diarylphosphines to Nitroalkenes. *Org. Lett.* **2013**, *15*, 5476−5479. (b) Xu, Y.; Yang, Z.; Ding, B.; Liu, D.; Liu, Y.; Sugiya, M.; Imamoto, T.; Zhang, W. Asymmetric Michael Addition of Diphenylphosphine to β,γ-Unsaturated α-Keto Esters Catalyzed by a P-Stereogenic Pincer-Pd Complex. *Tetrahedron* **2015**, *71*, 6832−6839.

(18) (a) Huang, Y.; Pullarkat, S. A.; Li, L.; Leung, P.-H. Palladium(II)-catalyzed asymmetric hydrophosphination of enones: efficient access to chiral tertiary phosphines. *Chem. Commun.* **2010**, *46*, 6950−6952. (b) Huang, Y.; Chew, R. J.; Li, Y.; Pullarkat, S. A.; Leung, P.-H. Direct Synthesis of Chiral Tertiary Diphosphines via Pd(II)-Catalyzed Asymmetric Hydrophosphination of Dienones. *Org. Lett.* **2011**, *13*, 5862−5865. (c) Huang, Y.; Pullarkat, S. A.; Li, Y.; Leung, P.-H. Palladacycle-Catalyzed Asymmetric Hydrophosphination of Enones for Synthesis of C*- and P*-Chiral Tertiary Phosphines. *Inorg. Chem.* **2012**, *51*, 2533−2540. (d) Huang, Y.; Li, Y.; Leung, P.-H.; Hayashi, T. Asymmetric Synthesis of P-Stereogenic Diarylphosphinites by Palladium-Catalyzed Enantioselective Addition of Diarylphosphines to Benzoquinones. *J. Am. Chem. Soc.* **2014**, *136*, 4865−4868.

(19) (a) Yue, W.-J.; Xiao, J.-Z.; Zhang, S.; Yin, L. Rapid Synthesis of Chiral 1,2-Bisphosphine Derivatives through Copper(I)-Catalyzed Asymmetric Conjugate Hydrophosphination. *Angew. Chem., Int. Ed.* **2020**, *59*, 7057−7062. (b) Li, Y.-B.; Li, Y.; Yin, L. Copper(I)-catalyzed diastereodivergent construction of vicinal P-chiral and C-chiral centers facilitated by dual "soft-soft" interaction. *Chin. Chem. Lett.* **2024**, *35*, No. 109294.

(20) (a) Pérez, J. M.; Postolache, R.; Castiñeira Reis, M.; Sinnema, E. G.; Vargova, D.; de Vries, F.; Otten, E.; Ge, L.; Harutyunyan, S. R. Manganese(I)-Catalyzed H-P Bond Activation via Metal-Ligand Cooperation. *J. Am. Chem. Soc.* **2021**, *143*, 20071−20076. (b) Chen, X.; Shi, Y.; Ma, H.; Liu, X.; Yi, T.; Huang, G.; Liu, W. Tailored Manganese-Catalyzed Enantioconvergent Hydrophosphination to Access Remote *P*, *C*-Stereogenic. *Phosphines. J. Am. Chem. Soc.* **2026**, *148*, 14535−14545.

(21) (a) Zhao, D.; Mao, L.; Yang, D.; Wang, R. Zinc-Mediated Asymmetric Additions of Dialkylphosphine Oxides to α,β-Unsaturated Ketones and N-Sulfinylimines. *J. Org. Chem.* **2010**, *75*, 6756−6763. (b) Zhao, D.; Wang, L.; Yang, D.; Zhang, Y.; Wang, R. Highly Efficient Asymmetric Michael Addition of Diaryl Phosphine Oxides to α,β-Unsaturated N-Acylated Oxazolidin-2-ones. *Chem. Asian. J.* **2012**, *7*, 881−883.

(22) (a) Wen, S.; Li, P.; Wu, H.; Yu, F.; Liang, X.; Ye, J. Enantioselective organocatalytic phospha-Michael reaction of α,β-unsaturated ketones. *Chem. Commun.* **2010**, *46*, 4806−4808. (b) Luo, X.; Zhou, Z.; Li, X.; Liang, X.; Ye, J. Enantioselective organocatalytic phospha-Michael reaction of α,β-unsaturated aldehydes. *RSC Advances* **2011**, *1*, 698−705.

(23) Hatano, M.; Horibe, T.; Ishihara, K. Chiral Magnesium(II) Binaphtholates as Cooperative Brønsted/Lewis Acid−Base Catalysts for the Highly Enantioselective Addition of Phosphorus Nucleophiles to α,β-Unsaturated Esters and Ketones. *Angew. Chem., Int. Ed.* **2013**, *52*, 4549−4553.

(24) (a) Bader, A.; Pabel, M.; Wild, S. B. First Resolution of a Free Secondary Phosphine Chiral at Phosphorus. *J. Chem. Soc., Chem. Commun.* **1994**, 1405−1406. (b) Bader, A.; Nullmeyers, T.; Pabel, M.; Salem, G.; Willis, A. C.; Wild, S. B. Stereochemistry and Stability of Free and Coordinated Secondary Phosphines. Crystal and Molecular Structure of $[S\text{-}[(R^*,R^*),(R^*)]]\text{-}(+)_{589}\text{-}[PtCl\{1,2\text{-}C_6H_4(PMePh)_2\}(PHMePh)]PF_6\ CH_2Cl_2$. *Inorg. Chem.* **1995**, *34*, 384−389.

(25) Wang, C.; Yang, Q.; Dai, Y.-H.; Xiong, J.; Zheng, Y.; Duan, W.-L. Nickel-Catalyzed Asymmetric Synthesis of P-Stereogenic Phosphanyl Hydrazine Building Blocks. *Angew. Chem., Int. Ed.* **2023**, *62*, No. e202313112.

(26) Li, C.; Li, W.; Xu, S.; Duan, W.-L. Pd-Catalyzed Asymmetric Alkylation of Methylphenylphosphine with Alkyl Halides for the

https://doi.org/10.1021/acs.accounts.6c00278
Acc. Chem. Res. XXXX, XXX, XXX−XXX

Synthesis of P-stereogenic Compounds. *Chin. J. Org. Chem.* **2013**, *33*, 799−802.
(27) Wang, C.; Dai, Y.-H.; Wang, Z.; Lu, B.; Cao, W.; Zhao, J.; Mei, G.; Yang, Q.; Guo, J.; Duan, W.-L. Nickel-Catalyzed Enantioselective Alkylation of Primary Phosphines. *J. Am. Chem. Soc.* **2024**, *146*, 27843−27851.
(28) Gibbons, S. K.; Xu, Z.; Hughes, R. P.; Glueck, D. S.; Rheingold, A. L. Chiral Bis(Phospholane) PCP Pincer Complexes: Synthesis, Structure, and Nickel-Catalyzed Asymmetric Phosphine Alkylation. *Organometallics* **2018**, *37*, 2159−2166.
(29) (a) Wencel-Delord, J.; Colobert, F. Asymmetric C(sp^2)−H Activation. *Chem.—Eur. J.* **2013**, *19*, 14010−14017. (b) Engle, K. M.; Yu, J.-Q. Developing Ligands for Palladium(II)-Catalyzed C−H Functionalization: Intimate Dialogue between Ligand and Substrate. *J. Org. Chem.* **2013**, *78*, 8927−8955. (c) Zheng, C.; You, S.-L. Recent Development of Direct Asymmetric Functionalization of Inert C−H Bonds. *RSC Adv.* **2014**, *4*, 6173−6214. (d) Newton, C. G.; Wang, S.-G.; Oliveira, C. C.; Cramer, N. Catalytic Enantioselective Transformations Involving C−H Bond Cleavage by Transition-Metal Complexes. *Chem. Rev.* **2017**, *117*, 8908−8976. (e) Saint-Denis, T. G.; Zhu, R.-Y.; Chen, G.; Wu, Q.-F.; Yu, J.-Q. Enantioselective C(sp^3)−H bond activation by chiral transition metal catalysts. *Science* **2018**, *359*, 759−770. (f) Loup, J.; Dhawa, U.; Pesciaioli, F.; Wencel-Delord, J.; Ackermann, L. Enantioselective C−H Activation with Earth-Abundant 3d Transition Metals. *Angew. Chem., Int. Ed.* **2019**, *58*, 12803−12818.
(30) (a) Ma, Y.-N.; Li, S.-X.; Yang, S.-D. New Approaches for Biaryl-Based Phosphine Ligand Synthesis via P = O Directed C−H Functionalizations. *Acc. Chem. Res.* **2017**, *50*, 1480−1492. (b) Li, Z.; Shi, Z. Late-Stage Diversification of Phosphines by C−H Activation: A Robust Strategy for Ligand Design and Preparation. *Acc. Chem. Res.* **2024**, *57*, 1057−1072. (c) Li, S.-X.; Ma, Y.-N.; Yang, S.-D. P(O)R_2-Directed Enantioselective C−H Olefination toward Chiral Atropoisomeric Phosphine−Olefin Compounds. *Org. Lett.* **2017**, *19*, 1842−1845. (d) Jang, Y.-S.; Dieckmann, M.; Cramer, N. Cooperative effects between chiral Cp^x-iridium(III) catalysts and chiral carboxylic acids in enantioselective C−H amidations of phosphine oxides. *Angew. Chem., Int. Ed.* **2017**, *56*, 15088−15092. (e) Jang, Y.-S.; Woźniak, Ł.; Pedroni, J.; Cramer, N. Access to P- and axially chiral biaryl phosphine oxides by enantioselective Cp*IrIII-catalyzed C−H arylations. *Angew. Chem., Int. Ed.* **2018**, *57*, 12901−12905.
(31) Lin, Z.-Q.; Wang, W.-Z.; Yan, S.-B.; Duan, W.-L. Palladium-Catalyzed Enantioselective C−H Arylation for the Synthesis of P-Stereogenic Compounds. *Angew. Chem., Int. Ed.* **2015**, *54*, 6265−6269.
(32) Albicker, M. R.; Cramer, N. Enantioselective Palladium-Catalyzed Direct Arylations at Ambient Temperature: Access to Indanes with Quaternary Stereocenters. *Angew. Chem., Int. Ed.* **2009**, *48*, 9139−9142.
(33) (a) Lapointe, D.; Fagnou, K. Overview of the Mechanistic Work on the Concerted Metallation−Deprotonation Pathway. *Chem. Lett.* **2010**, *39*, 1118−1126. (b) Livendahl, M.; Echavarren, A. M. Palladium-catalyzed arylation reactions: A mechanistic perspective. *Isr. J. Chem.* **2010**, *50*, 630−651.
(34) Yan, S.-B.; Zhang, S.; Duan, W.-L. Palladium-Catalyzed Asymmetric Arylation of C(sp^3)−H Bonds of Aliphatic Amides: Controlling Enantioselectivity Using Chiral Phosphoric Amides/Acids. *Org. Lett.* **2015**, *17*, 2458−2461.
(35) Li, Z.; Lin, Z.-Q.; Yan, C.-G.; Duan, W.-L. Pd-Catalyzed Asymmetric C−H Bond Activation for the Synthesis of P-Stereogenic Dibenzophospholes. *Organometallics* **2019**, *38*, 3916−3920.
(36) Yan, S.-B.; Li, Z.; Hu, X.-Q.; Zhang, S.; Duan, W.-L. Pd/Chiral Phosphoric Acid-Enabled Asymmetric Intramolecular Double C−H Activation Reaction for the Synthesis of P-Stereogenic Benzophosphole Oxides. *Org. Lett.* **2025**, *27*, 1481−1486.
(37) Mas-Roselló, J.; Herraiz, A. G.; Audic, B.; Laverny, A.; Cramer, N. Chiral Cyclopentadienyl Ligands: Design, Syntheses, and Applications in Asymmetric Catalysis. *Angew. Chem., Int. Ed.* **2021**, *60*, 13198−13224.
(38) Yan, S.-B.; Wang, R.; Li, Z.-G.; Li, A.-N.; Wang, C.; Duan, W.-L. Copper-catalyzed asymmetric C(sp^2)−H arylation for the synthesis of P- and axially chiral phosphorus compounds. *Nat. Commun.* **2023**, *14*, 2264.
(39) (a) Hartwig, J. F.; Stanley, L. M. Mechanistically Driven Development of Iridium Catalysts for Asymmetric Allylic Substitution. *Acc. Chem. Res.* **2010**, *43*, 1461−1475. (b) Qu, J.; Helmchen, G. Applications of Iridium-Catalyzed Asymmetric Allylic Substitution Reactions in Target-Oriented Synthesis. *Acc. Chem. Res.* **2017**, *50*, 2539−2555. (c) Cheng, Q.; Tu, H.-F.; Zheng, C.; Qu, J.-P.; Helmchen, G.; You, S.-L. Iridium-Catalyzed Asymmetric Allylic Substitution Reactions. *Chem. Rev.* **2019**, *119*, 1855−1969.
(40) (a) Butti, P.; Rochat, R.; Sadow, A. D.; Togni, A. Palladium-Catalyzed Enantioselective Allylic Phosphination. *Angew. Chem., Int. Ed.* **2008**, *47*, 4878−4881. (b) Duraud, A.; Jacquet, O.; Fiaud, J.-C.; Guillot, R.; Toffano, M. Stereoselective Palladium Catalyzed Allylic Phosphination. *ChemCatChem* **2011**, *3*, 883−886.
(41) Li, B.; Liu, M.; Rehman, S. U.; Li, C. Rh-Catalyzed Regio- and Enantioselective Allylic Phosphinylation. *J. Am. Chem. Soc.* **2022**, *144*, 2893−2898.
(42) Defieber, C.; Ariger, M. A.; Moriel, P.; Carreira, E. M.; Defieber, C.; Ariger, M. A.; Moriel, P.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 3139−3143.
(43) (a) Beaud, R.; Phipps, R. J.; Gaunt, M. J. Enantioselective Cu-Catalyzed Arylation of Secondary Phosphine Oxides with Diaryliodonium Salts toward the Synthesis of P-Chiral Phosphines. *J. Am. Chem. Soc.* **2016**, *138*, 13183−13186. (b) Zhang, Y.; He, H.; Wang, Q.; Cai, Q. Asymmetric synthesis of chiral P-stereogenic triaryl phosphine oxides via Pd-catalyzed kinetic arylation of diaryl phosphine oxides. *Tetrahedron Lett.* **2016**, *57*, 5308−5311. (c) Dai, Q.; Li, W.; Li, Z.; Zhang, J. P-Chiral Phosphines Enabled by Palladium/Xiao-Phos-Catalyzed Asymmetric P−C Cross-Coupling of Secondary Phosphine Oxides and Aryl Bromides. *J. Am. Chem. Soc.* **2019**, *141*, 20556−20564. (d) Liu, X.-T.; Zhang, Y.-Q.; Han, X.-Y.; Sun, S.-P.; Zhang, Q.-W. Ni-Catalyzed Asymmetric Allylation of Secondary Phosphine Oxides. *J. Am. Chem. Soc.* **2019**, *141*, 16584−16589.
(44) (a) Blasius, C. K.; Wadepohl, H.; Gade, L. H. *NNN*-Cobalt(II) Pincer Complexes: Paramagnetic NMR Spectroscopy in Solution and Application as Hydrosilylation Catalysts. *Eur. J. Inorg. Chem.* **2020**, *2020*, 2335−2342. (b) Bleith, T.; Gade, L. H. Mechanism of the Iron(II)-Catalyzed Hydrosilylation of Ketones: Activation of Iron Carboxylate Precatalysts and Reaction Pathways of the Active Catalyst. *J. Am. Chem. Soc.* **2016**, *138*, 4972−4983.
(45) Wu, Z.-H.; Cheng, A.-Q.; Yuan, M.; Zhao, Y.-X.; Yang, H.-L.; Wei, L.-H.; Wang, H.-Y.; Wang, T.; Zhang, Z.; Duan, W.-L. Cobalt-Catalysed Asymmetric Addition and Alkylation of Secondary Phosphine Oxides for the Synthesis of P-Stereogenic Compounds. *Angew. Chem., Int. Ed.* **2021**, *60*, 27241−27246.
(46) Dong, K.; Fang, X.; Gülak, S.; Franke, R.; Spannenberg, A.; Neumann, H.; Jackstell, R.; Beller, M. Highly active and efficient catalysts for alkoxycarbonylation of alkenes. *Nat. Commun.* **2017**, *8*, No. 14117.

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