JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
pubs.acs.org/JACS
Communication

Asymmetric Synthesis of P-Stereogenic Secondary Phosphine-Boranes by an Unsymmetric Bisphosphine Pincer-Nickel Complex

Chuanyong Wang,* Kesheng Huang, Jie Ye, and Wei-Liang Duan*

Cite This: J. Am. Chem. Soc. 2021, 143, 5685−5690
Read Online
ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: The first highly enantioselective catalytic synthesis of P-stereogenic secondary phosphine-boranes was realized by the asymmetric addition of primary phosphine to electron-deficient alkenes with a newly developed unsymmetric bisphosphine (PCP′) pincer-nickel complex. Various P-stereogenic secondary phosphine-boranes were obtained in 57−92% yields with up to 99% ee and >20:1 dr. The follow-up alkylation upon P−C bond formation with alkyl halides provided a practical way to access P-chiral compounds with diverse functional groups.

P-stereogenic molecules are an important class of compounds, which not only are widely utilized as chiral ligands or organocatalysts for diverse asymmetric transformations,[1−3] but also function as drugs and biological molecules.[4−6] Thus, the synthesis of P-stereogenic compounds is of paramount importance. In particular, the development of privileged P-chiral phosphine ligands, such as CAMP, DIPAMP, Tangphos, QuinoxPhos, BIBPO, etc., opens up a new research area for achieving interesting asymmetric catalysis.[7−27] Continuous efforts have been deployed to develop effective methodologies for the preparation of P-stereogenic tertiary phosphines.[28−35] For example, the dynamic kinetic resolution of racemic secondary phosphines with alkyl or aryl halides affording P-chiral compounds has been investigated with chiral palladium,[36−38] platinum,[39−42] and ruthenium[43,44] complexes as catalysts. In addition, catalytic asymmetric additions of racemic secondary phosphines to benzoquinones[45] or electron-deficient olefins[46−48] have been also exploited to produce P-stereogenic phosphines.[49−51] Compared to configurationally stable P-stereogenic tertiary phosphine, secondary phosphine is prone to racemization due to its low inversion barrier,[52] which makes the synthesis of optically active secondary phosphine more difficult and challenging. The reported methods limit to the resolution of secondary phosphine chiral at phosphorus via recrystallization[53] or using chiral auxiliaries.[10,28] Considering the importance of P-stereogenic secondary phosphines in serving as versatile building blocks for the divergent construction of chiral phosphorus ligands (Figure 1a)[10,28−30,32] and transition metal complexes,[54,55] new catalytic asymmetric strategies to the construction of P-stereogenic secondary phosphines are highly desirable. To the best of our knowledge, the direct preparation and application of P-chiral secondary phosphine via a catalytic process have not been reported.[56] To address the difficulties in chiral secondary phosphines synthesis and enrich the ligand portfolio for asymmetric catalysis, here we report for the first time the catalytic synthesis of P-stereogenic secondary phosphine-boranes with high enantio- and diastereoselectivities with a newly developed unsymmetric bisphosphine (PCP′) pincer-nickel complex (Figure 1b). The resulting chiral secondary phosphines are readily convertible into useful chiral phosphines ligands for asymmetric transformations.

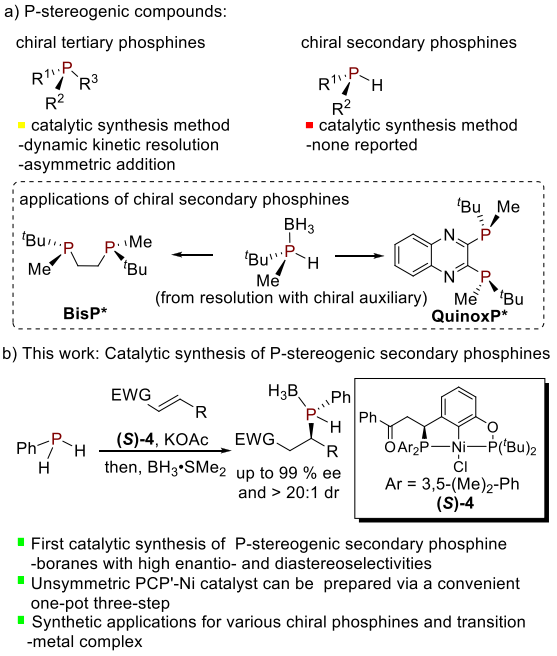
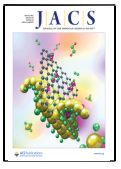


Figure 1. P-stereogenic phosphines.

At the onset of our study, we envisioned that our previously developed bisphosphine (PCP) pincer-palladium ((*S*,*S*)-**1**)[57] would be capable of controlling the stereochemistry of the

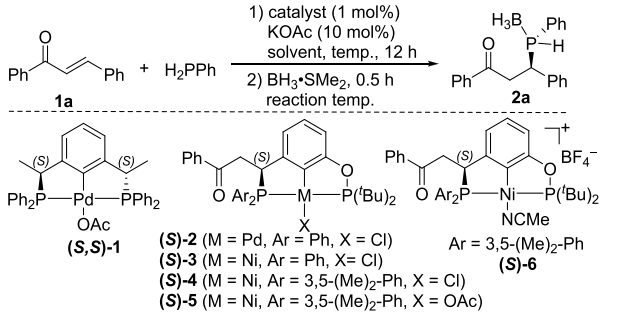
Received: March 14, 2021
Published: April 9, 2021



https://doi.org/10.1021/jacs.1c02772
J. Am. Chem. Soc. 2021, 143, 5685−5690

addition of phenylphosphine to enones by the chiral C2 symmetric-type palladium complex. When **1a** reacted with H_2PPh in the presence of (*S,S*)-**1** under −60 °C, the desired P−C bond formation product **2a** was obtained in 72% yield after BH_3 protection, but to our disappointment, poor enantio- and diastereoselectivity was observed (Table 1, entry 1), which

Table 1. Catalytic Synthesis of P-Stereogenic Secondary Phosphine-Boranes with PCP Pincer-Pd/Ni Complexes[a]



entry	catalyst	solvent	T (°C)	yield (%)[b]/dr[c]	ee of the major and minor product (%)[d]
1[e]	(*S,S*)-**1**	DCM	−60	72(1:1)	13/7
2	(*S*)-**2**	DCM	−60	84(1:1)	59/54
3	(*S*)-**3**	DCM	−60	75(5:1)	70/24
4	(*S*)-**4**	DCM	−60	80(13:1)	94/−
5[e]	(*S*)-**5**	DCM	−60	78(13:1)	94/−
6[e]	(*S*)-**6**	DCM	−60	0	n.a.
7	(*S*)-**4**	MeOH	−60	70(2:1)	40/32
8	(*S*)-**4**	$CHCl_3$	−60	60(4:1)	89/56
9	(*S*)-**4**	THF	−60	18(1:1)	44/17
10	(*S*)-**4**	DCM	−40	82(13:1)	94/−
11	(*S*)-**4**	DCM	−20	82(12:1)	90/−
12[e]	(*S*)-**4**	DCM	−40	0	n.a.
13	none	DCM	−40	0	n.a.

[a]Reaction conditions: enone **1a** (0.20 mmol) and phenylphosphine (0.30 mmol) with chiral catalyst (1.0 mol %) and KOAc (10 mol %) in DCM (1.4 mL) at the indicated temperature for 12 h under nitrogen atmosphere. [b]Isolated yield. [c]dr value shown in parentheses determined by crude ^{1}H NMR. [d]ee value determined by HPLC. [e]No KOAc. n.a. = no analysis.

is a sharp contrast to the high ee obtained with $HPPh_2$.[57] It is speculated that compared with diphenylphosphine, H_2PPh has a smaller size, and the rotation around Pd−P bond will be easier when it is bound to the Pd catalyst. We wondered if unsymmetric PCP′ pincer-metal complexes bearing two different neutral P and P′ donors in a larger size will be more flexible and effective for optimization of the catalyst and improvement of the stereoselectivity in the current reaction. Therefore, we designed and synthesized PCP′ pincer metal complexes containing phenyl-bridged phosphine−phosphinite ligand with a stereogenic carbon center based on our reported method with (*S,S*)-**1** as the catalyst.[57] The corresponding enantiopure Pd/Ni complexes (*S*)-**2**−**4** was obtained via a convenient one-pot three-step reaction (see Supporting Information). Encouragingly, when our newly developed Pd complex (*S*)-**2** bearing a PPh_2 and a larger OP^tBu_2 group combined with KOAc were applied to this system, the reaction proceeded in 59% ee, albeit with low dr (entry 2). A modification of the catalyst by changing the center metal to nickel provided **2a** in 70% ee and 5:1 dr (entry 3). Further optimization of the ligand by replacing the Ph ((*S*)-**3**) with a 3,5-$(Me)_2$-Ph ((*S*)-**4**) substituent improved the enantio- and diastereoselectivity to 94% ee and 13:1 dr (entry 4). With OAc anion (*S*)-**5** displayed similar catalytic activity compared to (*S*)-**4** (entry 5). In contrast, a cationic complex (*S*)-**6** did not catalyze the reaction (entry 6). This hydrophosphination is sensitive to the temperature and solvent, and the best results were obtained by using DCM at −40 °C (entries 7−11). Control experiments verified that both catalyst and base are essential for product formation (entries 12 and 13).

Under the optimized conditions (Table 1, entry 10), the hydrophosphination of a wide variety of enones with H_2PPh was then investigated using complex (*S*)-**4** as the catalyst (Figure 2). Both electron-withdrawing (F, Cl, and Br) and

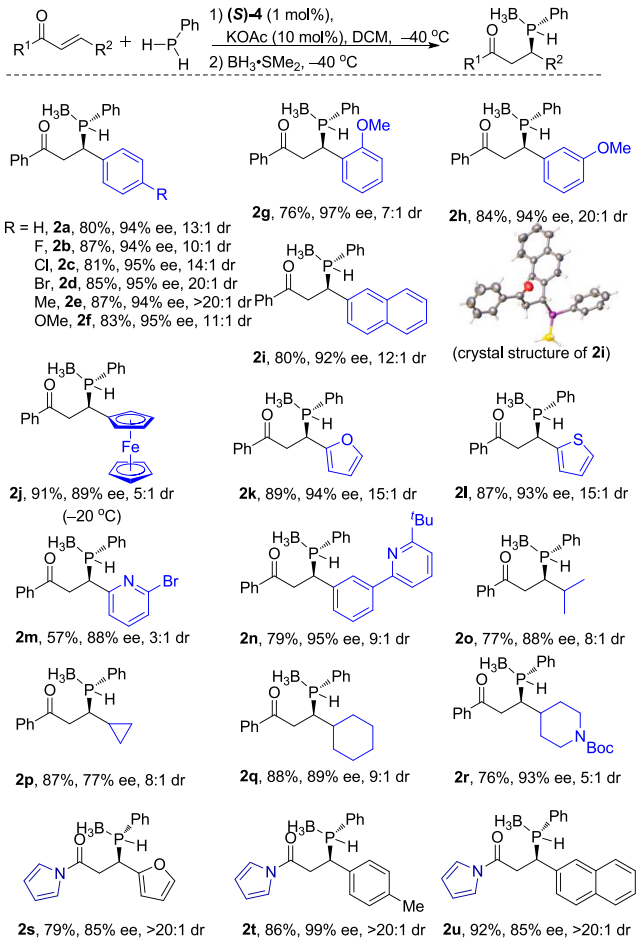


Figure 2. Substrate scope. An X-ray crystal structure[59] of **2i** was obtained to assign the absolute configuration of the products (see the Supporting Information).

electron-donating (Me and OMe) substituents attached to *β*-aryl *α,β*-unsaturated phenyl ketone substrates were tolerated, and all of them furnished high enantioselectivities and good diastereoselectivities (**2b**−**2f**). With substituents at the ortho-position or meta-position, the reaction proceeded well and provided the products in good yields with up to 97% ee and >20:1 dr (**2g** and **2h**). The *β*-naphthyl and *β*-ferrocenyl enones were also appropriate substrates for the current catalytic system (**2i** and **2j**). In the cases of *β*-heteroaryl species such as *β*-furyl, *β*-thienyl, *β*-pyridyl enones that may bind to the nickel center through the heteroatom, good stereocontrol could still be achieved (**2k**−**2n**). In addition, the enones bearing an alkyl

https://doi.org/10.1021/jacs.1c02772
J. Am. Chem. Soc. 2021, 143, 5685−5690

group in the β position such as ^{i}Pr (**2o**), cyclopropyl (**2p**), cyclohexyl (**2q**), and hetero-cyclohexyl (**2r**) afforded high levels of stereoselectivities. Gratifyingly, α,β-unsaturated *N*-acylpyrroles are also suitable substrates for this transformation under standard conditions (**2s**−**2u**).[58]

Upon scaling up the hydrophosphination reaction of β-naphthyl enone in the presence of 2 mol % of PCP′ pincer-nickel catalyst (*S*)-**4**, 1.12 g of product **2i** (99% yield, 92% ee, 12:1 dr) were obtained, displaying the robust nature of this reaction. The obtained P-stereogenic secondary phosphine is present as a useful precursor for the conversion into chiral tertiary phosphines (**3a**−**3e**) and bisphosphine compounds (**3f** and **3g**) with moderate to high yields by the reaction of optically active **2i** and alkyl halides in the presence of NaHMDS under −78 °C (Figure 3).[60]

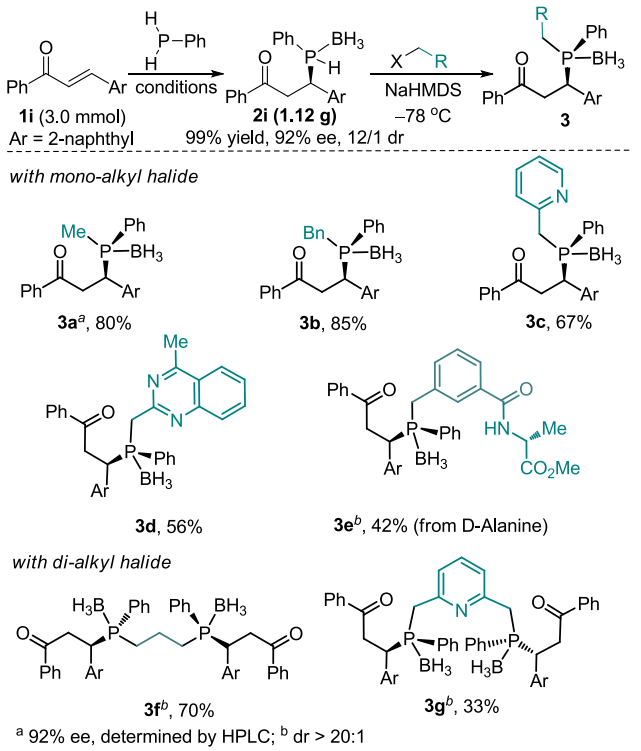


Figure 3. Synthetic transformations.

To further illustrate the utility of the present methodology, a bisenone **4** was reacted with H_2PPh in the presence of (*S*)-**4**, followed by BH_3 protection and methyl substitution to yield a bisphosphine **5** bearing four stereogenic centers in 99% ee (Figure 4). It is worth noting that this chiral bisphosphine compound was a useful ligand for the preparation of P-chiral pincer nickel complex, which was further verified as an effective catalyst in the asymmetric conjugate hydrophosphination, furnishing the desired product **6** in 93% yield with 94% ee (in toluene).

The proposed catalytic cycle for the nickel catalyzed asymmetric addition of H_2PPh to enones is illustrated in Figure 5. First, coordinated anion exchange forms the PCP′-Ni-OAc complex (*S*)-**5**. Second, transphosphination occurs between H_2PPh and (*S*)-**5**, which affords a nickel phosphido intermediate **A**[61−63] (^{31}P NMR spectrum: δ (ppm) 200.78 (d, J = 247.6 Hz), 55.22 (d, J = 245.4 Hz), −57.0 (brs); see Supporting Information). Then, the nucleophilic phosphorus addition to the β-position of **1** generates a nickel phosphine

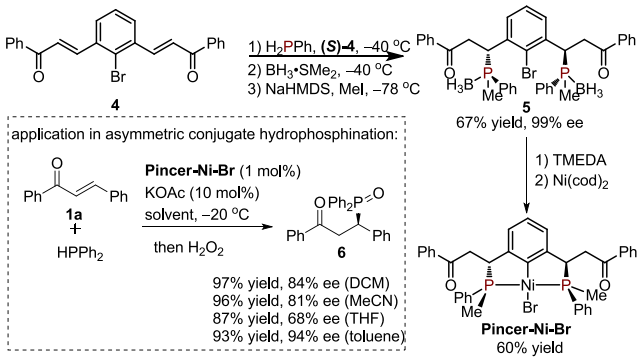


Figure 4. Synthetic approach to pincer−Ni-Br complex and its application.

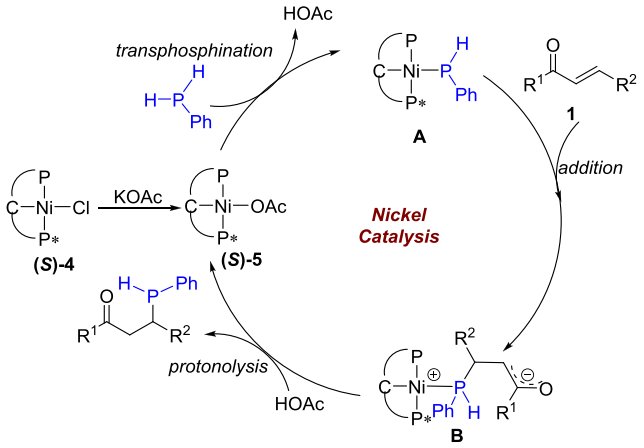


Figure 5. Proposed mechanism.

complex that bears a pendant anion **B**. Finally, the reaction of this nickel intermediate **B** with HOAc releases the product as well as regenerates active catalyst (*S*)-**5**. It is important to note that the product is unstable without protection and the racemization at phosphorus occurred when the temperature was raised, leading to the formation of two isomers with low diastereoselectivity (^{31}P NMR spectrum: δ (ppm) −22.0 (s), −29.0 (s); see Supporting Information).

The crystal structures of (*S*)-**2**, (*S*)-**3**, and (*S*)-**5** were determined by X-ray diffraction.[59] Figure 6 exhibits the superimposed crystal structures of (*S*)-**3** and (*S*)-**5** and reveals

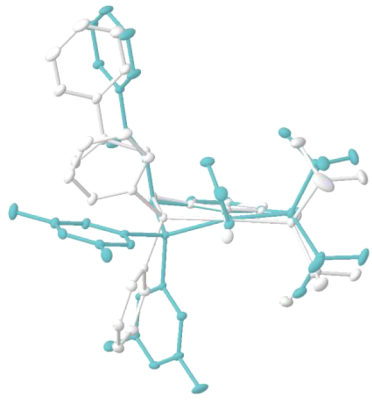


Figure 6. Superimposed crystal structure of (*S*)-**3** (gray) with (*S*)-**5** (blue). Fitted are the central metal together with the metal-bound phenyl carbon atoms. Hydrogen atoms are omitted for clarity.

https://doi.org/10.1021/jacs.1c02772
J. Am. Chem. Soc. 2021, 143, 5685−5690

differences in how the phosphorus groups flank the coordination site around nickel center. It is easy to observe that two phosphorus atoms are almost located in the same plane with the Ni-bound phenyl atoms in (*S*)-**3**, while distributed on both sides of the plane in (*S*)-**4**. This distortion (θ = 20.1(3)°, see the Supporting Information) should be attributed to the 3,5-methyl substituted phenyls and -OAc group. The inversion of phenylphosphine in nickel phosphido intermediate **A** might be limited due to the enhanced steric strain when (*S*)-**4** was used as catalyst. Experimental evidence for this steric hindrance effect by the unsymmetric PCP′ pincer-nickel complex (*S*)-**4** is supported by the improved enantio- and diastereoselectivity, which were obtained when utilizing 3,5-$(Me)_2$-Ph in place of Ph substituent (Table 1, entry 4 vs entry 3). Similarly, low reactivity was observed by the addition of chalcone with $HPPh_2$ using (*S*)-**4** as catalyst (14% yield and 12% ee with (*S*)-**4**; 27% yield and 38% ee with (*S*)-**3**, see the Supporting Information), which can be explained by the crowded steric environment around nickel center in (*S*)-**4**.

The tentative stereochemical pathway for this hydrophosphination is shown in Figure 7. The observed absolute

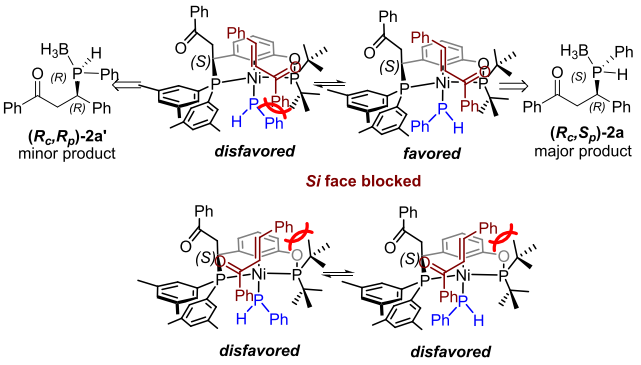


Figure 7. Tentative stereochemical pathway for the asymmetric hydrophosphination.

configuration of the major product **2** with *R* configuration at the carbon atom and *S* configuration at the phosphorus atom when (*S*)-**4** is used is consistent with this mechanistic picture in which the prochiral *Si* face of the nickel phosphido intermediate **A** is effectively shielded by *tert*-butyl groups of the unsymmetric PCP′ ligand sphere, providing excellent stereochemical control over the addition process.

In summary, we have developed an unsymmetric bisphosphine (PCP′) pincer-nickel complex for catalytic synthesis of P-stereogenic secondary phosphine-boranes in high yields with excellent enantio- and diastereoselectivities. Substrates with various functional groups were tolerated under current conditions. In addition, the obtained chiral secondary phosphines are useful precursors for the conversion into other phosphorus compounds, which can be used as chiral phosphine ligands for asymmetric catalysis. Further application of this chiral pincer-nickel catalyst in other asymmetric reactions are in progress.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.1c02772.

Experimental procedures, products, NMR spectra, HPLC traces, and X-ray structures (PDF)

Accession Codes

CCDC 2026045 and 2026047−2026049 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Authors

Chuanyong Wang − *College of Chemistry and Chemical Engineering, Yangzhou University, Yangzhou 225002, China;* orcid.org/0000-0001-9576-8589; Email: wangchuanyong@yzu.edu.cn

Wei-Liang Duan − *College of Chemistry and Chemical Engineering, Yangzhou University, Yangzhou 225002, China;* orcid.org/0000-0003-2791-1931; Email: duanwl@yzu.edu.cn

Authors

Kesheng Huang − *College of Chemistry and Chemical Engineering, Yangzhou University, Yangzhou 225002, China*

Jie Ye − *College of Chemistry and Chemical Engineering, Yangzhou University, Yangzhou 225002, China*

Complete contact information is available at: https://pubs.acs.org/10.1021/jacs.1c02772

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was financially supported by the National Natural Science Foundation of China (21801220, 21672183, and 22071139), the Natural Science Foundation of Jiangsu Province (BK20180892), the Priority Academic Program Development of Jiangsu Higher Education Institutions, and Top-notch Academic Programs Project of Jiangsu Higher Education Institutions. We thank Dr. Wei Cai (YZU) for her support during the preparation of the manuscript.

■ REFERENCES

(1) Börner, A. *Phosphorus Ligands in Asymmetric Catalysis; Synthesis and Applications*; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, 2008; pp 1−10.

(2) Guo, H.; Fan, Y. C.; Sun, Z.; Wu, Y.; Kwon, O. Phosphine Organocatalysis. *Chem. Rev.* **2018**, *118*, 10049−10293.

(3) Dutartre, M.; Bayardon, J.; Juge, S. Applications and Stereoselective Syntheses of P-chirogenic Phosphorus Compounds. *Chem. Soc. Rev.* **2016**, *45*, 5771−5794.

(4) Hecker, S. J.; Erion, M. D. Prodrugs of Phosphates and Phosphonates. *J. Med. Chem.* **2008**, *51*, 2328−2345.

(5) Clarion, L.; Jacquard, C.; Sainte-Catherine, O.; Decoux, M.; Loiseau, S.; Rolland, M.; Lecouvey, M.; Hugnot, J.-P.; Volle, J.-N.; Virieux, D.; Pirat, J.-L.; Bakalara, N. C-Glycoside Mimetics Inhibit Glioma Stem Cell Proliferation, Migration, and Invasion. *J. Med. Chem.* **2014**, *57*, 8293−8306.

(6) Iwamoto, N.; Butler, D. C. D.; Svrzikapa, N.; Mohapatra, S.; Zlatev, I.; Sah, D. W. Y.; Meena; Standley, S. M.; Lu, G.; Apponi, L. H.; Frank-Kamenetsky, M.; Zhang, J.; Vargeese, C.; Verdine, G. L. Control of Phosphorothioate Stereochemistry Substantially Increases the Efficacy of Antisense Oligonucleotides. *Nat. Biotechnol.* **2017**, *35*, 845−851.

(7) Vineyard, B. D.; Knowles, W. S.; Sabacky, M. J.; Bachman, G. L.; Weinkauff, D. J. Asymmetric Hydrogenation. Rhodium Chiral Bisphosphine Catalyst. *J. Am. Chem. Soc.* **1977**, *99*, 5946−5952.
(8) Knowles, W. S. Asymmetric Hydrogenation. *Acc. Chem. Res.* **1983**, *16*, 106−112.
(9) Imamoto, T.; Watanabe, J.; Wada, Y.; Masuda, H.; Yamada, H.; Tsuruta, H.; Matsukawa, S.; Yamaguchi, K. P-Chiral Bis-(trialkylphosphine) Ligands and Their Use in Highly Enantioselective Hydrogenation Reactions. *J. Am. Chem. Soc.* **1998**, *120*, 1635−1636.
(10) Imamoto, T.; Sugita, K.; Yoshida, K. An Air-Stable P-Chiral Phosphine Ligand for Highly Enantioselective Transition-Metal-Catalyzed Reactions. *J. Am. Chem. Soc.* **2005**, *127*, 11934−11935.
(11) Tang, W.; Zhang, X. A Chiral 1,2-Bisphospholane Ligand with a Novel Structural Motif: Applications in Highly Enantioselective Rh Catalyzed Hydrogenations. *Angew. Chem., Int. Ed.* **2002**, *41*, 1612−1614.
(12) Liu, D.; Zhang, X. Practical P-Chiral Phosphane Ligand for Rh-Catalyzed Asymmetric Hydrogenation. *Eur. J. Org. Chem.* **2005**, *2005*, 646−649.
(13) Hamilton, G. L.; Kang, E. J.; Mba, M.; Toste, F. D. A Powerful Chiral Counterion Strategy for Asymmetric Transition Metal Catalysis. *Science* **2007**, *317*, 496−499.
(14) Watson, M. P.; Jacobsen, E. N. Asymmetric Intramolecular Arylcyanation of Unactivated Olefins via C−CN Bond Activation. *J. Am. Chem. Soc.* **2008**, *130*, 12594−12595.
(15) Taylor, A. M.; Altman, R. A.; Buchwald, S. L. Palladium-Catalyzed Enantioselective α-Arylation and α-Vinylation of Oxindoles Facilitated by an Axially Chiral P-Stereogenic Ligand. *J. Am. Chem. Soc.* **2009**, *131*, 9900−9901.
(16) Shibata, Y.; Tanaka, K. Rhodium-Catalyzed Highly Enantioselective Direct Intermolecular Hydroacylation of 1,1-Disubstituted Alkenes with Unfunctionalized Aldehydes. *J. Am. Chem. Soc.* **2009**, *131*, 12552−12553.
(17) Jin, M.; Adak, L.; Nakamura, M. Iron-Catalyzed Enantioselective Cross-Coupling Reactions of α-Chloroesters with Aryl Grignard Reagents. *J. Am. Chem. Soc.* **2015**, *137*, 7128−7134.
(18) You, W.; Brown, M. K. Catalytic Enantioselective Diarylation of Alkenes. *J. Am. Chem. Soc.* **2015**, *137*, 14578−14581.
(19) Salomó, E.; Orgué, S.; Riera, A.; Verdaguer, X. Highly Enantioselective Iridium−Catalyzed Hydrogenation of Cyclic Enamides. *Angew. Chem., Int. Ed.* **2016**, *55*, 7988−7992.
(20) Gan, Z.; Zhi, M.; Han, R.; Li, E.-Q.; Duan, Z.; Mathey, F. P-Stereogenic Phosphines Directed Copper(I)-Catalyzed Enantioselective 1,3-Dipolar Cycloadditions. *Org. Lett.* **2019**, *21*, 2782−2785.
(21) 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.
(22) Du, X.; Xiao, Y.; Huang, J.-M.; Zhang, Y.; Duan, Y.-N.; Wang, H.; Shi, C.; Chen, G.-Q.; Zhang, X. Cobalt-Catalyzed Highly Enantioselective Hydrogenation of α,β-Unsaturated Carboxylic Acids. *Nat. Commun.* **2020**, *11*, 3239.
(23) Liu, Y.; Ding, B.; Liu, D.; Zhang, Z.; Liu, Y.; Zhang, W. A New and Convenient Approach for the Synthesis of P-stereogenic Intermediates Bearing a *Tert*-Butyl(methyl)phosphino Group. *Res. Chem. Intermed.* **2017**, *43*, 4959−4966.
(24) Li, B.; Chen, J.; Zhang, Z.; Gridnev, I. D.; Zhang, W. Nickel−Catalyzed Asymmetric Hydrogenation of N−Sulfonyl Imines. *Angew. Chem., Int. Ed.* **2019**, *58*, 7329−7334.
(25) Zhang, J.; Jia, J.; Zeng, X.; Wang, Y.; Zhang, Z.; Gridnev, I. D.; Zhang, W. Chemo- and Enantioselective Hydrogenation of α−Formyl Enamides: An Efficient Access to Chiral α−Amido Aldehydes. *Angew. Chem., Int. Ed.* **2019**, *58*, 11505−11512.
(26) 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.
(27) Liu, D.; Li, B.; Chen, J.; Gridnev, I. D.; Yan, D.; Zhang, W. Ni-Catalyzed Asymmetric Hydrogenation of N-Aryl Imino Esters for the Efficient Synthesis of Chiral α-Aryl Glycines. *Nat. Commun.* **2020**, *11*, 5935.
(28) Ohashi, A.; Kikuchi, S.-I.; Yasutake, M.; Imamoto, T. Unsymmetrical P-Chirogenic Bis(phosphane) Ligands: Their Preparation and Use in Rhodium-Catalyzed Asymmetric Hydrogenation. *Eur. J. Org. Chem.* **2002**, *2002*, 2535−2546.
(29) Bauduin, C.; Moulin, D.; Kaloun, E. B.; Darcel, C.; Jugé, S. Highly Enantiomerically Enriched Chlorophosphine Boranes: Synthesis and Applications as P-Chirogenic Electrophilic Blocks. *J. Org. Chem.* **2003**, *68*, 4293−4301.
(30) Han, Z. S.; Goyal, N.; Herbage, M. A.; Sieber, J. D.; Qu, B.; Xu, Y.; Li, Z.; Reeves, J. T.; Desrosiers, J.-N.; Ma, S.; Grinberg, N.; Lee, H.; Mangunuru, H. P. R.; Zhang, Y.; Krishnamurthy, D.; Lu, B. Z.; Song, J. J.; Wang, G.; Senanayake, C. H. Efficient Asymmetric Synthesis of P-Chiral Phosphine Oxides via Properly Designed and Activated Benzoxazaphosphinine-2-oxide Agents. *J. Am. Chem. Soc.* **2013**, *135*, 2474−2477.
(31) Berger, O.; Montchamp, J.-L. A General Strategy for the Synthesis of P-Stereogenic Compounds. *Angew. Chem., Int. Ed.* **2013**, *52*, 11377−11380.
(32) Gatineau, D.; Giordano, L.; Buono, G. Bulky, Optically Active P-Stereogenic Phosphine−Boranes from Pure H-Menthylphosphinates. *J. Am. Chem. Soc.* **2011**, *133*, 10728−10731.
(33) Yavari, K.; Moussa, S.; Ben Hassine, B.; Retailleau, P.; Voituriez, A.; Marinetti, A. 1H-Phosphindoles as Structural Units in the Synthesis of Chiral Helicenes. *Angew. Chem., Int. Ed.* **2012**, *51*, 6748−6752.
(34) Pizzolato, S. F.; Štacko, P.; Kistemaker, J. C. M.; Leeuwen, T.; Feringa, B. L. Phosphoramidite-Based Photoresponsive Ligands Displaying Multifold Transfer of Chirality in Dynamic Enantioselective Metal Catalysis. *Nat. Catal.* **2020**, *3*, 488−496.
(35) Xu, D.; Rivas-Bascón, N.; Padial, N. M.; Knouse, K. W.; Zheng, B.; Vantourout, J. C.; Schmidt, M. A.; Eastgate, M. D.; Baran, P. S. Enantiodivergent Formation of C−P Bonds: Synthesis of P-Chiral Phosphines and Methylphosphonate Oligonucleotides. *J. Am. Chem. Soc.* **2020**, *142*, 5785−5792.
(36) 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.
(37) Brunker, T. J.; Anderson, B. J.; Blank, N. F.; Glueck, D. S.; Rheingold, A. L. Enantioselective Synthesis of P-Stereogenic Benzophospholanes via Palladium-Catalyzed Intramolecular Cyclization. *Org. Lett.* **2007**, *9*, 1109−1112.
(38) 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.
(39) 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.
(40) Scriban, C.; Glueck, D. S.; Golen, J. A.; Rheingold, A. L. Platinum-Catalyzed Asymmetric Alkylation of a Secondary Phosphine: Mechanism and Origin of Enantioselectivity. *Organometallics* **2007**, *26*, 1788−1800.
(41) Anderson, B. J.; Glueck, D. S.; DiPasquale, A. G.; Rheingold, A. L. Substrate and Catalyst Screening in Platinum-Catalyzed Asymmetric Alkylation of Bis(secondary) Phosphines. Synthesis of an Enantiomerically Pure C2-Symmetric Diphosphine. *Organometallics* **2008**, *27*, 4992−5001.
(42) Chapp, T. W.; Glueck, D. S.; Golen, J. A.; Moore, C. E.; Rheingold, A. L. Platinum-Catalyzed Asymmetric Alkylation of Bis(isitylphosphino)ethane: Stereoselectivity Reversal in Successive Formation of Two P−C Bonds. *Organometallics* **2010**, *29*, 378−388.
(43) 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.
(44) Chan, V. S.; Chiu, M.; Bergman, R. G.; Toste, F. D. Development of Ruthenium Catalysts for the Enantioselective

https://doi.org/10.1021/jacs.1c02772
J. Am. Chem. Soc. 2021, 143, 5685−5690

Synthesis of P-Stereogenic Phosphines via Nucleophilic Phosphido Intermediates. *J. Am. Chem. Soc.* **2009**, *131*, 6021−6032.
(45) 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.
(46) 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.
(47) 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.
(48) Huang, Y.; Pullarkat, S. A.; Teong, S.; Chew, R. J.; Li, Y.; Leung, P.-H. Palladacycle-Catalyzed Asymmetric Intermolecular Construction of Chiral Tertiary P-Heterocycles by Stepwise Addition of H−P−H Bonds to Bis(enones). *Organometallics* **2012**, *31*, 4871−4875.
(49) Li, Z.; Duan, W.-L. Recent Advances in the Asymmetric Conjugate Addition Reactions of Phosphorus Nucleophiles to Electron-Deficient Alkenes. *Youji Huaxue* **2016**, *36*, 1805−1813.
(50) Sun, G.; Xiao, F.; Duan, W.-L. Palladium-Catalyzed Asymmetric 1,4-Addition of Diarylphosphines to Quinone Monoketals. *Youji Huaxue* **2020**, *40*, 61−68.
(51) Zhu, R.-Y.; Liao, K.; Yu, J.-S.; Zhou, J. Recent Advances in Catalytic Asymmetric Synthesis of P-Chiral Phosphine Oxides. *Huaxue Xuebao* **2020**, *78*, 193−216.
(52) 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-[(R*,R*),(R*)]]-(+)589-[PtCl{1,2-C_6H_4(PMePh)$_2$}(PHMePh)]PF_6 CH_2Cl_2. *Inorg. Chem.* **1995**, *34*, 384−389.
(53) Bader, A.; Pabel, M.; Wild, S. B. First Resolution of a Free Secondary Phosphine Chiral at Phosphorus. *J. Chem. Soc., Chem. Commun.* **1994**, *30*, 1405−1406.
(54) Albert, J.; Cadena, M. J.; Granell, J.; Muller, G.; Panyella, D.; Sañudo, C. Resolution of Secondary Phosphanes Chiral at Phosphorus by Means of Palladium Metallacycles. *Eur. J. Inorg. Chem.* **2000**, *2000*, 1283−1286.
(55) Yang, Z.; Liu, D.; Liu, Y.; Sugiya, M.; Imamoto, T.; Zhang, W. Synthesis and Structural Characterization of Nickel Complexes Possessing P-Stereogenic Pincer Scaffolds and Their Application in Asymmetric Aza-Michael Reactions. *Organometallics* **2015**, *34*, 1228−1237.
(56) 17% ee of P-stereogenic secondary phosphine was obtained by the monoalkylation of phenylphosphine borane with MeI using Cinchona alkaloid as catalyst, see: Lebel, H.; Morin, S.; Paquet, V. Alkylation of Phosphine Boranes by Phase-Transfer Catalysis. *Org. Lett.* **2003**, *5*, 2347−2349.
(57) 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.
(58) 53% ee and 1:1 dr were obtained by using H_2PCy as nucleophile.
(59) CCDC 2026045 (**2i**); 2026047 ((*S*)-**2**); 2026049 ((*S*)-**3**); 2026048 ((*S*)-**5**) contain the supplementary crystallographic data for this paper.
(60) Miura, T.; Yamada, H.; Kikuchi, S.; Imamoto, T. Synthesis and Reaction of Optically Active Secondary Dialkylphosphine-Boranes. *J. Org. Chem.* **2000**, *65*, 1877−1880.
(61) Jones, R. A.; Seeberger, M. H.; Cherkas, A. A.; Van Gastel, F.; Carty, A. J. Bis*Tert*-Butylphosphido (T-Bup(H)$^-$) Bridged Dimers of Rhodium(+1) and Nickel(+1) Containing Rh═Rh Double and Ni−Ni Single Bonds. *Inorg. Synth.* **2007**, *25*, 173−177.
(62) Melenkivitz, R.; Mindiola, D. J.; Hillhouse, G. L. Monomeric Phosphido and Phosphinidene Complexes of Nickel. *J. Am. Chem. Soc.* **2002**, *124*, 3846−3847.
(63) 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.

https://doi.org/10.1021/jacs.1c02772
J. Am. Chem. Soc. 2021, 143, 5685−5690