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Catalytic Asymmetric Hydrophosphination of α,β-Unsaturated Aza-heteroarenes

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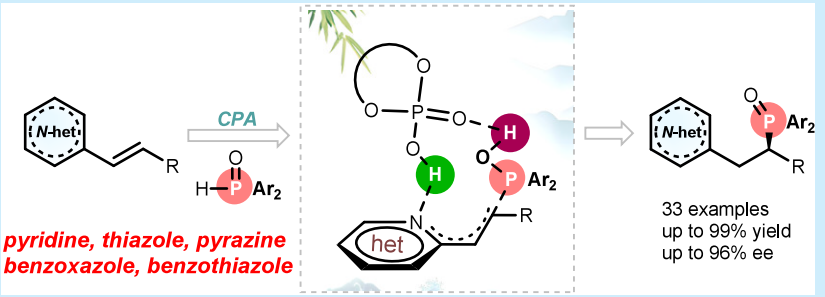

ABSTRACT: Here we report a comprehensive investigation of the asymmetric addition of diarylphosphorus oxides to a wide range of α,β-unsaturated pyridines and other N-heterocyclic substrates, catalyzed by commercial chiral phosphoric acid, affording the corresponding products in up to 99% yield and 96% ee. The experimental studies and density functional theory calculation suggest the possible mechanism and the role of chiral phosphoric acid in the control of enantioselectivity.

Transition metal-catalyzed asymmetric transformations represent the most prevalent method for the construction of chiral molecules.[1−5] However, this homogeneous catalytic process cannot function effectively without the presence of chiral ligands. Therefore, the design and synthesis of chiral ligands have emerged as a prominent area of research in recent decades.[6−10] Ligands that feature N-heterocyclic groups and phosphorus chiral centers are particularly valuable due to their strong binding capacity with transition metals, such as QuinaP, QuinoxP, PPhos, and N-heterocyclic pincers (Scheme 1a).[11−13] Hence, it seems particularly important to establish an optimal method for the preparation of these molecules.

Asymmetric hydrophosphination is one of the most direct and atom-economical strategies to furnish chiral phosphorus compounds that play a considerable role in transition metal catalysis as ligands and in organocatalysis as catalysts.[14] During the past decade, asymmetric hydrophosphination reactions have been well developed. The reported corresponding methodologies are mainly divided into two categories, including transition metal-catalyzed and organocatalyst-catalyzed strategies.[15−43] As mentioned previously, the N-containing heterocyclic phosphines possess immense potential as chiral ligands. Thereupon, asymmetric hydrophosphination of phosphorus nucleophiles to α,β-unsaturated aza-heterocyclic compounds is an interesting strategy to prepare these molecules. In 2021, Terada and co-workers established a metal-free asymmetric phospha-Michael addition strategy with a carbon stereocenter using the α-substituted *N*-oxide terminal alkenyls as substrates and catalyzed by chiral bis(guanidino)-iminophosphorane organosuperbase (Scheme 1b).[44]

Subsequently, Jiang, Yin, and Ban disclosed a new methodology for the asymmetric hydrophosphination of racemic P(V) oxides to terminal 2-vinylazaarenes catalyzed by chiral phosphoric acid (CPA) and a wide range of P-chiral phosphorus products were observed with high yields and ees (Scheme 1b).[45] Due to the good binding capacity of *P,N*-products with metal catalysts, the metal-catalyzed processes are limited. Recently, the copper-catalyzed enantioselective hydrophosphination of P(III) to alkenyl isoquinolines was introduced by the Wang group (Scheme 1b).[46] In addition, Harutyunyan and co-workers further presented the Mn(I)-catalyzed enantioselective hydrophosphination of terminal alkenyl aza-heteroarenes using a chiral *P,N,P*-pincer. However, moderate ees were obtained for Cu and Mn catalysts (Scheme 1b).[47,48]

Nevertheless, the limitations of only terminal alkenyl aza-heteroarenes through organocatalysis and observation of moderate enantioselectivities through Cu and Mn catalysis remain. In this work, the less reactive β-substituted α,β-unsaturated pyridines were selected to explore their asym-

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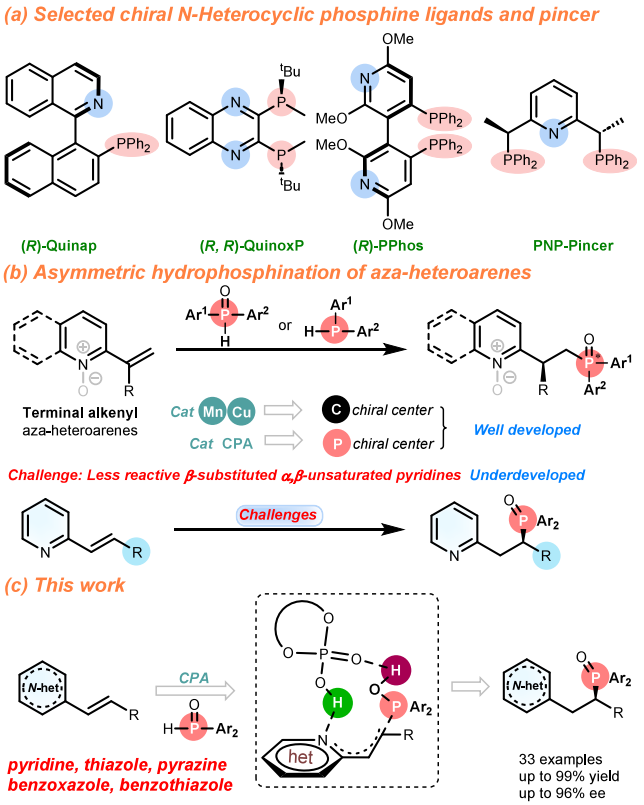
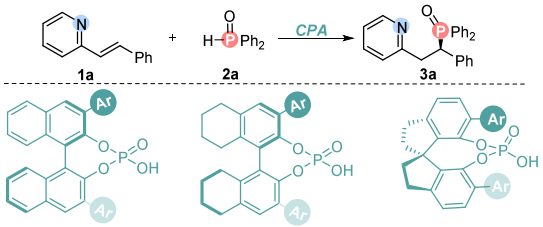
Scheme 1. (a) Selected Chiral N-Hetrocyclic Phosphine Ligands and a Pincer, (b) Asymmetric Hydrophosphination of Aza-heteroarenes, and (c) This Work



metric hydrophosphination abilities (Scheme 1c). Due to the poor reactivity of nonterminal alkenyl aza-heteroarenes, the racemic reactions need be catalyzed by $B(C_6F_5)_3$.[49] In this work, we employ commercially available CPA to activate aza-substrates and catalyze the asymmetric addition of diarylphosphine oxides to a diverse range of α,β-unsaturated pyridines and other N-heterocyclic substrates. Notably, this methodology demonstrates broad substrate tolerance, achieving high yields and excellent enantioselectivities (ees). Furthermore, subsequent reduction of the P(V) species can enable the transformation of these chiral *P,N*-products into a variety of novel ligands. The proposed mechanism is supported by density functional theory (DFT) calculations.

The initial study was carried out using the following model reaction: (*E*)-2-styrylpyridine (**1a**) and diphenylphosphine oxide (**2a**) in a solvent of toluene catalyzed by various CPAs. The optimization of the reaction conditions is summarized in Table 1. Based on previous studies, CPA catalysis typically achieves excellent enantioselectivity at lower temperature. Therefore, the initial experiment was conducted in toluene at 0 °C using **CPA 1** as the catalyst (entry 1). However, only trace amounts of **3a** were obtained, and the enantiomeric excess (ee) was not detected. Subsequently, when the temperature was increased to room temperature (20−25 °C), the yield remained below 10%. However, to our delight, an enantiomeric excess of 70% was observed (entry 2). Further increasing the temperature to 50 °C led to a significant improvement in both the yield (57%) and ee (80%) (entry 3). Unexpectedly, at temperatures of 60 and 70 °C, the yields ceased to increase, while a higher ee of 84% was achieved at 60 °C (entries 4 and 5, respectively). Subsequent solvent screening was conducted

Table 1. Optimization of the Reaction Conditions[a]



CPA 1: Ar= 9-phenanthryl
CPA 2: Ar= 9-anthracenyl
CPA 3: Ar= 4-CF_3-C_6H_4
CPA 4: Ar= 2.4,6-(iPr_3)C_6H_2
CPA 5: Ar= 4-Ph-C_6H_4
CPA 6: Ar= 2.4,6-(iPr_3)C_6H_2
CPA 7: Ar= 9-phenanthryl
CPA 8: Ar= 3,5-$OMeC_6H_3$
CPA 9: Ar= 2.4,6-MeC_6H_2
CPA 10: Ar= 4-(3,5-MeC_6H_3)-C_6H_4

entry	solvent	CPA (mol %)	*T* (°C)	yield (%)[b]	ee (%)[c]
1	toluene	**CPA 1** (10)	0	trace	–
2	toluene	**CPA 1** (10)	rt	<10	70
3	toluene	**CPA 1** (10)	50	57	80
4	toluene	**CPA 1** (10)	60	61	84
5	toluene	**CPA 1** (10)	70	62	82
6	DCE	**CPA 1** (10)	60	58	45
7	MeCN	**CPA 1** (10)	60	88	36
8	Et_2O	**CPA 1** (10)	60	33	56
9	THF	**CPA 1** (10)	60	77	83
10	2-Me-THF	**CPA 1** (10)	60	79	86
11	CPME	**CPA 1** (10)	60	81	86
12	CPME	**CPA 2** (10)	60	95	91
13	CPME	**CPA 3−4** (10)	60	82−90	71−76
14	CPME	**CPA 5** (10)	60	88	81
15	CPME	**CPA 6−7** (10)	60	91−92	66−72
16	CPME	**CPA 8−10** (10)	60	82−88	67−70
17	CPME	**CPA 2** (5)	60	88	86
18	CPME	**CPA 2** (15)	60	96	92

[a]Reactions performed with **1a** (0.24 mmol), **2a** (0.2 mmol), and CPA (10 mol %) in a solvent (2 mL) for 24 h. [b]The reported yields correspond to isolated yields. [c]Enantiomeric excesses were determined by HPLC analysis on the chiral stationary phase.

at 60 °C. The results indicated that chlorinated solvent DCE yielded only 58% with an ee of 45% (entry 6). Additionally, several solvents, including CH_3CN, Et_2O, THF, 2-Me-THF, and CPME, were evaluated (entries 8−11). Notably, Et_2O exhibited a lower yield (33%) and ee (56%), whereas the cyclic ethers provided superior results in both yield and ee. In particular, CPME achieved a yield of 81% and an ee of 86% (entry 11). To further enhance the enantioselectivity, various CPA catalysts were evaluated. Notably, **CPA 2** significantly improved both the yield and the ee to 95% and 91%, respectively (entry 12). Additionally, **CPA 3−10** were tested using the model reaction, and the results demonstrated that **CPA 2** was the optimal catalyst (entries 13−16). Furthermore, experiments investigating the catalyst loading (ranging from 5 to 15 mol %) indicated that 10 mol % **CPA 2** was the most effective amount for subsequent substrate scope studies (entries 17 and 18). In summary, the optimized reaction conditions for further substrate exploration were as follows: 10 mol % **CPA 2** at 60 °C in a CPME solvent for 24 h.

With the optimal conditions established, a diverse range of α,β-unsaturated pyridine substrates were evaluated, and the results are summarized in Scheme 2. Initially, as detailed in Table 1, compound **3a** was obtained in 95% yield with 91% ee under these conditions. Subsequently, substrates bearing an electron-donating methyl group at the *ortho*, *meta*, and *para*

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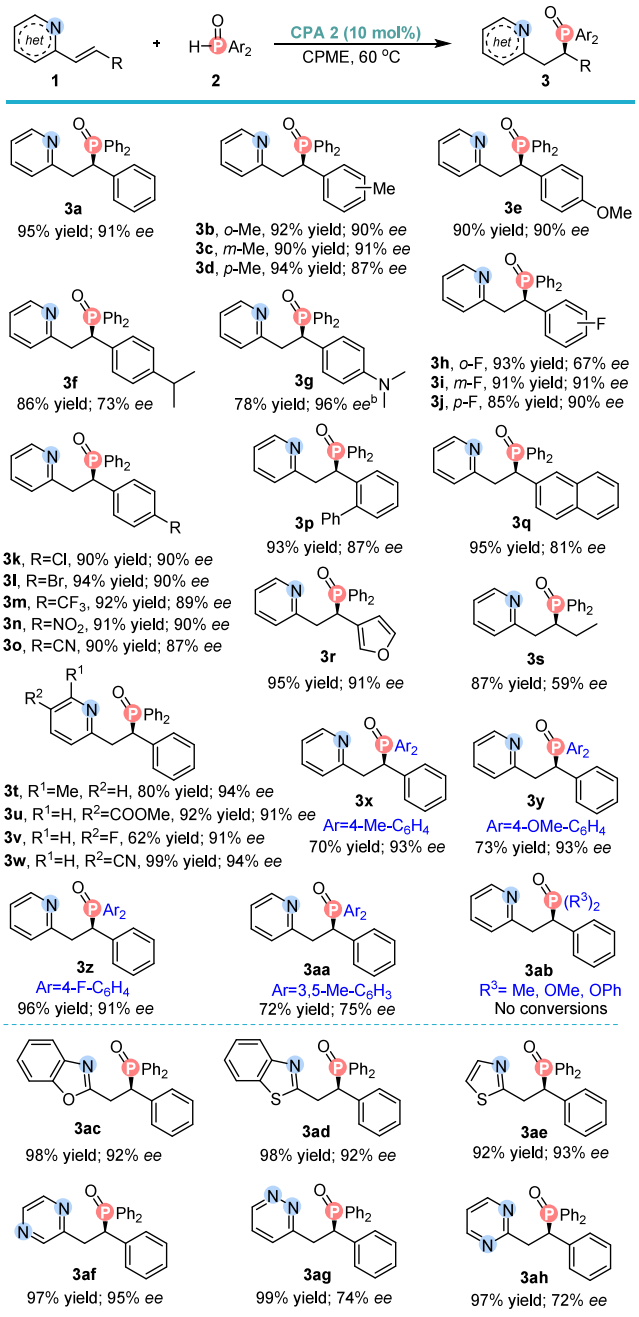
Scheme 2. Substrate Scope[a]

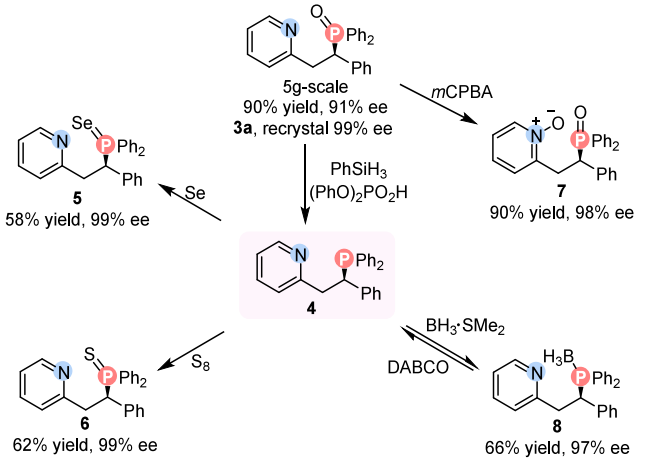


[a]Reaction conditions: **CPA 2** (10 mol %), **1** (0.24 mmol), and **2** (0.2 mmol) in CPME (2 mL) at 60 °C for 24 h. The reported yields correspond to isolated yields. Enantiomeric excesses were determined by HPLC analysis on the chiral stationary phase. [b]With 0.01 mmol of $B(C_6F_5)_3$.

positions of the *β*-phenyl substituents were examined by using this methodology (Scheme 2). The results indicated that the position of the methyl group did not significantly affect the yields or enantioselectivities, resulting in compounds **3b**–**3d** with yields ranging from 90% to 94% and ees from 87% to 91%. Moreover, substrates bearing multiple electron-donating groups, such as -OMe, -*i*Pr, and -NMe_2, were investigated, yielding the corresponding products (**3e**–**3g**) in 83–90% yields and 73–96% ees. Interestingly, when examining substrates with an electron-withdrawing fluoro substituent, *m*- and *p*-fluoro-substituted *β*-phenyl groups produced compounds **3i** and **3j**, respectively, in 85–91% yield and 90–91% ees. However, *o*-fluoro-substituted product **3h** was obtained with only 67% ee. Furthermore, a wide range of *β*-position aromatic electron-withdrawing substituents, including -Cl, -Br, -CF_3, -NO_2, and -CN, were evaluated, resulting in products **3k**–**3o**, respectively, in high yields (90–94%) and ees (87–90%). To further demonstrate the compatibility of this methodology, phenyl, naphthyl, and furyl substituents were also examined, affording compounds **3p**–**3r**, respectively, in 93–95% yields and 81–91% ees. Ethyl-substituted substrate **1s** was performed, furnishing **3s** in 87% yield and 59% ee. Moreover, various pyridine ring-substituted substrates were explored, leading to products **3t**–**3w** in up to 62–99% yields and 91–94% ees. Additionally, various diarylphosphine oxides (**2**) were tested with the model substrates, producing products **3x**-**3aa** in 70–96% yields and 75–93% ees. Unfortunately, dimethylphosphine oxide, dimethyl phosphonate, and diphenyl phosphonate were not tolerated with this method, and product **3ab** was not detected. Moreover, a variety of other N-heterocyclic compounds were evaluated. As shown in Scheme 2, unsaturated benzoxazole, benzothiazole, and thiazole substrates were assessed using this protocol, providing products **3ac**–**3ae**, respectively, in 92–98% yields with 92–93% ees. Additionally, the pyrazine-based substrate was also tolerated, furnishing **3af** in excellent yield (97%) and enantioselectivity (95%). Furthermore, high yields (97–99%) were achieved for **3ag** and **3ah**, although moderate enantiomeric excesses (72–74%) still require improvement.

To further examine the applications of this methodology, a 5 g scale model reaction was conducted under the optimal conditions (Scheme 3). To our delight, model product **3a** was

Scheme 3. Synthetic Transformations of 3a



obtained in 90% yield and 91% ee. Subsequently, **3a** (91% ee) was further purified by recrystallization, achieving 99% ee. The synthetic transformations of **3a** were also conducted (Scheme 3b). Initially, P(V) was reduced to intermediate P(III) compound **4**, which is unstable and rapidly oxidized by air. Therefore, compound **4** was used without further purification. For example, P(III) was transformed through oxidation processes using Se and S_8, generating compounds **5** and **6**, respectively, in 58–62% yields and retaining 99% ee. Moreover, the nitrogen in **3a** could be converted to *N*-oxide **7** in 90% yield and 98% ee. Additionally, intermediate **4** could

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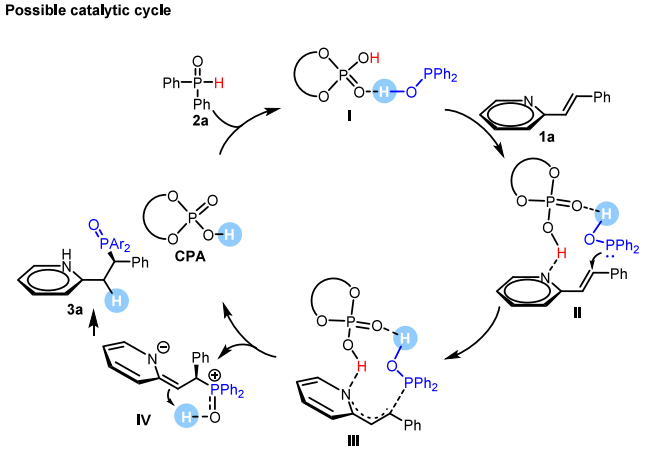
be protected by BH_3 to form stable compound **8** (66% yield, 97% ee), which could be conveniently deprotected by DABCO.

To gain deeper insights into the plausible reaction mechanism and the origin of the enantioselectivity, we conducted a detailed DFT study utilizing the SMD M06-2X/Def2-TZVP//B3LYP-D3/Def2-SVP method. This investigation focused on the transformation between pentavalent 2-styrylpyridine (**1a**) and diphenylphosphine oxide (**2a**) in the presence of CPA as the catalyst (see Figure S1). Initially, the CPA catalyst is expected to react with **2a** to form a stable intermediate (**IN0R**). Subsequently, the pentavalent phosphorus oxide undergoes tautomerization to yield a tertiary phosphorus compound via **TS0R**, with a free energy barrier of 11.8 kcal/mol above **IN0R**, resulting in the formation of intermediate **IN1R**. This is followed by the introduction of substrate **1a**, leading to the formation of a relatively stable intermediate, **IN2R**. Notably, the free energy barrier in the presence of the CPA catalyst is significantly lower compared to the scenario without CPA (37.0 or 61.9 kcal/mol (Figure S2)).

Intermediate **IN2R** can undergo nucleophilic addition to produce intermediates **IN3R** via **TS1R**, with a free energy barrier of 21.3 kcal/mol above **IN0R**. Finally, the hydroxyl group in **IN3R** transfers a proton to the pyridine α-carbanion via **TS2R**, resulting in the desired major (*R*)-product with a barrier of 15.8 kcal/mol above **IN0R** (see Figure S1). In contrast, the nucleophilic addition through the **TS1S** pathway to form the minor (*S*)-product is energetically less favorable than that through the **TS1R** pathway (major product) by approximately 1.3 kcal/mol. These computational results qualitatively align with the observed enantioselectivity. Furthermore, our computed energy profiles indicate that the rate-determining and enantio-determining steps occur during the nucleophilic addition.

With the results from DFT studies, we propose a catalytic mechanism, illustrated in Scheme 4. Initially, **CPA** binds to **2a** to form intermediate **I**, which then reacts with substrate **1a** to generate intermediate **II**. Subsequently, under heating conditions, intermediate **III** is formed. Finally, the chiral C–P bond is constructed, leading to the formation of product **3a** via a proton transfer process (**IV**).

Scheme 4. Possible Catalytic Cycle



In summary, a general metal-free strategy for the enantioselective construction of N-containing heterocyclic phosphines has been established. A wide range of pyridines and other N-heterocyclic substrates were successfully tolerated by this methodology, yielding high yields and excellent enantioselectivities. DFT studies and experimental results suggest a plausible mechanism and elucidate the interplay between chiral phosphoric acid and reactants in controlling the enantioselectivity. This metal-free methodology not only provides a versatile approach for catalytic asymmetric hydrophosphination reactions but also offers a practical route for constructing valuable chiral *P,N*-compounds, which have significant potential applications in the synthesis of chiral *P,N*-ligands.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.5c01255.

Experimental procedures, analytical data for all new compounds, NMR spectra, HPLC data, HRMS data, and DFT calculations (PDF)

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) Chakraborty, P.; Mandal, R.; Garg, N.; Sundararaju, B. Recent advances in transition metal-catalyzed asymmetric electrocatalysis. *Coordin. Chem. Rev.* **2021**, *444*, 214065.

(2) Zhuo, C.; Zheng, C.; You, S. Transition-metal-catalyzed asymmetric allylic dearomatization reactions. *Acc. Chem. Res.* **2014**, *47*, 2558−2573.

(3) Xie, J.; Zhu, S.; Zhou, Q. Recent advances in transition metal-catalyzed enantioselective hydrogenation of unprotected enamines. *Chem. Soc. Rev.* **2012**, *41*, 4126−4139.

(4) Wang, K.; Kong, W. Recent advances in transition metal-catalyzed asymmetric radical reactions. *Chin. J. Chem.* **2018**, *36*, 247−256.

(5) Lu, F.; Chen, J.; Jiang, X.; Chen, J.; Lu, L.; Xiao, W. Recent advances in transition-metal-catalysed asymmetric coupling reactions with light intervention. *Chem. Soc. Rev.* **2021**, *50*, 12808−12827.

(6) Zhang, W.; Chi, Y.; Zhang, X. Developing chiral ligands for asymmetric hydrogenation. *Acc. Chem. Res.* **2007**, *40*, 1278−1290.

(7) Zhang, S.; Ouyang, Y.; Gao, Y.; Li, P. Design and application of new pyridine-derived chiral ligands in asymmetric catalysis. *Acc. Chem. Res.* **2024**, *57*, 957−970.

(8) 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.

(9) Liu, X.; Lin, L.; Feng, X. Chiral N,N′-dioxide ligands: synthesis, coordination chemistry and asymmetric catalysis. *Org. Chem. Front.* **2014**, *1*, 298−302.

(10) Li, W.; Zhang, J. Recent developments in the synthesis and utilization of chiral β-aminophosphine derivatives as catalysts or ligands. *Chem. Soc. Rev.* **2016**, *45*, 1657−1677.

(11) Iwamoto, T.; Mizuhata, Y.; Tokitoh, N.; Nakamura, M. Development of P- and N-chirogenic ligands based on chiral induction from a phosphorus donor to a nitrogen donor in palladium complexes. *Organometallics* **2020**, *39*, 1672−1677.

(12) Munzeiwa, W. A.; Omondi, B.; Nyamori, V. O. Architecture and synthesis of *P,N*-heterocyclic phosphine ligands. *Beilstein J. Org. Chem.* **2020**, *16*, 362−383.

(13) Chen, L.; Liu, X.; Zou, Y. Recent advances in the construction of phosphorus-substituted heterocycles, 2009−2019. *Adv. Synth. Catal.* **2020**, *362*, 1724−1818.

(14) Pullarkat, S. A. Recent progress in palladium-catalyzed asymmetric hydrophosphination. *Synthesis* **2016**, *48*, 493−503.

(15) Zhao, D.; Wang, R. Recent developments in metal catalyzed asymmetric addition of phosphorus nucleophiles. *Chem. Soc. Rev.* **2012**, *41*, 2095−2108.

(16) Liu, X.; Han, X.; Wu, Y.; Sun, Y.; Gao, L.; Huang, Z.; Zhang, Q. Ni-catalyzed asymmetric hydrophosphination of unactivated alkynes. *J. Am. Chem. Soc.* **2021**, *143*, 11309−11316.

(17) Li, H.; Yin, L. Research progress on catalytic asymmetric synthesis of P-chiral compounds. *Chin. J. Org. Chem.* **2022**, *42*, 3183−3200.

(18) Feng, J.; Chen, X.; Shi, M.; Duan, W. Palladium-catalyzed asymmetric addition of diarylphosphines to enones toward the synthesis of chiral phosphines. *J. Am. Chem. Soc.* **2010**, *132*, 5562−5563.

(19) Lu, J.; Ye, J.; Duan, W. 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.

(20) Yang, X.; Tay, W. S.; Li, Y.; Pullarkat, S. A.; Leung, P. H. Asymmetric 1,4-conjugate addition of diarylphosphines to α,β,γ,δ-unsaturated ketones catalyzed by transition-metal pincer complexes. *Organometallics* **2015**, *34*, 5196−5201.

(21) Huang, Y.; Chew, R. J.; Pullarkat, S. A.; Li, Y.; Leung, P. H. Asymmetric synthesis of enaminophosphines via palladacyclecatalyzed addition of Ph_2PH to α,β-unsaturated imines. *J. Org. Chem.* **2012**, *77*, 6849−6854.

(22) Zhao, D.; Yuan, Y.; Chan, A. S. C.; Wang, R. Highly enantioselective 1,4-addition of diethyl phosphite to enones using a dinuclear Zn catalyst. *Chem. - Eur. J.* **2009**, *15*, 2738−2741.

(23) Saito, B.; Egami, H.; Katsuki, T. Synthesis of an optically active Al(salalen) complex and its application to catalytic hydrophosphonylation of aldehydes and aldimines. *J. Am. Chem. Soc.* **2007**, *129*, 1978−1986.

(24) Li, Y.; Tian, H.; Yin, L. Copper(I)-catalyzed asymmetric 1,4-conjugate hydrophosphination of α,β-unsaturated amides. *J. Am. Chem. Soc.* **2020**, *142*, 20098−20106.

(25) Yue, W.; Xiao, J.; 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.

(26) Pérez, J. M.; Postolache, R.; Castiñeira Reis, M.; Sinnema, E. G.; Vargová, 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.

(27) Postolache, R.; Pérez, J. M.; Castiñeira Reis, M.; Ge, L.; Sinnema, E. G.; Harutyunyan, S. R. Manganese(I)-catalyzed asymmetric hydrophosphination of α,β-unsaturated carbonyl derivatives. *Org. Lett.* **2023**, *25*, 1611−1615.

(28) Wang, C.; Huang, K.; Ye, J.; Duan, W. Asymmetric synthesis of P-stereogenic secondary phosphineboranes by an unsymmetric bisphosphine pincer-nickel complex. *J. Am. Chem. Soc.* **2021**, *143*, 5685−5690.

(29) Lu, Z.; Zhang, H.; Yang, Z.; Ding, N.; Meng, L.; Wang, J. Asymmetric hydrophosphination of heterobicyclic alkenes: facile access to phosphine ligands for asymmetric catalysis. *ACS Catal.* **2019**, *9*, 1457−1463.

(30) Wu, Z.; Cheng, A.; Yuan, M.; Zhao, Y.; Yang, H.; Wei, L.; Wang, H.; Wang, T.; Zhang, Z.; Duan, W. 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.

(31) Yu, X.; Lu, L.; Zhang, Z.; Shi, D.; Xiao, W. Cobalt-catalyzed asymmetric phospha-Michael reaction of diarylphosphine oxides for the synthesis of chiral organophosphorus compounds. *Org. Chem. Front.* **2022**, *10*, 133−139.

(32) Maria Faisca Phillips, A. Organocatalytic asymmetric synthesis of chiral phosphonates. *Mini-Rev. Org. Chem.* **2014**, *11*, 164−185.

(33) Zhu, Y.; Malerich, J. P.; Rawal, V. H. Squaramide-catalyzed enantioselective Michael addition of diphenyl phosphite to nitroalkenes. *Angew. Chem., Int. Ed.* **2010**, *49*, 153−156.

(34) Guo, F.; Chen, J.; Huang, Y. A bifunctional N-heterocyclic carbene as a noncovalent organocatalyst for enantioselective Aza-Michael addition reactions. *ACS Catal.* **2021**, *11*, 6316−6324.

(35) Li, E.; Chen, J.; Huang, Y. Enantioselective seleno-Michael addition reactions catalyzed by a chiral bifunctional N-heterocyclic carbene with noncovalent activation. *Angew. Chem., Int. Ed.* **2022**, *61*, No. e202202040.

(36) Hu, H.; Ren, X.; He, J.; Zhu, L.; Fang, S.; Su, Z.; Wang, T. Stereodivergently asymmetric synthesis of chiral phosphorus compounds by synergistic combination of ion-pair catalyst and base. *Sci. China Chem.* **2022**, *65*, 2500−2511.

(37) Maiti, R.; Yan, J.; Yang, X.; Mondal, B.; Xu, J.; Chai, H.; Jin, Z.; Chi, Y. R. Carbene-catalyzed enantioselective hydrophosphination of abromoenals to prepare phosphine-containing chiral molecules. *Angew. Chem., Int. Ed.* **2021**, *60*, 26616−26621.

(38) Arai, R.; Hirashima, S.; Nakano, T.; Kawada, M.; Akutsu, H.; Nakashima, K.; Miura, T. Asymmetric conjugate addition of phosphonates to enones using cinchona-diaminomethylenemalononitrile organocatalysts. *J. Org. Chem.* **2020**, *85*, 3872−3878.

(39) Terada, M.; Ikehara, T.; Ube, H. Enantioselective 1,4-addition reactions of diphenyl phosphite to nitroalkenes catalyzed by an axially chiral guanidine. *J. Am. Chem. Soc.* **2007**, *129*, 14112−14113.

https://doi.org/10.1021/acs.orglett.5c01255
Org. Lett. XXXX, XXX, XXX−XXX

(40) Shi, Y.; Chen, L.; Gao, Q.; Li, J.; Guo, Y.; Fan, B. Application of oxazaborolidine catalysts (CBS) on enantioselective 1,4-addition of diarylphosphine oxides to α,β-unsaturated thioesters. *Org. Lett.* **2023**, *25*, 6495−6500.
(41) Qian, J.; Zhao, H.; Gao, Q.; Chen, L.; Shi, Y.; Li, J.; Guo, Y.; Fan, B. Enantioselective 1,4-addition of diarylphosphine oxides to α,β-unsaturated ketones catalyzed by oxazaborolidines. *Org. Chem. Front.* **2023**, *10*, 5672−5679.
(42) Lu, G.; Xiao, L.; Que, Q.; Leng, T.; Li, J.; Guo, Y.; Fan, B. Metal-free enantioselective 1,4-addition of diarylphosphine oxides to α,β-unsaturated carboxylic esters. *J. Org. Chem.* **2024**, *89*, 7573−7578.
(43) Chen, L.; Wang, G.; Nong, X.; Shao, W.; Li, J.; Guo, Y.; Fan, B. Asymmetric 1,4-addition of diarylphosphine oxides to α,β-unsaturated 2-acyl imidazoles. *Chem. - Eur. J.* **2024**, *30*, No. e202401017.
(44) Das, S.; Hu, Q.; Kondoh, A.; Terada, M. Enantioselective Protonation: Hydrophosphinylation of 1,1-Vinyl Azaheterocycle *N*-Oxides Catalyzed by Chiral Bis(guanidino)iminophosphorane Organosuperbase. *Angew. Chem., Int. Ed.* **2021**, *60*, 1417−1422.
(45) Wang, B.; Liu, Y.; Jiang, C.; Cao, Z.; Cao, S.; Zhao, X.; Ban, X.; Yin, Y.; Jiang, Z. Catalytic asymmetric hydrophosphinylation of 2-vinylazaarenes to access P-chiral 2-azaaryl-ethylphosphine oxides. *Angew. Chem., Int. Ed.* **2023**, *62*, No. e202216605.
(46) Yang, Q.; Zhou, J.; Wang, J. Enantioselective copper-catalyzed hydrophosphination of alkenyl isoquinolines. *Chem. Sci.* **2023**, *14*, 4413−4417.
(47) Ni, C.; Ramspoth, T.; Reis, M. C.; Harutyunyan, S. R. Manganese(I)-Catalyzed Highly Enantioselective Synthesis ofAziridine Phosphines. *Angew. Chem., Int. Ed.* **2025**, *64*, No. e202415623.
(48) Sinnema, E. G.; Ramspoth, T.; Bouma, R. H.; Ge, L.; Harutyunyan, S. R. Enantioselective Hydrophosphination of Terminal Alkenyl Aza-Heteroarenes. *Angew. Chem., Int. Ed.* **2024**, *63*, No. e202316785.
(49) Han, J.; Kim, J.; Lee, J.; Kim, Y.; Lee, S. Y. Boron Lewis acid-catalyzed hydrophosphinylation of *N*-heteroaryl-substituted alkenes with secondary ohosphine oxides. *J. Org. Chem.* **2020**, *85*, 15476−15487.

https://doi.org/10.1021/acs.orglett.5c01255
Org. Lett. XXXX, XXX, XXX−XXX