Nickel-Catalyzed Enantioselective Hydrophosphinylation of 2-Azadienes to Access Enantioenriched α-Aminophosphine Oxides

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ABSTRACT: The practical synthesis of *C*-stereogenic α-aminophosphine oxides, which exhibit a wide range of applications in medicinal chemistry, biochemistry, material science and asymmetric catalysis, represents an unmet need. Herein is developed a unique Ni/(*S*,*S*)-BenzP* catalyst system for asymmetric synthesis of branched α-aminophosphine oxides through an enantioselective Markovnikov addition of H-phosphine oxides to 2-azadienes. A variety of readily available 2-azadienes and H-phosphine oxides, undergo hydrophosphinylation with high enantioselectivities (up to 99%) and good yields (up to 96%). These products can be readily hydrolyzed to afford synthetically valuable chiral α-aminophosphine oxides, which are key building blocks for the synthesis of bioactive compounds (such as phospholeucine synthesized herein), organocatalysts and ligands. Mechanistic studies suggest a hydrofunctionalization process.

KEYWORDS: *α-aminophosphines, hydrophosphinylation, 2-azadienes, Nickel, phospholeucine*

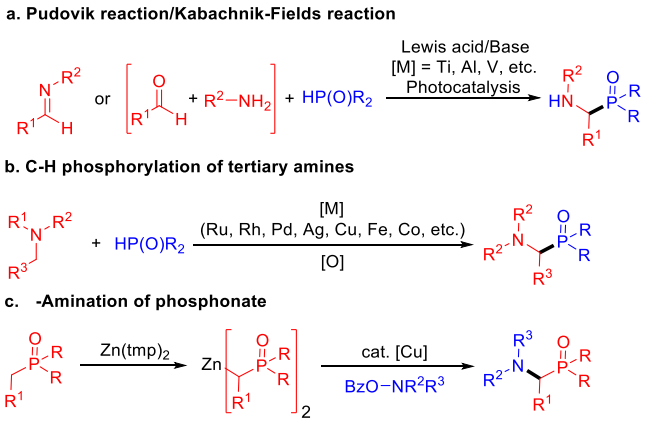
1. INTRODUCTION

Enantioenriched phosphine oxides are an important class of organophosphorus compounds that exhibit a wide range of biological properties,[1] such as antiviral, antitumor, antibacterial, and antituberculosis activities.[2] They are also important intermediates in organic chemistry[3] and have been widely used as enantioenriched catalysts[4] and ligands[5] in asymmetric catalysis.[6] More elaborate enantioenriched α-aminophosphine oxides are attracting growing attention due to their use as P,N-ligands in coordination chemistry[7] and their significant biological and pharmacological properties.[8] Consequently, much effort has been devoted to developing efficient approaches for the construction of enantioenriched α-aminophosphine oxides bearing various functional groups.

The addition of H-phosphine oxides to C=X (X = O or N) or C=C double bonds provides an atom-economic method for the synthesis of organophosphorus derivatives.[9] In particular, traditional methods for constructing α-aminophosphine oxides are mainly based on the nucleophilic addition of H-phosphine oxides to imines catalyzed by Lewis acids or bases, transition metals and photoredox catalysis. These include the Pudovik[10] and Kabachnik-Fields reactions[11] (Scheme 1a), which provide an efficient route to α-aminophosphine oxides. These traditional methods are generally limited in scope or are challenging because of the poor availability and stability associated with some imines.[12]

In recent years, transition-metal-catalyzed dehydrogenative cross-coupling of tertiary amines with H-phosphone oxides has been developed as an alternative approach toward phosphinoylation. This strategy represents a direct protocol for the preparation of α-aminophosphine oxides (Scheme 1b).[13] The utility of these reactions is balanced by their harsh reaction conditions, including high temperatures and stoichiometric quantities of oxidants. To address these limitations, an impressive α-amination of phosphonates was reported by Wang's group[14] who employed α-phosphonate zincates and *O*-acyl hydroxylamines in the presence of a copper-catalyst to form C−N bonds (Scheme 1c).

Scheme 1. Approaches to the synthesis of α-aminophosphine oxide derivatives



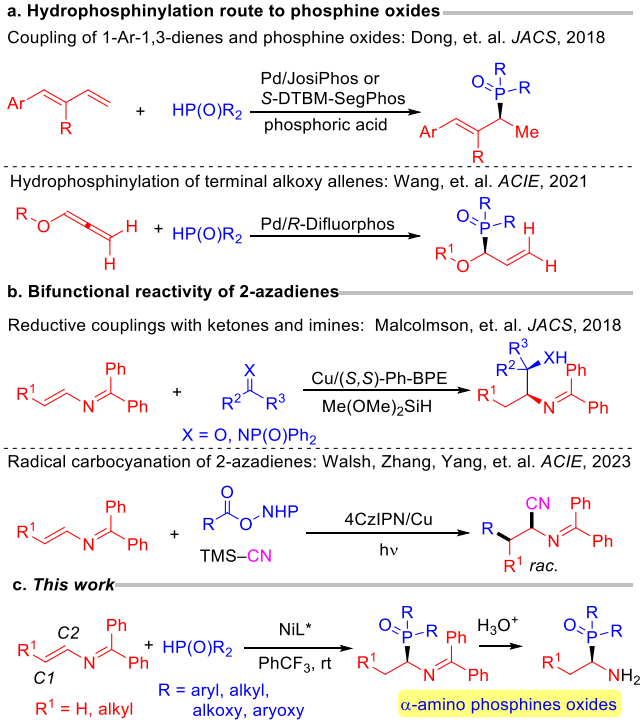
The second common approach is the enantioselective hydrofunctionalization of alkynes,[15] olefins,[16] 1,3-dienes[17] and allenes,[18] which represent an efficient and atom-economic strategy for uniting functional groups with organic frameworks.[19] These approaches are attractive because they have the potential to convert unsaturated hydrocarbons into polyfunctional molecules.[20] Reported methods for the construction of C–P bonds by hydrophosphinylation, however, are rare.[21] In 2018, pioneering work by Dong and coworkers[22] reported the Pd-catalyzed enantioselective addition of H-phosphine oxides to 1,3-dienes, providing enantioenriched allylic phosphine oxides (Scheme 2a). Wang's group[23] recently described an efficient hydrophosphinylation of alkyl and aryl-oxyallenes with H-phosphine oxides using a Pd/R-Difluorphos-based catalyst (Scheme 2b). Related methods for the synthesis of amino-containing phosphine oxides have yet to be documented.

Our journey toward the synthesis of amino-containing phosphine oxides began with the synthesis of amines. To prepare amines, our team[24] and other groups[25] have focused on the umpolung reactivity of ketimines and aldemines, which upon deprotonation give nucleophilic 2-azaallyl anions. Another layer of complexity, however, is introduced, in the asymmetric synthesis of heteroatom-containing enantioenriched amines via 2-azaallyl chemistry.[26] The increased functionality of such products furthers their synthetic utility.

2-Azaallyl anion intermediates have also been employed in a related approach for the synthesis of heteroatom-functionalized amines.[27] Malcolmson has successfully developed the chemistry of 2-azadienes for the synthesis of enantio- and diastereoenriched amino alcohols[28] or diamines.[29] The key step in this chemistry is an enantioselective hydrocupration, in which a Cu–H intermediate inserts the 2-azadiene to give a Cu-bound 2-azaallyl anion. This reactive intermediate adds in an enantio- and diastereoselective fashion to ketones and aldimines (Scheme 2b). Inspired by Malcolmson's elegant studies we investigated the radical carbocyanation of 2-azadienes. In that study,[30] 2-azadienes acted as radical acceptors to capture alkyl radicals and generate 2-azaallyl radical intermediates. Oxidative capture by a L_nCu–CN and subsequent reductive elimination produced *rac*-α-aminonitriles (Scheme 2b).[30] Based on these studies, we were curious if 2-azadienes could be hydrofunctionalized in the presence of an enantioenriched metal catalyst toward the synthesis of enantioenriched α-aminophosphine oxides.

Herein, we disclose the first asymmetric addition of H-phosphine oxides to 2-azadienes (Scheme 2c). This mild hydrophosphinylation tolerates a variety of functional groups that are frequently found in bioactive molecules. This hydrofunctionalization method can also be extended to the synthesis of enantioenriched α-aminophosphonates from commercially available H-phosphates. Key to the success of these processes is the Ni/(*S*,*S*)-BenzP* catalyst system that mediates the hydrophosphorylation with high chemo-, regio-, and enantioselectivities (46 examples, up to 96% yield and 99% ee).

Scheme 2. Hydrophosphinylation of C=C double bonds and reactivity of 2-azadienes



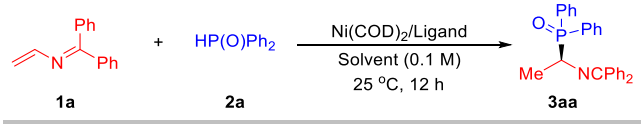
2. RESULTS AND DISCUSSION

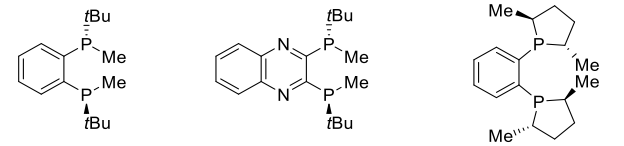
Reaction development and optimization. To optimize the reaction conditions, we began with 1,1-diphenyl-*N*-vinylmethanimine (**1a**) and diphenylphosphine oxide (**2a**) as the model substrates in the presence of 10 mol% $Ni(COD)_2$ in $PhCF_3$ at room temperature for 12 h. First, various classes of commercially available ligands were evaluated (including BOX ligands and mono- and bidentate phosphine ligands, see Supporting Information for full details). Fortunately, many enantioenriched bisphosphine ligands were effective in this transformation (**L1**–**L6**, 12 mol%, Table 1). In terms of chelating bisphosphine ligands with *P*-stereogenic centers, (*S*,*S*)-BenzP* (**L1**) generated the desired product **3aa** in 99% assay

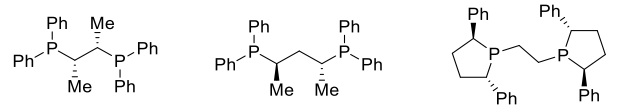
yield (AY, determined by ^{1}H NMR integration against an internal standard) with 98% ee (entry 1, Table 1). In sharp contrast, structurally similar (*S*,*S*)-QuinoxP* (**L2**) showed poor reactivity and enantioselectivity (entry 2, Table 1). It is gratifying that *C*-stereogenic bisphosphine ligands showed efficiency as well. For example, the use of (*S*,*S*)-Me-DuPhos (**L3**) also afforded **3aa** in 99% AY with 93% ee (entry 3, Table 1). (*S*,*S*)-ChiraPhos (**L4**) and (*R*,*R*)-BDPP (**L5**) exhibited good reactivities, yet only moderate enantioselectivities were observed (entries 4 and 5, Table 1). In particular, (*S*,*S*)-Ph-BPE (**L6**) delivered **3aa** in 95% AY with 96% ee, exhibiting only a small difference compared with **L1** (entry 6 *vs.* entry 1, Table 1). Further optimization with ligand **L1** was conducted.

The impact of solvent was next explored. A solvent screen (PhMe, PhCl, THF, Dioxane, MeCN, DCM and DCE) revealed that other than DCM and DCE, the other solvents gave very good results (85–96% AY, 93–97% ee; entries 7–13, Table 1), but not reaching the level of $PhCF_3$. Reducing the loading of $Ni(COD)_2$ catalyst from 10 mol% to 7.5 mol% furnished **3aa** in 99 % AY and 95% isolated yield with 98% ee (entry 14, Table 1). Reducing the catalyst loading to 5 mol%, however, resulted in a decrease in product yield and enantioselectivity (entry 15, Table 1). Notably, under otherwise identical conditions to entry 14, switching from $Ni(COD)_2$ to other metal catalysts [$Pd(OAc)_2$, $Cu(OAc)_2$ and CoI_2] as well as other Ni sources provided the desired product **3aa** in low to moderate AY but without any enantioselectivities (entries 16–18, Table 1; see Supporting Information for full details).

Table1. Optimization of hydrophosphinylation of 2-azadiene 1a[a]







Entry	L	Ni/L (mol%)	Solvent	**3aa** (%)[b]	ee (%)[c]
1	**L1**	10/12	$PhCF_3$	99	98
2	**L2**	10/12	$PhCF_3$	32	50
3	**L3**	10/12	$PhCF_3$	99	93
4	**L4**	10/12	$PhCF_3$	80	70
5	**L5**	10/12	$PhCF_3$	99	50
6	**L6**	10/12	$PhCF_3$	95	96
7	**L1**	10/12	PhMe	85	96
8	**L1**	10/12	PhCl	95	95
9	**L1**	10/12	THF	95	97
10	**L1**	10/12	Dioxane	89	93
11	**L1**	10/12	MeCN	96	94
12	**L1**	10/12	DCM	<5	-
13	**L1**	10/12	DCE	<5	-
14	**L1**	7.5/9	$PhCF_3$	99(95)[d]	98
15	**L1**	5/6	$PhCF_3$	86	94
16[e]	**L1**	7.5/9	$PhCF_3$	32	0
17[f]	**L1**	7.5/9	$PhCF_3$	66	0
18[g]	**L1**	7.5/9	$PhCF_3$	75	0

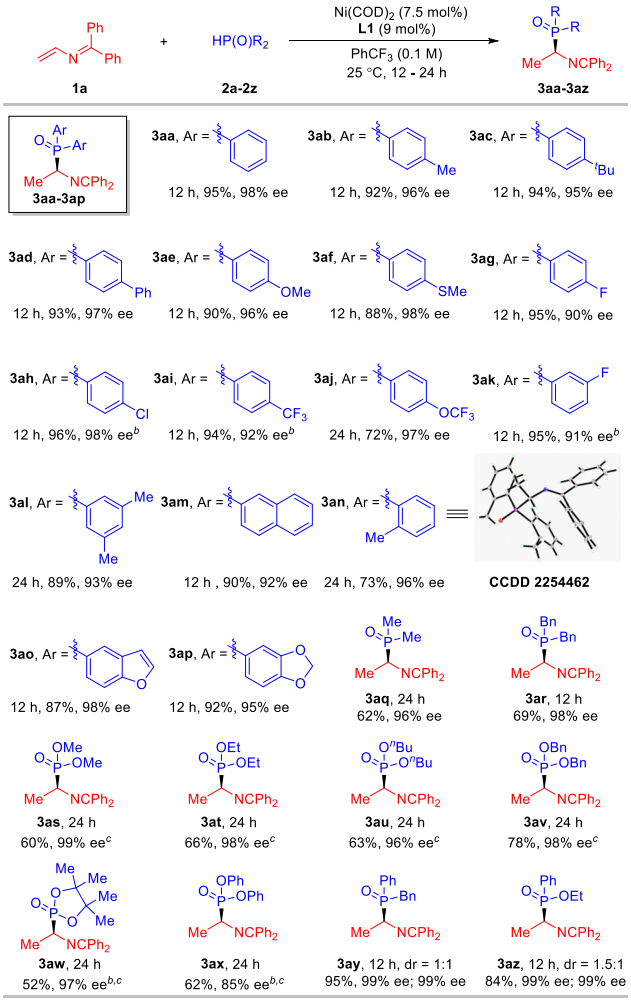
[a]Reactions conducted on a 0.1 mmol scale using 1.5 equiv. of **1a**, 1.0 equiv. of **2a**. [b]Assay yields (AY) were determined by ^{1}H NMR spectroscopy with $C_2H_2Cl_4$ as internal standard. [c]Enantiomeric excesses (ee) of **3aa** was determined by chiral-phase HPLC. [d]Isolated yield (IY) of **3aa** after chromatographic purification. [e]$Pd(OAc)_2$ instead of $Ni(COD)_2$. [f]$Cu(OAc)_2$ instead of $Ni(COD)_2$. [g]CoI_2 instead of $Ni(COD)_2$.

Scope of the phosphine oxides. With a concrete set of conditions in hand using **L1** (entry 14, Table 1), as well as two highly enantioselective backup ligands, the substrate scope of H-phosphine oxides was initially explored (Scheme 3). Under the standard reaction conditions, a broad array of diarylphosphine oxides were tolerated in the reaction with excellent yields and enantioselectivities (**3aa**–**3ag**). In general, substituents at different positions on the *P*–Ar groups, or with different electronic properties, had no significant effect on the reaction. Substrates with methyl, *tert*-butyl and phenyl groups at the 4-position were transformed into the corresponding products in 92–94% yields with 95–97% ee values (**3ab**–**3ad**). 4-Methoxy-substituted diarylphosphine oxide **2e** afforded the desired product **3ae** in 90% yield and 96% enantioselectivity, which was close to the values observed for 4-methylthio-substituted diarylphosphine oxide **3af** (88% yield, 98% ee). A substrate with a 4-fluoro phenyl group reacted under the standard conditions to afford the product **3ag** in 95% yield with 90% ee. With substrates bearing 4-Cl and 4-CF_3, **L1** furnished the products in 90–95% yields but with reduced enantioselectivities (75–85% ee). In contrast, using **L6** in place of **L1** provided 4-Cl and 4-CF_3 containing products in 94–96% yields with 92–98% ee.

4-Trifluoromethoxy-substituted diarylphosphine oxide **2j** performed well with **L1**, giving the corresponding product (**3aj**) in 72% yield with 97% ee. Similarly, the 3-fluoro phenyl substrate **2k** also furnished the desired product **3ak** with the use of ligand **L6** (91% ee with 95% yield). Diarylphosphine oxides with 3,5-dimethyl phenyl or 2-naphthyl groups (**2l** and **2m**) provided the expected products (**3al** and **3am**) with good enantioselectivities (93% and 92% ee, respectively). Additionally, 2-methyl substituted diarylphosphine oxide, possessing increased steric hindrance, was effective as well, providing the desired product **3an** with 96% ee (73% yield). The configuration of product **3an** was determined to be (*R*) by X-ray crystallography (Scheme 3, CCDC 2254462; see Supporting Information for full details). In terms of heterocyclic groups, benzofuranyl and piperonyl substituted phosphine oxides were viable in this reaction, affording the products **3ao** and **3ap** in 87–92% yields with 95–98% ee.

We next turned our attention to alkyl-substituted H-phosphine oxides and phosphonates. We were pleased to find that alkyl substituted phosphine oxides reacted smoothly with good efficiency, giving products **3aq** and **3ar** in 96–98% ee, albeit with somewhat diminished yields (62–69%). Importantly, phosphonates with various substituents (**2s**–**2x**) were also competent to afford related products (**3as**–**3ax**) in moderate yields when using MeCN in place of $PhCF_3$, leading to satisfying enantioselectivities (85–99% ee). We next examined racemic phosphine oxides. The benzyl phenyl or ethoxy phenyl substituted phosphine oxides **2y** and **2z** were converted to products **3ay** or **3az** with very good yields and enantioselectivities (84–95% yields, 98–99% ee). Not surprisingly, there was next to no diastereoselectivity in these processes.

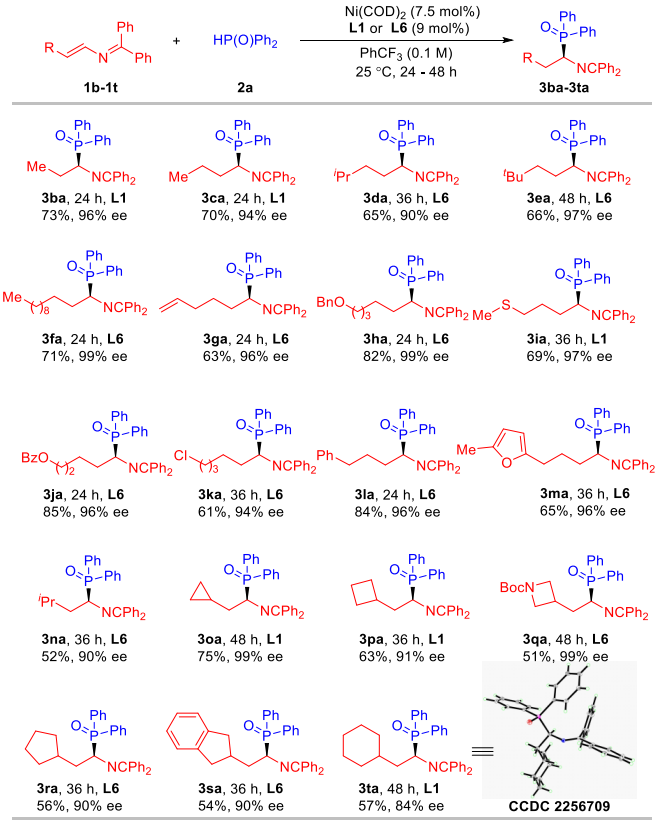
Scheme 3. Scope of phosphine oxides[a]



[a]Reactions conducted on a 0.4 mmol scale using 1.5 equiv. **1a**, 1.0 equiv. **2** at 0.1 M. Isolated yields after chromatographic purification. Ee determined by HPLC analysis. [b]**L6** was used as the ligand. [c]MeCN was used as the solvent.

Scope of the 2-azadienes coupling partners. For further substrate expansion, we introduced different substituents (R) into the 1-position of 2-azadiene coupling partners (Scheme 4). Given the increase steric hindrance about the 2-azadienes, longer reaction time (24–48 h) were required than with substrates with no substituent (**1a**). In some cases, (*S*,*S*)-Ph-BPE (**L6**) was superior to (*S*,*S*)-BenzP* (**L1**) in terms of enantioselectivity and served as the ligand of choice. Overall, 2-azadienes encompassing a range of functional groups could be employed. With simple primary aliphatic groups, moderate yields (63–73%) and excellent enantioselectivities (90–99% ee) of the products (**3ba**–**3ga**) were afforded. Substrates containing ether groups (**1h** and **1i**) gave the desired products (**3ha** and **3ia**) in moderate to good yields with very high enantioselectivities (97–99% ee). Ester **1j** and alkyl chloride **1k** were also compatible coupling partners, furnishing products with good yields (85% and 61%) and high ee values (96% and 94%). 2-Azadienes containing pendent aryl groups were smoothly converted to the related products **3la** and **3ma** with ee values up to 96%. It is noteworthy that substrates containing secondary aliphatic groups, such as *i*-Pr, cyclic and heterocyclic groups, including 3-, 4-, 5- and 6-membered ring systems (**1n**–**1t**) were all suitable and furnished the expected products with 84–99% ee. Among them, the ee value of **3ta** could be increased to >99% by recrystallization. X-ray crystallography was conducted to confirm the structure of **3ta** (Scheme 4, CCDC 2256709; see Supporting Information for full details).

Scheme 4. Scope of 2-azadienes[a]

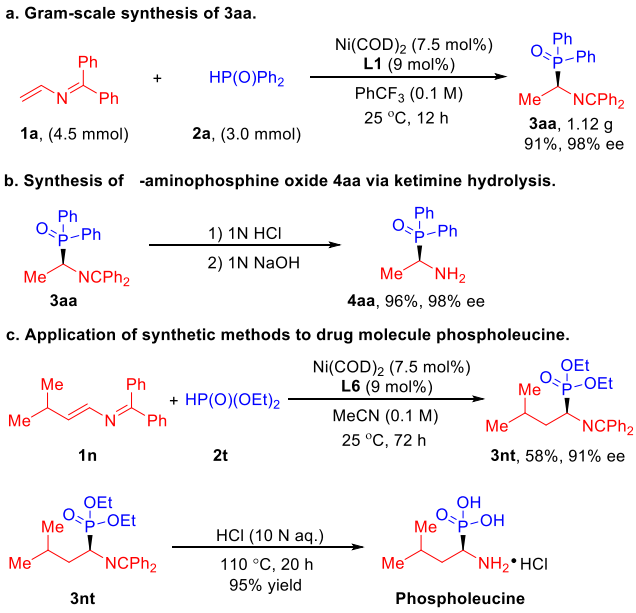


[a]Reactions conducted on a 0.4 mmol scale using 1.5 equiv. **1**, 1.0 equiv. **2a** at 0.1 M. Isolated yields after chromatographic purification. Ee determined by HPLC analysis.

Gram scale synthesis and product derivatization. The preparation of **3aa** was accomplished on gram-scale (3.0 mmol) demonstrating the robustness and scalability of the hydrophosphinylation protocol. Under the standard conditions, 2-azadiene **1a** coupled smoothly with diphenylphosphine oxide **2a** to provide 1.12 g of **3aa** in 91% isolated yield and 98% ee (Scheme 5a). These values are very close to those achieved on 0.4 mmol scale (95% yield, 98% ee, Scheme 3). The hydrolysis of **3aa** was conducted by adding 1N HCl in an ice-water bath with stirring at room temperature for 1 h. Neutralization with 1N NaOH successfully afforded α-aminophosphine oxide **4aa** as a white solid in 96% isolated yield with 98% ee (Scheme 5b). The abovementioned experiments establish the potential of the hydrophosphinylation protocol developed herein for applications in organic synthesis.

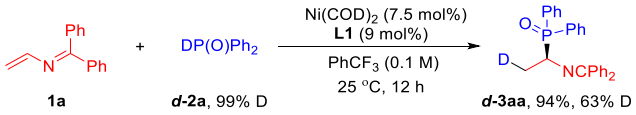
In order to demonstrate the synthetic utility of our method toward drug-like molecules, we carried out a two-step transformation to synthesize phospholeucine, an effective inhibitor of leucine aminopeptidase.[31] Commercially available diethylphosphite **2t** reacted smoothly with the substrate **1n** under otherwise identical conditions, providing the corresponding product **3nt** in 58% isolated yield with 91% ee. Next, 10 N HCl was added slowly to **3nt** in an ice-water bath followed by reflux at 110 °C for 20 h. The phospholeucine was obtained in 95% yield (Scheme 5c).

Scheme 5. Gram-scale synthesis of 3aa, product hydrolysis, and synthesis of phospholeucine.



Deuterium labeling experiment. To obtain further information on this transformation, we employed a deuterium-labeling experiment with 2-azadiene **1a** with D-phosphine oxide ***d*-2a** under the standard reaction conditions. This experiment afforded ***d*-3aa** with 63% yield of product deuterated at C1 (Scheme 6) which is comparable with the results of 51–80% deuterium in previous works deuteration studies.[22,23,32] A ^{2}H NMR experiment was conducted to support deuteration tests, and only a single deuterium was found in each product by MS, suggesting that the insertion step is irreversible (see Supporting Information for full details).

Scheme 6. Deuterium labeling.



Based on the above experiment and previous works on hydrofunctionalizations of unsaturated substrates,[33] a working mechanism for the nickel catalyzed hydrophosphinylation of 2-azadienes is presented (Figure 1). The Ni(0) precatalyst undergoes ligand substitution with the bisphosphine to form the chiral Ni^0 complex **I**. The enantioenriched Ni^0 complex **I** undergoes oxidative addition of the P–H bond, to give **II** as has been demonstrated by García and coworkers[34] in the hydrophosphonation of alkynes and as observed in many other transition metal complexes as summarized by Glueck.[35] Binding of the 2-azadiene **1a** generated the 2-azadiene-complex **III**. The 2-azadiene undergoes insertion into the Ni–H bond at the least hindered site to form the delocalized 2-azaallyl anion, Ni(2-azaallyl) intermediate **IV**. It is not clear if this intermediate is η^1- or η^3-bound. Reductive elimination then takes place at the least hindered carbon, preserving the conjugated benzophenone imine **3**.

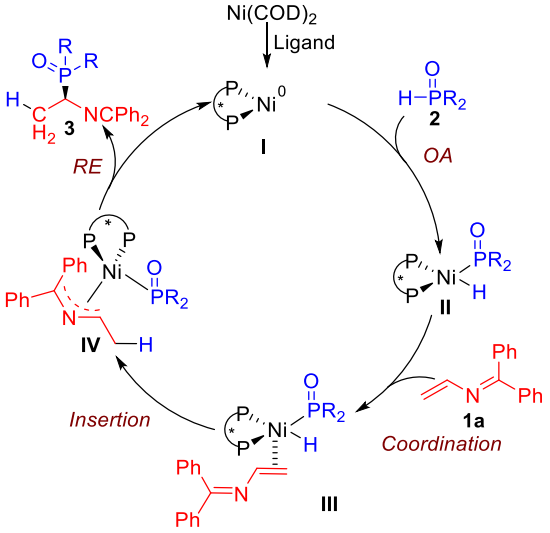


Figure 1. Proposed Mechanism.

3. CONCLUSION

In summary, we have successfully developed a nickel-catalyzed chemo-, regio- and enantioselective hydrophosphinylation of 2-azadienes with H-phosphine oxides, providing an efficient and mild approach for the synthesis of enantioenriched α-aminophosphine oxides and related derivatives. A wide range of functionalized H-phosphine

oxides and 2-azadienes can be employed to afford products in this unique nickel catalyzed process with good yields and high enantioselectivities (46 examples, up to 96% yield and 99% ee). The potential synthetic utility of this chemistry has been demonstrated by the gram scale synthesis and facile hydrolysis of the products. The proposed mechanism consists of a key oxidative addition of the H-phosphine oxide, Ni–H insertion into the olefin to give the 2-azaallyl anion, and P–C reductive elimination. Efforts are underway to expand the synthetic utility of the 2-azaallyl intermediates in enantioselective C–element bond-forming reactions to afford functionalized amines.

ASSOCIATED CONTENT

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Notes
The authors declare no competing financial interest.

Supporting Information
The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.0c0xxxx.

General procedures for the enantioselective hydrophosphinylation of 2-azadienes, condition optimization, characterization of new compounds, copies of NMR spectra, and HPLC traces (PDF)
X-ray data of **3an** (CCDC 2254462) (CIF)
X-ray data of **3ta** (CCDC 2256709) (CIF)

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REFERENCES

(1) (a) Lacbay, C. M.; Mancuso, J.; Lin, Y.-S.; Bennett, N.; Götte, M.; Tsantrizos, Y. S. Modular Assembly of Purine-like Bisphosphonates as Inhibitors of HIV-1 Reverse Transcriptase. *J. Med. Chem.* **2014,** *57*, 7435−7449. (b) Horsman, G. P.; Zechel, D. L. Phosphonate Biochemistry. *Chem. Rev.* **2017,** *117*, 5704−5783.
(2) Moonen, K.; Laureyn, I.; Stevens, C. V. Synthetic Methods for Azaheterocyclic Phosphonates and Their Biological Activity. *Chem. Rev.* **2004,** *104*, 6177−6215.
(3) Methot, J. L.; Roush, W. R. Nucleophilic Phosphine Organocatalysis. *Adv. Synth. Catal.* **2004,** *346*, 1035–1050.
(4) Ni, H.; Chan, W.-L.; Lu, Y. Phosphine-Catalyzed Asymmetric Organic Reactions. *Chem. Rev.* **2018,** *118*, 9344−9411.
(5) Dutartre, M.; Bayardon, J.; Jugé, S. Applications and Stereoselective Syntheses of P-Chirogenic Phosphorus Compounds. *Chem. Soc. Rev.* **2016,** *45*, 5771−5794.
(6) (a) Leeuwen, P. W. N. M. V.; Kamer, P. C. J.; Reek, J. N. H.; Dierkes, P. Ligand Bite Angle Effects in Metal-catalyzed C−C Bond Formation. *Chem. Rev.* **2000,** *100*, 2741−2769. (b) Tang, W.; Zhang, X. New Chiral Phosphorus Ligands for Enantioselective Hydrogenation. *Chem. Rev.* **2003,** *103*, 3029−3069.
(7) Carroll, M. P.; Guiry, P. J. P,N Ligands in Asymmetric Catalysis. *Chem. Soc. Rev.* **2014,** *43*, 819–833.
(8) (a) Smith, III, A. B.; Yager, K. M.; Taylor, C. M. Enantioselective Synthesis of Diverse α-Amino Phosphonate Diesters. *J. Am. Chem. Soc.* **1995,** *117*, 10879–10888. (b) Grembecka, J.; Mucha, A.; Cierpicki, T.; Kafarski, P. The Most Potent Organophosphorus Inhibitors of Leucine Aminopeptidase. Structure-Based Design, Chemistry, and Activity. *J. Med. Chem.* **2003,** *46*, 2641−2655. (c) Conway, S. J.; Miller, G. J. Biology-Enabling Inositol Phosphates, Phosphatidylinositol Phosphates and Derivatives. *Nat. Prod. Rep.* **2007,** *24*, 687–707.
(9) Qian, Y.; Dai, Q.; Li, Z.; Liu, Y.; Zhang, J. *O*-Phosphination of Aldehydes/Ketones toward Phosphoric Esters: Experimental and Mechanistic Studies. *Org. Lett.* **2020,** *22*, 4742−4748.
(10) (a) Pettersen, D.; Marcolini, M.; Bernardi, L.; Fini, F.; Herrera, R. P.; Sgarzani, V.; Ricci, A. Direct Access to Enantiomerically Enriched α-Amino Phosphonic Acid Derivatives by Organocatalytic Asymmetric Hydrophosphonylation of Imines. *J. Org. Chem.* **2006,** *71*, 6269−6272. (b) Abell, J. P.; Yamamoto, H. Catalytic Enantioselective Pudovik Reaction of Aldehydes and Aldimines with Tethered Bis(8-quinolinato) (TBOx) Aluminum Complex. *J. Am. Chem. Soc.* **2008,** *130*, 10521–10523.
(11) (a) Fields, E. K. The Synthesis of Esters of Substituted Amino Phosphonic Acids. *J. Am. Chem. Soc.* **1952,** *74*, 1528−1531. (b) Manabe, K.; Kobayashi, S. Facile Synthesis of α-Amino Phosphonates in Water Using a Lewis Acid-Surfactant-Combined Catalyst. *Chem. Commun.* **2000**, 669–670. (c) Tibhe, G. D.; Lagunas-Rivera, S.; Vargas-Díaz, E.; García-Barradas, O.; Ordoñez, M. Uncatalyzed One-Pot Diastereoselective Synthesis of α-Amino Phosphonates Under Solvent-Free Conditions. *Eur. J. Org. Chem.* **2010**, *34*, 6573–6581.
(12) Huang, W.-B.; Qiu, L.-Q.; Ren, F.-Y.; He, L.-N. Facile Synthesis of α-Aminophosphine Oxides from Diarylphosphine Oxides, Arynes and Formamides. *Chem Commun.* **2021,** *57*, 9578–9581.
(13) (a) Genet, J. P.; Uzifl, J.; Juge, S. Synthesis of α-aminophosphonic acids by Pd(0) alkylation of diethyl aminomethylphosphonate Schiff Bases. *Tetrahedron Lett.* **1988,**

29, 4559–4562. (b) Cheng, M.-X.; Ma, R.-S.; Yang, Q.; Yang, S.-D. Chiral Bronsted Acid Catalyzed Enantioselective Phosphonylation of Allylamine via Oxidative Dehydrogenation Coupling. *Org. Lett.* **2016,** *18*, 3262−3265. (c) Mao, L.-L.; Li, C.-C.; Yang, Q.; Cheng, M.-X.; Yang, S.-D. One-pot Synthesis of α-Aminophosphonates via a Cascade Sequence of Allylamine Isomerization/Hydrophosphonylation. *Chem. Commun.* **2017,** *53*, 4473−4476. (d) Lin, B.; Shi, S.; Lin, R.; Cui, Y.; Fang, M.; Tang, G.; Zhao, Y. Cobalt-Catalyzed Oxidative C(sp^3)−H Phosphonylation for α-Aminophosphonates via C(sp^3)−H/P(O)−H Coupling. *J. Org. Chem.* **2018,** *83*, 6754−6761. (e) Huang, Q.; Dong, K.; Bai, W.; Yi, D.; Ji, J. X.; Wei, W. TEMPO-Catalyzed Aminophosphinoylation of Ethers via Tandem C(sp^3)−H and C(sp^3)−O Bond Cleavage. *Org. Lett.* **2019,** *21*, 3332−3336. (f) Wang, J.; Deng, G.; Liu, C.; Chen, Z.; Yu, K.; Chen, W.; Zhang, H.; Yang, X. Transition Metal-Free Synthesis of α-Aminophosphine Oxides through C(sp^3)−P Coupling of 2-Azaallyls. *Adv. Synth. Catal.* **2020,** *362*, 2268–2273.

(14) McDonald, S. L.; Wang, Q. Copper-Catalyzed α-Amination of Phosphonates and Phosphine Oxides: A Direct Approach to a-Amino Phosphonic Acids and Derivatives. *Angew. Chem. Int. Ed.* **2014,** *53*, 1867–1871.

(15) (a) Guo, J.; Cheng, Z.; Chen, J.; Chen, X.; Lu, Z. Iron- and Cobalt-Catalyzed Asymmetric Hydrofunctionalization of Alkenes and Alkynes. *Acc. Chem. Res.* **2021,** *54*, 2701−2716. (b) Zhang, X.-W.; Zhu, M.-H.; Zeng, H.-X.; Li, Q.-Y.; Liu, W.-B. Precatalyst-Enabled Selectivity: Enantioselective NiH-Catalyzed *anti*-Hydrometalative Cyclization of Alkynones to *Endo*- and Heterocyclic Allylic Alcohols. *Angew. Chem. Int. Ed.* **2021,** *60*, 27225–27229. (c) Gao, D.-W.; Gao, Y.; Shao, H.; Qiao, T.-Z.; Wang, X.; Sanchez, B. B.; Chen, J. S.; Liu, P.; Engle, K. M. Cascade CuH-Catalysed Conversion of Alkynes into Enantioenriched 1,1-Disubstituted Products. *Nat. Catal.* **2020,** *3*, 23–29. (d) Jin, S.; Liu, K.; Wang, S.; Song, Q. Enantioselective Cobalt-Catalyzed Cascade Hydrosilylation and Hydroboration of Alkynes to Access Enantioenriched 1,1-Silylboryl Alkanes. *J. Am. Chem. Soc.* **2021,** *143*, 13124−13134. (e) Dai, Q.; Liu, L.; Qian, Y.; Li, W.; Zhang, J. Construction of P-Chiral Alkenylphosphine Oxides through Highly Chemo-, Regio-, and Enantioselective Hydrophosphinylation of Alkynes. *Angew. Chem. Int. Ed.* **2020,** *59*, 20645–20650.

(16) (a) Crossley, S. W. M.; Obradors, C.; Martinez, R. M.; Shenvi, R. A. Mn-, Fe-, and Co-Catalyzed Radical Hydrofunctionalizations of Olefins. *Chem. Rev.* **2016,** *116*, 8912−9000. (b) Shigehisa, H.; Hayashi, M.; Ohkawa, H.; Suzuki, T.; Okayasu, H.; Mukai, M.; Yamazaki, A.; Kawai, R.; Kikuchi, H.; Satoh, Y.; Fukuyama, A.; Hiroya, K. Catalytic Synthesis of Saturated Oxygen Heterocycles by Hydrofunctionalization of Unactivated Olefins: Unprotected and Protected Strategies. *J. Am. Chem. Soc.* **2016,** *138*, 10597−10604. (c) Czyz, M. L.; Taylor, M. S.; Horngren, T. H.; Polyzos, A. Reductive Activation and Hydrofunctionalization of Olefins by Multiphoton Tandem Photoredox Catalysis. *ACS Catal.* **2021,** *11*, 5472−5480. (d) Luo, Y.; Ma, Y.; Hou, Z. α-C—H Alkylation of Methyl Sulfides with Alkenes by a Scandium Catalyst. *J. Am. Chem. Soc.* **2018,** *140*, 114−117.

(17) (a) Perry, G. J. P.; Jia, T.; Procter, D. J. Copper-Catalyzed Functionalization of 1,3-Dienes: Hydrofunctionalization, Borofunctionalization, and Difunctionalization. *ACS Catal.* **2019,** *10*, 1485−1499. (b) Flaget, A.; Zhang, C.; Mazet, C. Ni-Catalyzed Enantioselective Hydrofunctionalizations of 1,3-Dienes. *ACS Catal.* **2022,** *12*, 15638−15647. (c) Chen, X. W.; Zhu, L.; Gui, Y. Y.; Jing, K.; Jiang, Y. X.; Bo, Z. Y.; Lan, Y.; Li, J.; Yu, D. G. Highly Selective and Catalytic Generation of Acyclic Quaternary Carbon Stereocenters via Functionalization of 1,3-Dienes with CO_2. *J. Am. Chem. Soc.* **2019,** *141*, 18825−18835. (d) Yang, S.-Q.; Han, A.-J.; Liu, Y.; Tang, X.-Y.; Lin, G.-Q.; He, Z.-T. Catalytic Asymmetric Hydroalkoxylation and Formal Hydration and Hydroaminoxylation of Conjugated Dienes. *J. Am. Chem. Soc.* **2023,** *145*, 3915–3925.

(18) (a) Blieck, R.; Taillefer, M.; Monnier, F. Metal-Catalyzed Intermolecular Hydrofunctionalization of Allenes: Easy Access to Allylic Structures via the Selective Formation of C−N, C−C, and C−O Bonds. *Chem. Rev.* **2020,** *120*, 13545−13598. (b) El-Sepelgy, O.; Brzozowska, A.; Sklyaruk, J.; Jang, Y. K.; Zubar, V.; Rueping, M. Cooperative Metal-Ligand Catalyzed Intramolecular Hydroamination and Hydroalkoxylation of Allenes Using a Stable Iron Catalyst. *Org. Lett.* **2018,** *20*, 696−699. (c) Jung, M. S.; Kim, W. S.; Shin, Y. H.; Jin, H. J.; Kim, Y. S.; Kang, E. J. Chemoselective Activities of Fe(III) Catalysts in the Hydrofunctionalization of Allenes. *Org. Lett.* **2012,** *14*, 6262–6265.

(19) (a) Hu, M.-Y.; Lian, J.; Sun, W.; Qiao, T.-Z.; Zhu, S.-F. Iron-Catalyzed Dihydrosilylation of Alkynes: Efficient Access to Geminal Bis(silanes). *J. Am. Chem. Soc.* **2019,** *141*, 4579−4583. (b) Zhang, Y.-D.; Li, X.-Y.; Mo, Q.-K.; Shi, W.-B.; Zhao, J.-B.; Zhu, S.-F. Highly Regioselective Cobalt-Catalyzed Hydroboration of Internal Alkynes. *Angew. Chem. Int. Ed.* **2022,** *61*, e202208473.

(20) (a) Zhou, X. L.; Yang, F.; Sun, H. L.; Yin, Y. N.; Ye, W. T.; Zhu, R. Cobalt-Catalyzed Intermolecular Hydrofunctionalization of Alkenes: Evidence for a Bimetallic Pathway. *J. Am. Chem. Soc.* **2019,** *141*, 7250−7255. (b) Zhao, W.; Lu, H.-X.; Zhang, W.-W.; Li, B.-J. Coordination Assistance: A Powerful Strategy for Metal-Catalyzed Regio- and Enantioselective Hydroalkynylation of Internal Alkenes. *Acc. Chem. Res.* **2023,** *56*, 308−321. (c) Xi, Y.; Hartwig, J. F., Diverse Asymmetric Hydrofunctionalization of Aliphatic Internal Alkenes through Catalytic Regioselective Hydroboration. *J. Am. Chem. Soc.* **2016,** *138*, 6703−6706. (d) Sun, X.-Y.; Yao, B.-Y.; Xuan, B.; Xiao, L.-J.; Zhou, Q.-L. Recent Advances in Nickel-catalyzed Asymmetric Hydrofunctionalization of Alkenes. *Chem. Catal.* **2022,** *2*, 3140–3162.

(21) Adamson, N. J.; Malcolmson, S. J. Catalytic Enantio- and Regioselective Addition of Nucleophiles in the Intermolecular Hydrofunctionalization of 1,3-Dienes. *ACS Catal.* **2019,** *10*, 1060−1076.

(22) Nie, S.-Z.; Davison, R. T.; Dong, V. M. Enantioselective Coupling of Dienes and Phosphine Oxides. *J. Am. Chem. Soc.* **2018,** *140*, 16450−16454.

(23) Yang, Z.; Wang, J. Enantioselective Palladium-Catalyzed Hydrophosphinylation of Allenes with Phosphine Oxides: Access to Chiral Allylic Phosphine Oxides. *Angew. Chem. Int. Ed.* **2021,** *60*, 27288–27292.

(24) (a) Duan, S.; Deng, G.; Zi, Y.; Wu, X.; Tian, X.; Liu, Z.; Li, M.; Zhang, H.; Yang, X.; Walsh, P. J. Nickel-Catalyzed Enantioselective Vinylation of Aryl 2-Azaallyl Anions. *Chem. Sci.* **2021,** *12*, 6406–6412. (b) Li, M.; Berritt, S.; Matuszewski, L.; Deng, G.; Pascual-Escudero, A.; Panetti, G. B.; Poznik, M.; Yang, X.; Chruma, J. J.; Walsh, P. J. Transition-Metal-Free Radical $C(sp^3)$−$C(sp^2)$ and $C(sp^3)$−$C(sp^3)$ Coupling Enabled by 2-Azaallyls as Super-Electron-Donors and Coupling-Partners. *J. Am. Chem. Soc.* **2017,** *139*, 16327−16333. (c) Deng, G.; Li, M.; Yu, K.; Liu, C.; Liu, Z.; Duan, S.; Chen, W.; Yang, X.; Zhang, H.; Walsh, P. J. Synthesis of Benzofuran Derivatives through Cascade Radical Cyclization/Intermolecular Coupling of 2-Azaallyls. *Angew.Chem. Int. Ed.* **2019,** *58*, 2826 –2830. (d) Deng, G.; Duan, S.; Wang, J.; Chen, Z.; Liu, T.; Chen, W.; Zhang, H.; Yang, X.; Walsh, P. J. Transition-Metal-Free Allylation of 2-Azaallyls with Allyl Ethers through Polar and Radical Mechanisms. *Nat. Commun.* **2021,** *12*, 3860.

(25) (a) Peng, Y.; Han, C.; Luo, Y.; Li, G.; Huo, X.; Zhang, W., Nickel/Copper-Cocatalyzed Asymmetric Benzylation of Aldimine Esters for the Enantioselective Synthesis of α-Quaternary Amino Acids. *Angew. Chem. Int. Ed.* **2022,** *61*, e202203448. (b) Matsumoto, Y.; Sawamura, J.; Murata, Y.; Nishikata, T.; Yazaki, R.; Ohshima, T. Amino Acid Schiff Base Bearing Benzophenone Imine As a Platform for Highly Congested Unnatural α-Amino Acid Synthesis. *J. Am. Chem. Soc.* **2020,** *142*, 8498–8505.

(26) Tang, S.; Zhang, X.; Sun, J.; Niu, D.; Chruma, J. J. 2-Azaallyl Anions, 2-Azaallyl Cations, 2-Azaallyl Radicals, and Azomethine Ylides. *Chem. Rev.* **2018,** *118*, 10393−10457.

(27) (a) Zhou, P.; Shao, X.; Malcolmson, S. J. A Diastereodivergent and Enantioselective Approach to *syn*- and *anti*-Diamines: Development of 2-Azatrienes for Cu-Catalyzed Reductive Couplings with Imines That Furnish Allylic Amines. *J. Am. Chem. Soc.* **2021,** *143*, 13999−14008. (b) Daniel, P. E.; Onyeagusi, C. I.; Ribeiro, A. A.; Li, K.; Malcolmson, S. J. Palladium-Catalyzed Synthesis of α-Trifluoromethyl Benzylic Amines via Fluoroarylation of *gem*-Difluoro-2-azadienes Enabled by Phosphine-Catalyzed Formation of an Azaallyl-Silver Intermediate. *ACS Catal.* **2019,** *9*, 205−210.

(28) Li, K.; Shao, X.; Tseng, L.; Malcolmson, S. J. 2-Azadienes as Reagents for Preparing Chiral Amines: Synthesis of 1,2-Amino Tertiary Alcohols by Cu-Catalyzed Enantioselective Reductive Couplings with Ketones. *J. Am. Chem. Soc.* **2018,** *140*, 598−601.

(29) Shao, X.; Li, K.; Malcolmson, S. J. Enantioselective Synthesis of *anti*-1,2-Diamines by Cu-Catalyzed Reductive Couplings of Azadienes with Aldimines and Ketimines. *J. Am. Chem. Soc.* **2018,** *140*, 7083−7087.

(30) Duan, S.; Du, Y.; Wang, L.; Tian, X.; Zi, Y.; Zhang, H.; Walsh, P. J.; Yang, X. Catalytic Chemo- and Regioselective Radical Carbocyanation of 2-Azadienes for the Synthesis of α-Amino Nitriles. *Angew. Chem. Int. Ed.* **2023,** *62*, e202300605.

(31) (a) Stamper, C.; Bennett, B.; Edwards, T.; Holz, R. C.; Ringe, D.; Petsko, G. Inhibition of the Aminopeptidase from Aeromonas proteolytica by L-Leucinephosphonic Acid. Spectroscopic and Crystallographic Characterization of the Transition State of Peptide Hydrolysis. *Biochemistry* **2001,** *40*, 7035–7046. (b) Reich, D.; Noble, A.; Aggarwal, V. K. Facile Conversion of α-Amino Acids into α-Amino Phosphonates by Decarboxylative Phosphorylation using Visible-Light Photocatalysis. *Angew. Chem. Int. Ed.* **2022**, *61*, e202207063.

(32) (a) Li, Q.; Wang, Z.; Dong, V. M.; Yang, X.-H. Enantioselective Hydroalkoxylation of 1,3-Dienes via Ni-Catalysis. *J. Am. Chem. Soc.* **2023,** *145*, 3909−3914. (b) Long, j.; Li, Y.; Zhao, W.; Yin, G. Nickel/Brønsted Acid Dual-Catalyzed Regio- and Enantioselective Hydrophosphinylation of 1,3-Dienes: Access to Chiral Allylic Phosphine Oxides. *Chem. Sci.* **2022,** *13*, 1390–1397.

(33) (a) Sadow, A. D.; Haller, I.; Fadini, L.; Togni, A. Nickel(II)-Catalyzed Highly Enantioselective Hydrophosphination of Methacrylonitrile. *J. Am. Chem. Soc.* **2004,** *126*, 14704−14705. (b) Ortial, S.; Fisher, H. C.; Montchamp, J.-L. Hydrophosphinylation of Unactivated Terminal Alkenes Catalyzed by Nickel Chloride. *J. Org. Chem.* **2013,** *78*, 6599–6608. (c) Liu, X.-T.; Han, X.-Y.; Wu, Y.; Sun, Y.-Y.; Gao, L.; Huang, Z.; Zhang, Q.-W. Ni-Catalyzed Asymmetric Hydrophosphination of Unactivated Alkynes. *J. Am. Chem. Soc.* **2021,** *143*, 11309−11316.

(34) (a) Islas, R. E.; García, J. J. Hydrophosphonylation of Alkynes with Trialkyl Phosphites Catalyzed by Nickel. *ChemCatChem* **2017,** *9*, 1–8. (b) Islas, R. E.; García, J. J. Nickel-Catalyzed Hydrophosphonylation and Hydrogenation of Aromatic Nitriles Assisted by Lewis Acid. *ChemCatChem* **2019,** *11*, 1337–1345.

(35) Glueck, D. S. Metal-Catalyzed P−C Bond Formation via P−H Oxidative Addition: Fundamentals and Recent Advances. *J. Org. Chem.* **2020,** *85*, 14276−14285.

Table of Contents (TOC)