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Communication

Ni-Catalyzed Asymmetric Hydrophosphination of Unactivated Alkynes

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ABSTRACT: The practical synthesis of *P*-stereogenic tertiary phosphines, which have wide applications in asymmetric catalysis, materials, and pharmaceutical chemistry, represents a significant challenge. A regio- and enantioselective hydrophosphination using cheap and ubiquitous alkynes catalyzed by a nickel complex was designed, in which the toxic and air-sensitive secondary phosphines were prepared *in situ* from bench-stable secondary phosphine oxides. This methodology has been demonstrated with unprecedented substrate scope and functional group compatibility to afford electronically and structurally diversified P(III) compounds. The products could be easily converted into various precursors of bidentate ligands and organocatalysts, as well as a variety of transition-metal complexes containing both *P*- and metal-stereogenic centers.

P-Stereogenic phosphines played a key role in the early stages of homogeneous asymmetric catalysis as chiral ligands of transition metals.[1] Further development in this area has culminated in the discovery of the ligand DiPAMP, which led to the industrial production of L-Dopa by an asymmetric hydrogenation reaction.[2] As a continuous effort, several new types of *P*-stereogenic phosphines have been developed in the past two decades with significant applications as both ligands and organocatalysts (Figure 1a).[3−5]

However, the challenges in the asymmetric synthesis of *P*-stereogenic phosphines have been a persistent barrier to their further investigations and applications.[6,7] Among the strategies developed, the catalytic asymmetric synthesis of *P*-stereogenic phosphines,[8] especially with strategies that could directly create the chiral center by carbon−phosphine bond formation, has shown great potential in the past two decades.[9] Significant advances have been made, in which the dynamic kinetic resolution (DKR) of secondary phosphines is regarded as the most straightforward and promising strategy (Figure 1b).[10] However, there are two formidable challenges: i.e., the handling of highly sensitive, volatile, and toxic secondary phosphines and the catalyst inhibition or poisoning caused by competitive coordination of P(III) starting materials and products to transition metals. As a result, these reactions have been accomplished with limited substrate scope and restricted catalytic systems.

The hydrophosphination reaction of unactivated alkenes and alkynes represents an economical and straightforward method to acquire valuable tertiary phosphines.[11] However, the reaction often suffers from harsh conditions and elusive regioselectivities and the catalytic asymmetric syntheses of the *P*-stereogenic center by hydrophosphination type reactions have had limited success.[12−14] In particular, the direct synthesis of P(III) stereogenic phosphines by the asymmetric hydrophosphination of alkynes with free secondary phosphines is unprecedented, and a general method to structurally diversify chiral phosphines with universal applications is highly desirable.

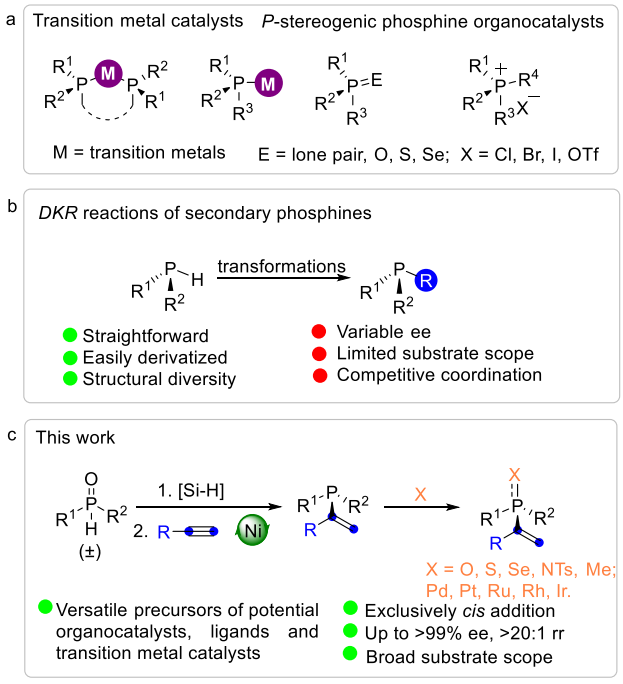

Figure 1. Construction of *P*-chiral phosphines: (a) application of *P*-stereogenic phosphines; (b) DKR reactions of secondary phosphines; (c) this work.

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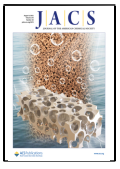

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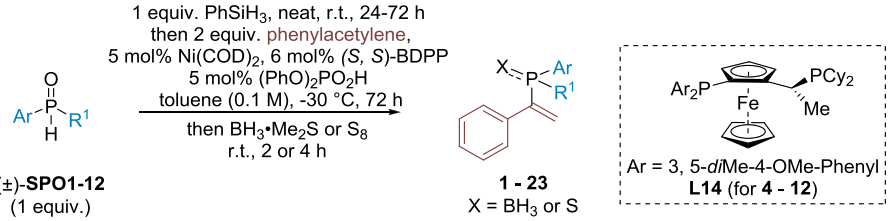
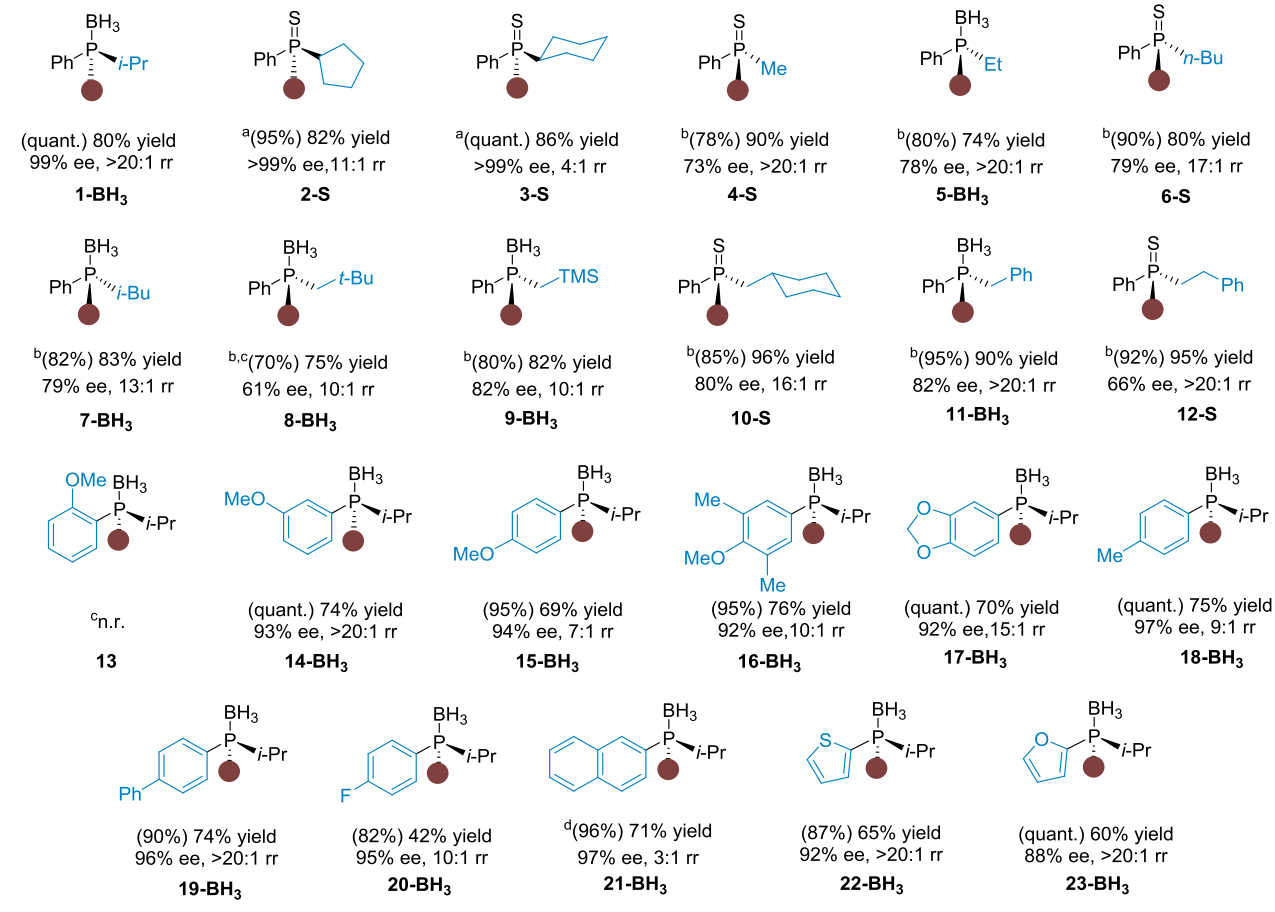
Table 1. Substrate Scope of Secondary Phosphine Oxides[e]





[a]−20 °C. [b]**L14** (6 mol %) as a chiral ligand. [c]25 °C. [d]0 °C. [e]All reactions were performed on a 0.1 mmol scale. Reduction yields are given in parentheses on the basis of ^{31}P NMR analyses with P(O)(OMe)$_3$ as an internal standard. Isolated yields were the combined yields of two isomers based on secondary phosphines. ee values of the major isomers are shown and were determined by chiral HPLC analyses. rr values (branched/linear) were determined by ^{1}H NMR analyses of the crude reaction mixtures.

Herein, we conceived an enantioselective hydrophosphination reaction with inexpensive alkynes and free secondary phosphines by solving the two challenges arising from both the substrate and the catalyst. We acquired the labile secondary phosphines by *in situ* reduction of bench-stable secondary phosphine oxides, avoiding their isolation and purification while maintaining their structural diversity. In addition, the relatively "hard" Ni along with universal bidentate ligands was introduced as the catalyst to minimize the competitive coordination of relatively "soft" monodentate secondary phosphines and the tertiary phosphine products, thus eliminating the possible background reactions (Figure 1c).[15]

The hypothesis started from the reduction of secondary phosphine oxides (**SPO**s), which could serve as bench-stable precursors of secondary phosphines (**SP**s). PhSiH$_3$ was found to be an ideal reductant to realize the transformation under mild conditions.[16] After an extensive evaluation, we identified the optimized reaction conditions with *in situ* generated secondary phosphines. The reaction was accomplished with the best results by introducing [Ni(COD)$_2$] (5 mol %) as the catalyst, (*S*,*S*)-BDPP (6 mol %) as the ligand, and (PhO)$_2$PO$_2$H (5 mol %) as an additive in toluene (0.1 M) at −30 °C. The Markovnikov product was obtained in excellent regio- and enantioselectivity (see Tables S1−S4 for details).[17]

We then evaluated the scope of secondary phosphines (Table 1). A variety of secondary phosphines were synthesized via *in situ* reduction of the corresponding **SPO** with PhSiH$_3$ in 78% to quantitative NMR yield. The tertiary phosphine products were protected as either phosphine boranes or sulfides, which could be easily deprotected or derivatized.[18] The Markovnikov addition products were generally obtained

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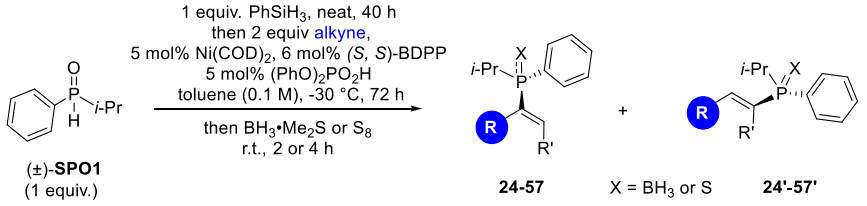
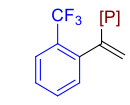
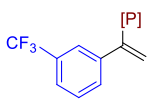
Table 2. Substrate Scope of Alkynes[e]



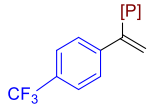
terminal alkynes:



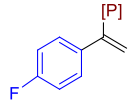
[a]X = BH_3, 74% yield
86/56% ee, 3:1 rr
24/24'-BH_3



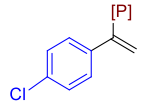
X = BH_3, 65% yield
91% ee, 6:1 rr
25-BH_3



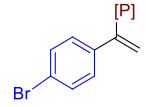
X = BH_3, 86% yield
X = S, 99% yield
>99% ee, 8:1 rr
26-BH_3, 26-S



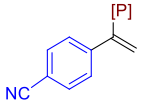
X = BH_3, 88% yield
99% ee, 9:1 rr
27-BH_3



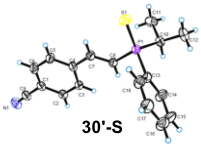
X = BH_3, 81% yield
X = S, 99% yield
>99% ee, 12:1 rr
28-BH_3, 28-S



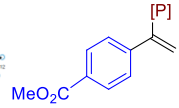
X = BH_3, 80% yield
X = S, 96% yield
>99% ee, 15:1 rr
29-BH_3, 29-S



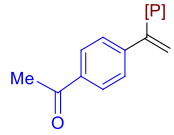
X = S, 90% yield
98% ee, 6:1 rr
30/30'-S



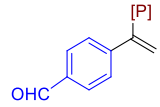
30'-S



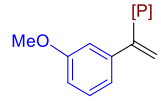
X = BH_3, 75% yield
X = S, 99% yield
>99% ee, 12:1 rr
31-BH_3, 31-S



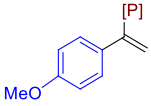
X = S, 87% yield
98% ee, 7:1 rr
32-S



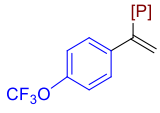
X = S, 56% yield
98% ee, 6:1 rr
33-S



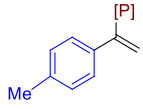
X = BH_3, 76% yield
97 % ee, 16:1 rr
34-BH_3



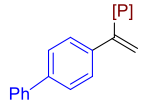
X = BH_3, 79% yield
98% ee, 9:1 rr
35-BH_3



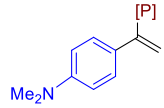
X = BH_3, 72% yield
X = S, 81% yield
>99% ee, 6:1 rr
36-BH_3, 36-S



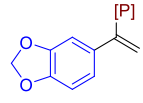
X = BH_3, 96% yield
98% ee, 6:1 rr
37-BH_3



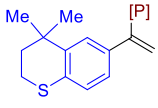
X = BH_3, 85% yield
95% ee, >20:1 rr
38-BH_3



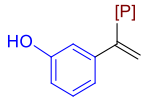
[a]X = S, 80% yield
83% ee, 9:1 rr
39-S



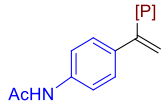
[a]X = BH_3, 79% yield
93% ee, 15:1 rr
40-BH_3



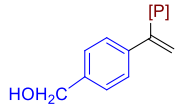
[b]X = S, 97% yield
93% ee, 11:1 rr
41-S



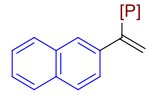
X = S, 75% yield
91%/26 % ee, 1:1 rr
42/42'-S



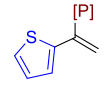
[a]X = S, 78% yield
87% ee, 3:1 rr
43-S



X = S, 77% yield
96/73% ee, 1:1 rr
44/44'-S

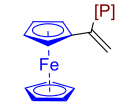


X = BH_3, 82% yield
98% ee, >20:1 rr
45-BH_3



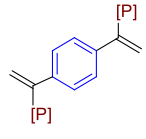
X = BH_3, 84% yield
96% ee, >20:1 rr
46-BH_3

[d]*internal alkynes:*

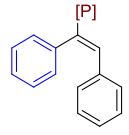


X = S, 80% yield
96% ee, 12:1 rr
47-S

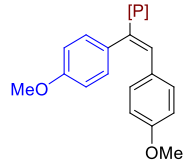
[a]X = BH_3, 67% yield
51% ee, >20:1 rr
48-BH_3



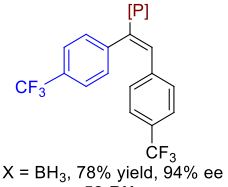
[ac]X = BH_3, 56% yield
95% ee, >20:1 rr, >20:1 dr
49-BH_3



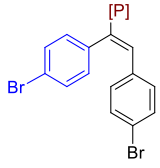
X = BH_3
82% yield, 80% ee
50-BH_3



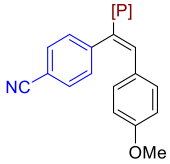
X = S
65% yield, 93% ee
51-S



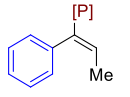
X = BH_3, 78% yield, 94% ee
52-BH_3
X = LP, 82% yield, 94% ee
52



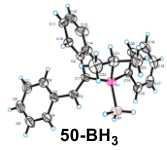
X = BH_3
76% yield, 76% ee
53-BH_3



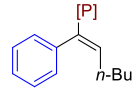
X = S, 67% yield
84% ee, 7:1 rr
54-S



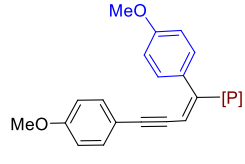
X = BH_3, 85% yield
87% ee, >20:1 rr
55-BH_3



50-BH_3



X = BH_3, 78% yield
83% ee, >20:1 rr
56-BH_3



X = S, 88% yield
48% ee, >20:1 rr
57-S

[a]0 °C. [b]−10 °C. [c]0.2 mmol of **SPO1** and 0.1 mmol of alkyne were employed. [d]rt, w/o $(PhO)_2PO_2H$, 48 h. [e]All reactions were performed on a 0.1 mmol scale. Isolated yields are the combined yields of two isomers based on **SPO1**. ee values were determined by chiral HPLC analyses. rr values (branched/linear) were determined by ^1H NMR analyses of crude reaction mixtures.

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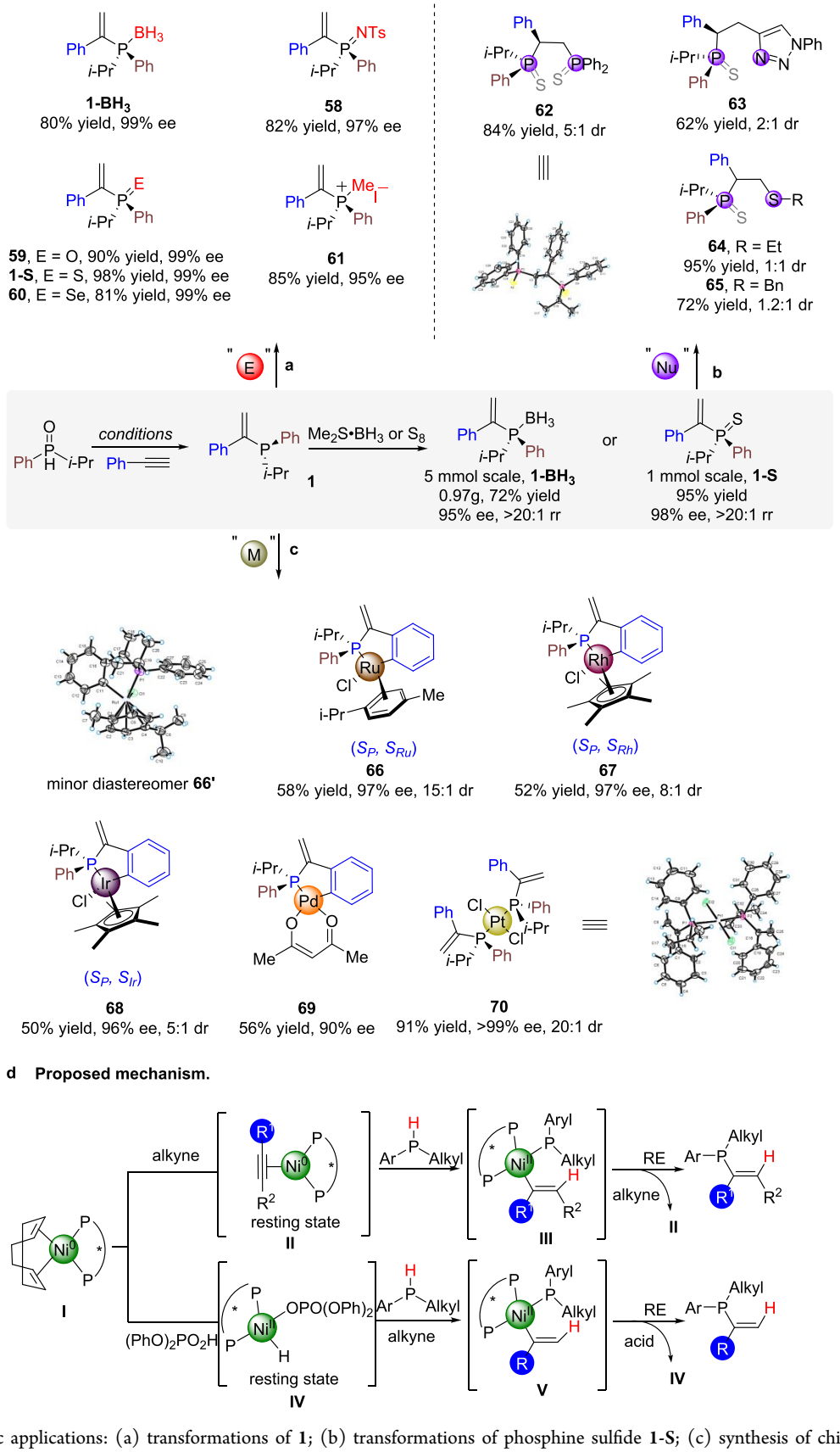

d Proposed mechanism.

Figure 2. Synthetic applications: (a) transformations of **1**; (b) transformations of phosphine sulfide **1-S**; (c) synthesis of chiral transition-metal complexes; (d) proposed mechanism. See the Supporting Information for experimental details.

with moderate to excellent results (Table 1). The stereohindrance of the alkyl group substituent of phosphines was critical to the enantioselectivities of the reaction. Secondary alkyl groups including isopropyl (**1**), cyclopentyl (**2**), and cyclohexyl (**3**) could give excellent enantioselectivities (99 to >99% ee) and high yields and regioselectivities (80−86% yield,

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4:1 to >20:1 rr), while primary alkyl groups could only give moderate enantioselectivities. In these cases, **L14** was used instead as the chiral ligand and the reactions could give the desired products in 74−96% yield, 61−82% ee, and 10:1 to >20:1 rr (**4**−**12**). Substituents at the *para* and *meta* positions of the phenyl group were all compatible to give excellent enantioselectivities and regioselectivities along with moderate to high yields (**14**−**20**). Unfortunately, the secondary phosphine with an *o*-MeO-phenyl group was unreactive even at rt, possibly because the substrate could serve as a bidentate ligand to the nickel catalyst and deactivate the reaction. The reactions of secondary phosphines with naphthyl, thiophenyl, and furyl groups could also proceed facilely to afford the corresponding products in high to excellent ee (97%, 92%, and 88% ee; **21**−**23**, respectively).

The scope of alkynes was then evaluated (Table 2). Substituents with various electronic properties and at different positions were considered. Trifluoromethyl groups at the *ortho*, *meta*, and *para* positions could all give the chiral phosphine products in 86%, 91%, and >99% ee with 65−99% yields (**24**−**26**, respectively). Terminal alkynes with a variety of functional groups, including electron-withdrawing groups (**27**−**34**) and electron-donating groups (**35**−**41**) were all amenable to the reaction, affording the corresponding phosphine boranes and/or phosphine sulfides in 56−99% yield and 83−>99% ee. It is worth mentioning that the labile aldehyde and bromide groups were both compatible with the nickel catalysis system and afforded the desired products in moderate to high yields (56% and 80/96%). Functional groups with an acidic proton including phenol, acetamido, and alcohol were tolerated in the reaction, affording the major Markovnikov products with 91% (**42**), 87% (**43**), and 96% ee (**44**) albeit in modest regioselectivity (1:1 to 3:1). Alkynes with naphthyl, thienyl, and ferrocenyl groupd could generate the corresponding phosphine adducts with excellent yields and enantio- and regioselectivities (**45**−**47**) as well. Cyclopropylacetylene with an alkyl substituent exhibited a moderate yield and stereocontrol (**48**) without the ring-opening product (67% yield, 51% ee). 1,4-Diethynylbenzene with two ethynyl groups could also participate in the reaction, affording the double-hydrophosphination product **49-BH$_3$** in 56% yield with 95% ee and >20:1 rr and excellent dr (>20:1).

Internal alkynes were also examined. Symmetrical diaryl alkynes could give exclusively the *cis*-hydrophosphination products (**50**−**53**) in 76−94% ee and 65−82% yields. The absolute configuration (S_P) was also confirmed by an X-ray single-crystal diffraction analysis of the compound **50-BH$_3$**. Among them, the tertiary *P*-stereogenic phosphine **52** was stable to oxygen and was isolated in 82% yield and 94% ee directly without a protecting group. Unsymmetrical alkyne with varied electronic properties could afford the desired product **54-S** in 84% ee, 67% yield, and 7:1 rr, in which the electron-poor site of the alkyne was prone to P−C bond formation. Internal alkynes with one aryl group and one alkyl group could afford the desired products (**55-BH$_3$** and **56**-BH$_3$) in excellent regioselectivities (>20:1), as well as high enanantioselectivities (87%, 83% ee) and high yields (85%, 78%). Interestingly, the reaction of a diacetylene substrate proceeded through monohydrophosphination, selectively providing the desired product **57-S** in 88% yield, 48% ee, and >20:1 rr.

To demonstrate the synthetic utility of our protocols, further transformations of P-stereogenic phosphines were investigated. Initially, the reaction was scaled up to 1 mmol with comparable results (98% ee, 95% yield, >20:1 rr) and further to a 5 mmol scale, accomplishing the synthesis of **1-BH$_3$** in 72% isolated yield with 95% ee and >20:1 rr under the standard conditions. Derivatives of phosphine, including phosphine oxides, sulfide, and selenides, had been shown to exhibit diverse catalytic activities in a series of reactions.[19−21] Those compounds were synthesized efficiently by adding respectively H_2O_2, S_8 (also see Table 1), and Se to the reaction mixture to afford the corresponding products in high yields while maintaining the ee values. A Staudinger reaction occurred smoothly when the reaction mixture was treated with tosyl azide to afford the *P*-stereogenic iminophosphorane product **58** in 82% overall yield and 97% ee. The quaternary phosphonium salt **61** (85% yield, 95% ee) that could serve as a potential phase transfer catalyst[22] was obtained when the reaction system was treated with methyl iodide (Figure 2a).

The phosphine sulfide product **1-S** (from 1 mmol scale) could undergo 1,4-addition reactions with a variety of nucleophiles to synthesize the potential chiral bidentate ligands (Figure 2b). For example, diphenylphosphine can react with **1-S** under basic conditions to generate diphosphine sulfide **62** in 84% yield with 5:1 dr upon quenching with S_8. The absolute and relative configurations of **62** were determined by a X-ray single-crystal diffraction analysis. Similarly, a triazole derivative (**63**) and thioethers (**64** and **65**) were also accessible through the 1,4-addition in good to excellent yields. These compounds might serve as precursors of P−P, P−N, and P−S chiral bidentate ligands to transition metals.

More importantly, *P*-stereogenic phosphines play a significant role in transition-metal catalysis. Herein we investigated the coordination of the chiral phosphine products to transition metals. The tertiary phosphine **1** with 98% ee was used in the following reactions. When the reaction mixture containing **1** was treated with late transition metals, including $[Ru(p\text{-cymene})Cl_2]_2$, $[Cp^*RhCl_2]_2$, and $[Cp^*IrCl_2]_2$, coordination followed by C−H bond metalation reaction occurred[23] to afford complexes **66**−**68** with both phosphorus and metal stereogenic centers[24] in 50−58% overall yields, 96−97% ee, and (5−15):1 dr (Figure 2c). Palladium dichloride also underwent C−H activation with the chiral phosphine product under mild conditions to afford **69** in 56% yield with a slightly decreased 90% ee, when it was treated further with sodium acetylacetonate. In addition, the *trans* product **70** with two chiral phosphine ligands was obtained without C−H bond activation in 91% yield, >99% ee, and 20:1 dr when platinum dichloride was introduced. The absolute configuration of **70** was also determined by an X-ray single-crystal analysis. It is worth mentioning that all of the transition-metal complexes could be easily isolated and purified by flash column chromatography or by precipitation from the reaction mixture.

To further understand the mechanism of this reaction, several experiments were carried out and analyzed by ^{31}P NMR (see the Supporting Information for details). The resting state of the catalyst was different with or without the additive $(PhO)_2PO_2H$ in our reaction according to an NMR analysis. As predicted, although the secondary phosphines (**SP1**) could coordinate to the nickel complex to some extent, the coordination is much weaker in comparison with alkynes (**A52**) and (*S*,*S*)-BDPP. The binding between P(III) compounds with Ni was reversible and could transform back to the resting state when an alkyne was added. We also monitored the ee of the product intermittently, and it did not

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change throughout the reaction period. Thus, we can conclude as predicted that both the secondary phosphine starting material and the tertiary phosphine product to a large extent would not interfere with the enantioselectivity of the reaction. On the basis of our observation and previous results, the mechanism is proposed in Figure 2d.[12,25] When the additive is absent, the catalyst resting state **II** was generated from Ni-BDPP-COD and alkyne via ligand exchange, which could undergo hydronickelation with a secondary phosphine to afford the intermediate **II**. Then the vinyl nickel intermediate **III** could undergo reductive elimination to produce the chiral phosphine product. On the other hand, the Ni(0) complex **I** was first converted into Ni(II) intermediate **IV** via oxidative addition in the presence of $(PhO)_2PO_2H$ (please see the Supporting Information). Ligand exchange by the secondary phosphine and subsequent hydronickelation with alkyne could produce intermediate **V**, which could then undergo reductive elimination to afford the final product (Figure 2d).

In summary, an efficient and straightforward access to *P*-stereogenic phosphines with excellent enantioselectivity was developed. The products could be easily transformed directly to a plethora of potential organocatalysts, chiral ligands, or their precursors, as well as transition-metal complexes. Notably, this method avoids the direct handling of toxic, air-sensitive secondary phosphines, enables the synthesis of *P*-stereogenic phosphines with a broad substrate scope and better practicality, and offers new exciting opportunities in related areas.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.1c05649.

Materials and optimization studies, experimental details, characterization data, and NMR and HPLC spectra (PDF)

Accession Codes

CCDC 2048638−2048642 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.

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Notes

The authors declare no competing financial interest.

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