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Intermolecular Enantiospecific Reductive C–P Bond Reorganization of Atropisomeric Bisphosphines with Alkynes via Nickel Catalysis

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Abstract

Selective C–P bond activation of bisphosphines remains a major challenge in organophosphorus chemistry. Current strategies are largely restricted to intramolecular cyclization or require pre-activated substrates, while one-step intermolecular enantiospecific C–P functionalization of axially chiral bisphosphines has not been realized. Herein we report the first direct, intermolecular, enantiospecific reductive C–P bond reorganization of atropisomeric bisphosphines with alkynes via alcohol-assisted nickel catalysis. This single-step protocol provides rapid and divergent access to chiral P/olefin hybrid ligands and vinyl phosphine derivatives (67 examples in total, with ≥99% ee for the majority). The transformation proceeds via in situ generation of an alkenylalkoxy nickel species, which undergoes an unconventional reductive elimination involving a dative P–Ni interaction to deliver a phosphonium intermediate, thereby activating the otherwise inert C–P bond. This late-stage editing not only constitutes a versatile platform for expediting ligand library assembly and constructing P-containing bioactive molecules, but also establishes a new mechanistic paradigm for C–P bond functionalization.

Introduction

Phosphorus is ubiquitous in bioactive molecules and widely applied in industrial, agricultural, and pharmaceutical chemistry.[1,2] In particular, organophosphorus compounds serve as essential ligands or organocatalysts, enabling fine control over selectivity and reactivity.[3-10] Thus, developing efficient and precise methods for constructing functionalized organophosphorus compounds is of central importance. Compared with multistep de novo approaches,[11,12] late-stage C–P functionalization of pre-existing phosphorus platform molecules offers a more streamlined and efficient route to structural diversity (Fig. 1a, left),[13-15] while avoiding air-sensitive and toxic halophosphines or hydrophosphines. This strategy has therefore attracted growing interest.

Considerable progress has been made in transition-metal-catalyzed C–P functionalization of monophosphines through rational substrate design and novel catalytic systems (Fig. 1a, right).[16-31] In contrast, selective C–P activation of diphosphines remains far less explored. Early efforts were largely limited to stoichiometric metal-mediated cleavage, precluding catalysis.[32-35] This difficulty stems from two factors: the strong coordination of diphosphines to metals, which forms more stable, catalytically inert complexes, and the presence of multiple C–P bonds of similar strength, which complicates selectivity control. Despite these challenges, Morandi[36] and Tobisu[37,38] achieved a breakthrough in intramolecular dephosphinative cyclization of biaryl bisphosphines using aryl halides for in situ C–P activation (Fig 1b, left), with the second phosphorus atom serving as both a directing group and an internal participant. However, this method favors planar phosphorus heterocycles and is not amenable to chiral phosphine synthesis. In 2022, Wang's group realized an enantiospecific intermolecular reduction of (*R*)-BINAP via substrate pre-activation, affording (*R*)-H-MOP in two steps (Fig 1b, right).[39] Nevertheless, a general, one-step, intermolecular

enantiospecific C–P functionalization of diphosphines remains unavailable.

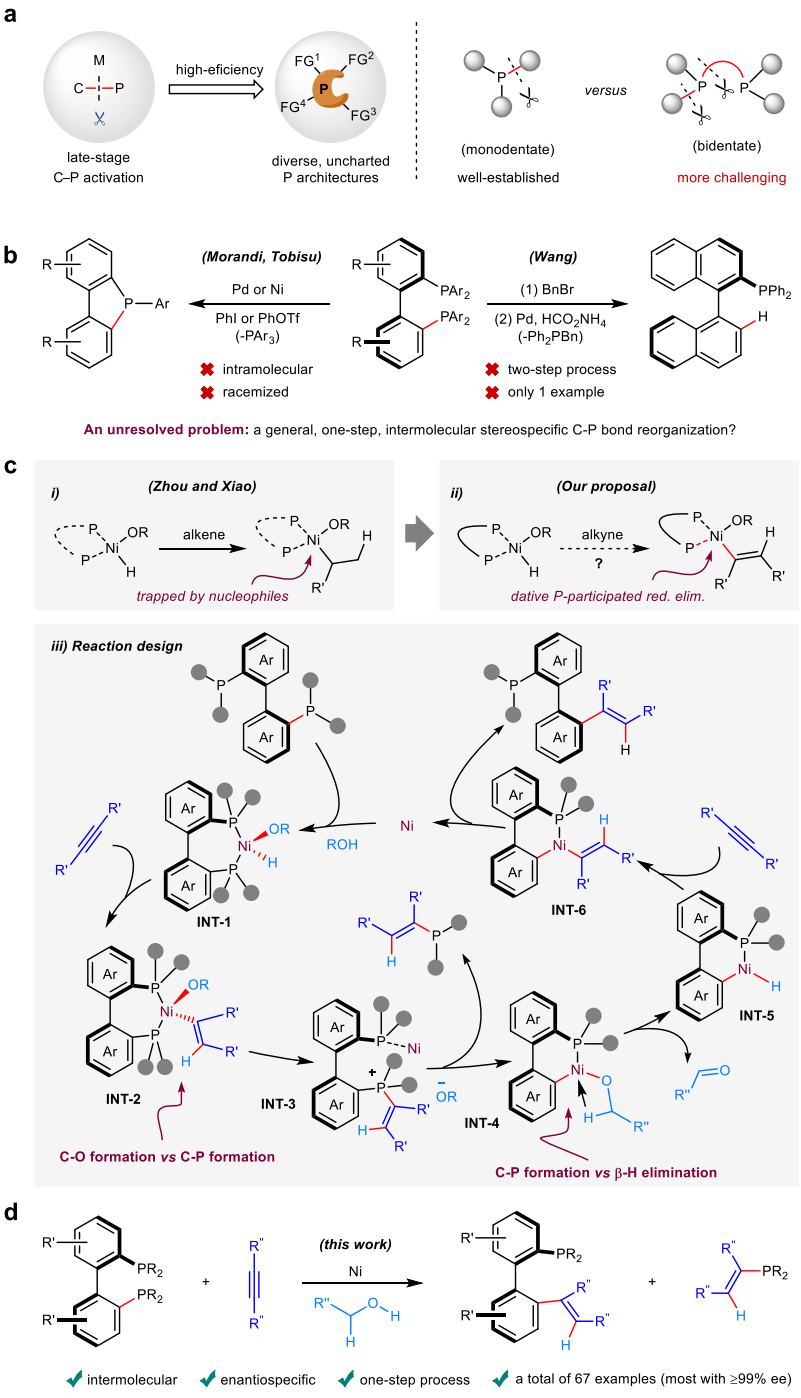
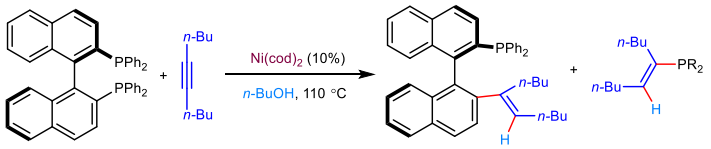


Fig. 1 Transition-metal-catalyzed C–P activation. a, State of the art in C–P bond activation. **b**, Reported C–P bond activation of atropisomeric bisphosphines. **c**, Research conception and reaction design. **d**, Intermolecular enantiospecific reductive C–P bond reorganization via one-step process (this work).

In our search for a viable solution, we noted that Zhou, Xiao, and co-workers realized the hydroarylation of alkenes using alcohols as both solvent and hydrogen donor with a nickel–phosphine catalyst (Fig. 1c, i).[40] Since then, various nucleophiles were developed to trap the key alkylalkoxy nickel species, enabling diverse transformations.[41] Based on these studies, we designed a strategy involving an alkenylalkoxy nickel intermediate generated from alkynes and alcohols (Fig. 1c, ii). Given the poor facility of C–O bond formation via direct reductive elimination of a covalent alkoxy group under nickel catalysis (Fig. 1c, iii), we anticipated that a non-classical reductive elimination involving a dative phosphorus atom would instead form a C–P bond (**INT-2** → **INT-3**),[42] giving a quaternary phosphonium salt (**INT-3**). Assisted by the second phosphorus atom, **INT-3** then undergoes P(III)-directed C–P cleavage to release vinyl phosphine and form **INT-4**. The presence of β-H atom in the H donor suppresses direct reductive elimination to form C–P bond[36-38] and promotes rapid β-hydride elimination to generate Ni–H species **INT-5**. A second alkyne insertion into **INT-5**, followed by reductive elimination, thereby enantiospecifically affords the hydroarylation product and regenerates the nickel catalyst.

Guided by this rationale, we report the first alcohol-assisted, nickel-catalyzed intermolecular enantiospecific reductive C–P bond reorganization between atropisomeric bisphosphines and alkynes in a one-step process (Fig. 1d). This late-stage phosphorus-framework editing rapidly delivers structurally diverse chiral P/olefin hybrid ligands and vinyl phosphine derivatives (67 examples in total, with ≥99% ee for the majority), providing efficient access to broad ligand libraries and P-containing bioactive molecules while establishing a new mechanistic paradigm for C–P bond functionalization.



1, *99.5% ee* **2** **3**

Entry	Deviation from the standard conditions	Yield (**2**/**3**, %)	Ee (**2**, %)
1	***none***	**>99/96**	**>99**
2	w/o $Ni(cod)_2$	0/0	---
3	$Ni(cod)_2$ replaced by $Pd_2(dba)_3$	0/0	---
4	CoI_2/Zn powder	0/0	---
5	$FeCl_3$/Zn powder	0/0	---
6	NiI_2	0/0	---
7	NiI_2/Mn powder	20/10	>99
8	*n*-BuOH replaced by MeOH (1 mL)	20/8	98
9	EtOH (1 mL)	96/92	98
10	*n*-PrOH (1 mL)	96/90	98
11	*i*-PrOH (1 mL)	94/92	98
12	Toluene, THF, DMF or Anisole	0/0	---
13	EtOH (1.0 eq)/toluene	20/20	92
14	BnOH (1.0 eq)/toluene	32/24	92
15	*i*-PrOH (1.0 eq)/toluene	20/20	86
16	*i*-PrOH (5.0 eq)/toluene	24/28	86
17	*i*-PrOH (20.0 eq)/toluene	40/60	90

Table 1. Reaction optimization. Reaction conditions: (*R*)-BINAP (0.1 mmol), 5-decyne (0.25 mmol), *n*-BuOH (1 mL) under N_2 for 12 h; all reactions were performed in sealed tubes. Yield was determined by ^1H NMR with CH_2Br_2 as the internal standard. Ee values of products were determined by chiral HPLC analysis.

Results

Reaction optimization. Given the commercial availability of (*R*)-BINAP (**1**) and 5-decyne, we selected them as model substrates to validate our hypothesis (Table 1). To our delight, using 10 mol% $Ni(cod)_2$ as the catalyst and *n*-butanol as the hydrogen donor at 110 °C for 12 h, the intermolecular C–P bond reorganization products **2** and **3** were obtained in nearly quantitative yields (entry 1, >99% and 96%, respectively), with product **2** showing complete stereospecificity (>99% ee). Control experiments confirmed the essential role of $Ni(cod)_2$, as no product was detected in its absence or when other metal catalysts were employed (entries 2–5). Air-stable Ni(II) precursors such as NiI_2 were also tested but proved inactive (entry 6); however, in situ reduction with Mn powder to generate

Ni(0) species restored catalytic activity, indicating that Ni(0) is the active species entering the catalytic cycle (entry 7). Solvent screening revealed that replacing *n*-butanol with methanol, ethanol, propanol, or isopropanol led to moderate decreases in both yield and enantiomeric excess (entries 8–11). As expected, aprotic solvents failed to afford the product in the absence of a hydrogen source (entry 12). Further variation of the hydrogen donor loading showed that reducing the amount of alcohol significantly lowered the yield (entries 13–17), highlighting that an excess of alcohol is crucial for efficient Ni–H formation.

Substrate scope for hydroarylation. Under the optimized conditions, we first examined the scope of chiral biaryl bisphosphines (Fig. 2, top). All products were oxidized to the corresponding phosphine oxides for characterization. (*R*)-BINAP derivatives reacted smoothly (**4**–**6**), giving 76–99% yields with >99% ee. Alkyl-substituted analogue gave a lower yield (35%) while retaining complete stereospecificity (**7**); this diminished reactivity is likely due to the stronger coordinating ability of alkylphosphines, which hampers catalyst dissociation and thus reduces overall activity. (*R*)-H_8-BINAP (**8**) afforded 88% yield with >99% ee. Other commercial chiral bisphosphines, including (*R*)-SYNPHOS (**9**), (*R*)-MeOBIPHEP (**10**), (*R*)-Garphos (**11**), and (*R*)-C_3-TunePhos (**12**), delivered the products in 78–99% yields with excellent stereospecificity (94% to >99% ee). (*R*)-Segphos and (*R*)-DIFLUORPHOS (**13** and **14**) reacted efficiently but suffered from substantial racemization (4% and 8% ee), likely due to low rotational barriers of the products. An achiral biaryl diphosphine gave the product in 92% yield (**15**). However, bisphosphines with wide natural bite angles (e.g., (*R*)-SDP, Xantphos, DPEphos, dppf; see Supplementary Figure 1) failed to react, presumably because the increased distance between the metal center and the reaction site hinders C–P bond cleavage.[43]

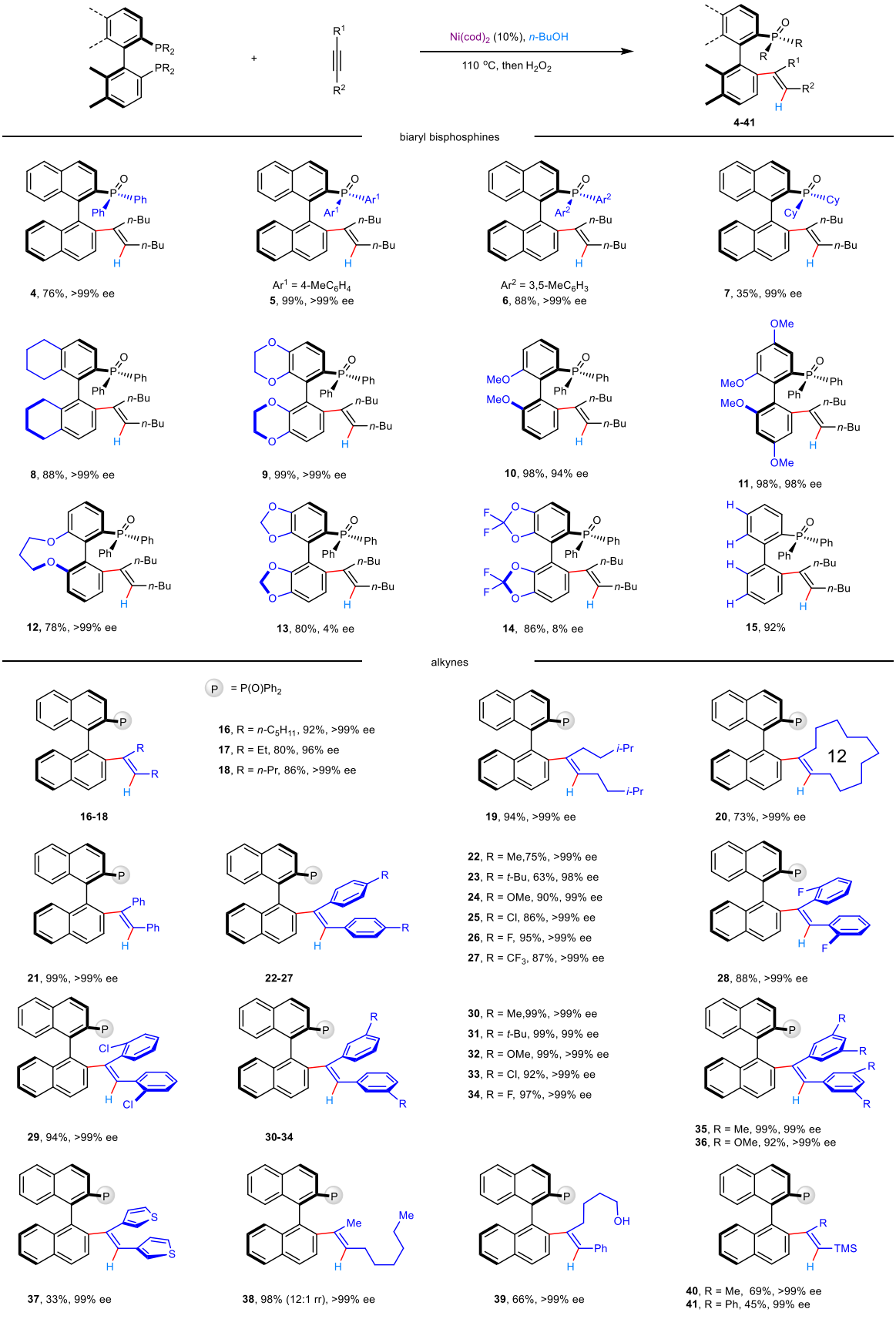


Fig. 2 Substrate scope for hydroarylation. Reaction conditions: bisphosphine (0.2 mmol), 5-decyne (0.5 mmol), *n*-BuOH (2.0 mL) under N_2 for 12 h in a sealed tube; For aryl-substituted

alkynes, a mixture of *n*-BuOH and toluene (v/v = 1:1) was used, and the reaction time was extended to 48 h; All yields refer to the isolated yields of the products after oxidation with H_2O_2. Enantiomeric excess (ee) values were determined by HPLC analysis.

We next examined the alkyne scope (Fig. 2, bottom). Symmetrical dialkyl alkynes (**16**–**19**) reacted smoothly (80–94% yield, 96% to >99% ee), and macrocyclic alkyne gave 73% yield with >99% ee (**20**). Diphenylacetylene (**21**) also showed high reactivity with only toluene as cosolvent to improve solubility. Both electron-donating and electron-withdrawing *para*-substituted diarylalkynes were well tolerated (**22**–**27**, 63–95% yield, with 98% to >99% ee). *Ortho*-fluoro and *ortho*-chloro derivatives (**28**,**29**) gave 88% and 94% yield with full stereospecificity, and *meta*-substituted analogues (**30**–**34**) afforded 92–99% yield with >99% ee. Multiply substituted diarylalkynes (**35**,**36**) delivered 99% and 92% yield with complete stereospecificity. A heterocyclic thiophene-containing alkyne (**37**) could also be accommodated, albeit with a diminished yield, which may be attributed to partial inhibition of reactivity by coordination of the sulfur atom to the nickel center. Finally, unsymmetrical alkynes were examined: 2-nonyne (**38**) gave high regioselectivity (12:1 rr), while substrates with greater steric differentiation (**39**–**41**) provided single regioisomers exclusively.

Substrate scope for hydrophosphination. Encouraged by the above results, we turned our attention to the substrate scope of alkyne hydrophosphination (Fig. 3). Using commercially available (±)-BINAP as a stable phosphorus source and alcohols as a hydrogen donor, we were able to efficiently access a diverse array of synthetically valuable vinyl phosphines. This strategy circumvents the need for highly volatile and sensitive P(III)–H compounds[44-46] or less accessible reagents such as $Ph_2P–PPh_2$ and $Ph_2P–SiR_3$,[47-49] which are typically required in conventional approaches. Under the optimized conditions, symmetrical linear dialkyl alkynes (**3**, **42**–**44**) reacted smoothly to give 67–85% yields. Branched isopropyl-substituted and cyclic internal alkynes (**45** and **46**) were also compatible, affording 53% and 85% yields, respectively. Diphenylacetylene (**47**) deli-

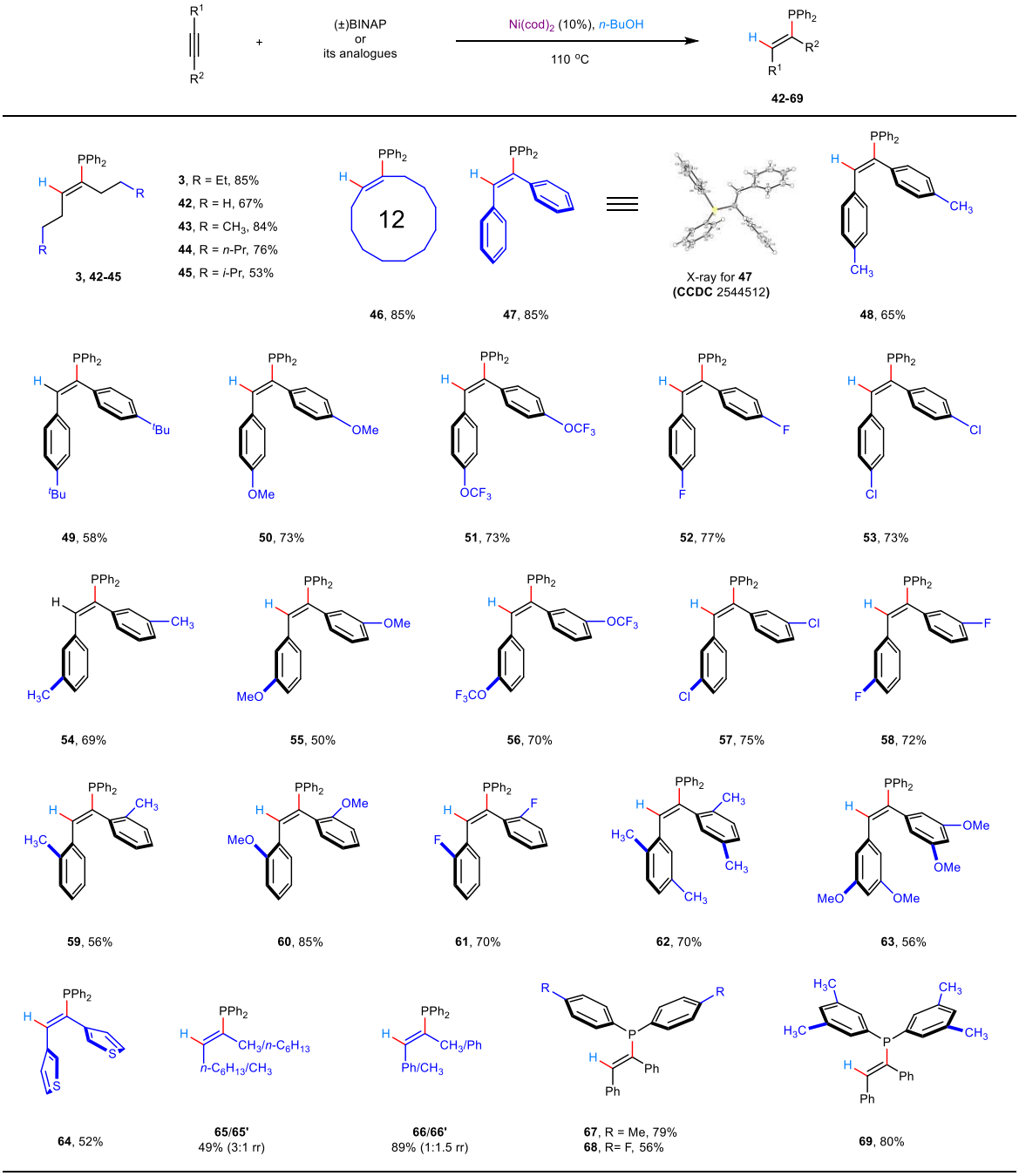


Fig. 3 Substrate scope for hydrophosphination. Reaction conditions: alkyne (0.5 mmol), (±)-BINAP or its analogues (0.2 mmol), *n*-BuOH (2.0 mL) under N_2 for 12 h in a sealed tube; For aryl-substituted alkynes, a mixture of *n*-BuOH and toluene (v/v = 1:1) was used, and the reaction time was extended to 48 h; All yields refer to the isolated yields of the products.

vered the product in 85% yield, and its structure was unambiguously confirmed by single-crystal X-ray diffraction. A systematic examination of substituent effects on diaryl alkynes revealed that both electron-donating (methyl, *tert*-butyl, methoxy, trifluoromethoxy) and electron-withdrawing (fluoro, chloro) groups at the para position were well tolerated (**48-53**, 58–77% yield).

Meta-substituted derivatives bearing methyl, methoxy, trifluoromethoxy, chloro, or fluoro groups also reacted smoothly (**54**–**58**), as did *ortho*-substituted analogues (**59**–**61**). Multi-substituted diaryl alkynes, including 1,2-bis(2,5-dimethylphenyl)ethyne and 1,2-bis(3,5-dimethoxyphenyl)ethyne, afforded the desired products in 70% and 56% yield, respectively (**62** and **63**). A heterocyclic thiophene-containing alkyne was also viable, albeit in 52% yield (**64**). Unsymmetrical alkynes were examined but exhibited poor regioselectivity (**65**/**65'** and **66**/**66'**). Finally, the electronic and steric effects on biaryl bisphosphines were probed: *para*-methyl, *para*-fluoro, and bulkier 3,5-dimethylphenyl substituents (**67**–**69**) were all compatible, providing 56–80% yields.

Reaction utility. To demonstrate the synthetic utility of this strategy, we performed gram-scale reactions without H_2O_2 protection (Fig. 4a). Through a single C–P bond editing step, inexpensive (*R*)-BINAP (**1**) was efficiently converted into a range of chiral phosphine/olefin hybrid ligands with tunable steric and electronic properties (**2** and **70**–**79**), outperforming the traditional four-step de novo synthesis.[50] These ligands readily formed stable complexes with $(Me_2S)AuCl$ (**80** and **81**), offering potential precatalysts for asymmetric transformations (Fig. 4b).[51] Notably, whereas classic bisphosphines such as (*R*)-BINAP were ineffective in palladium-catalyzed hydrosilylation of styrene **82**,[52] the newly derived ligands **2** and **79** delivered product **83** in high yield with excellent enantioselectivity (Fig. 4c). The hydroarylation products were amenable to further derivatization, including alkene reduction (**84**), chlorination (**85**), and ozonolysis (**86**), as well as P-centered amination (**87**), sulfuration (**88**), and selenation (**89**) (Fig. 4d, left). Similarly, the hydrophosphination product **3** could be scaled up to gram level (1.23g, 75% yield) and further elaborated into more complex phosphorus-containing building blocks (**90**–**96**) (Fig. 4d, right). The in vitro antibacterial activities of selected compounds are shown in Fig. 4e (see Supplementary Information for more deta-

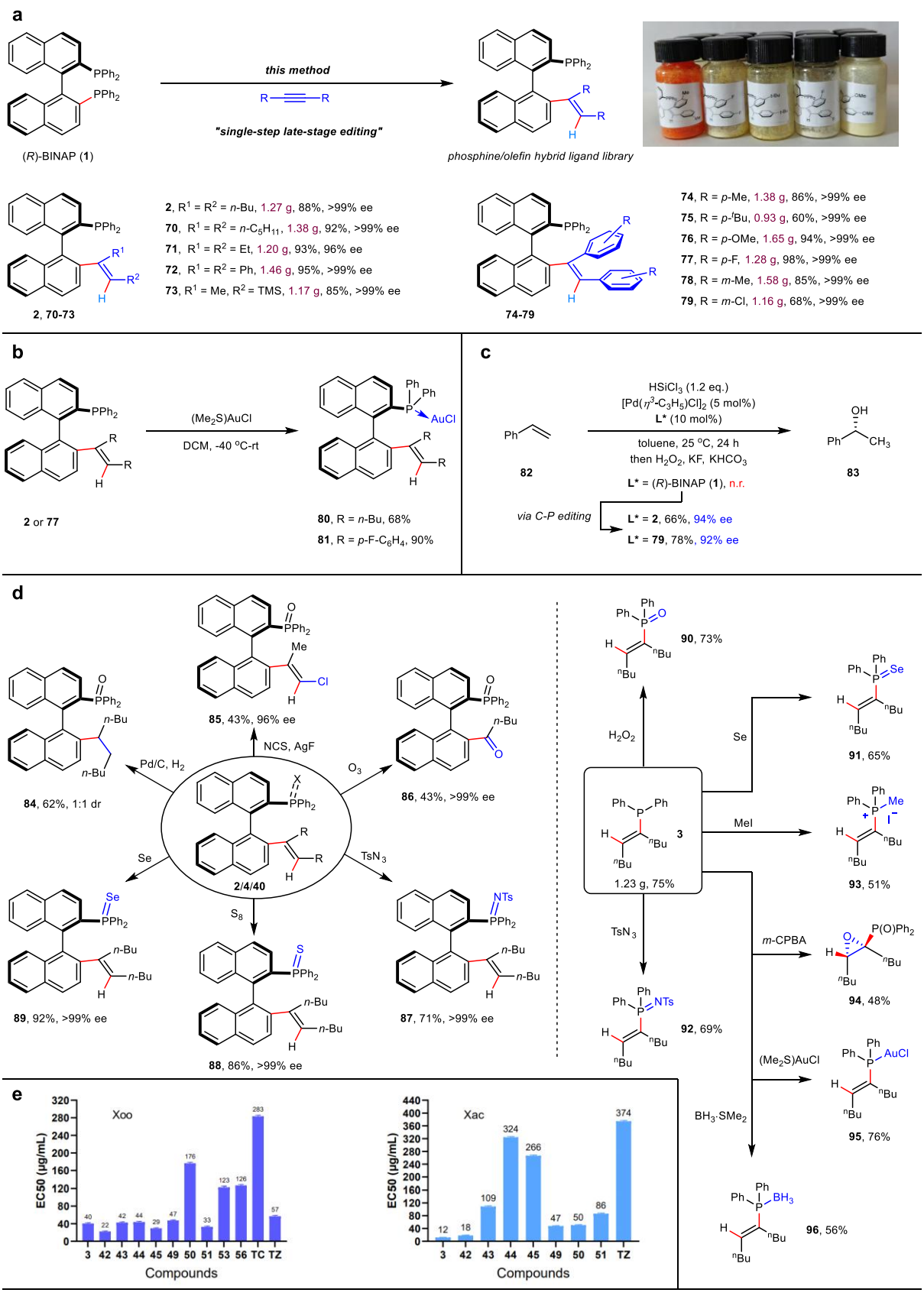


Fig. 4 Synthetic utility. **a**, Scalable preparation without oxidative protection. **b**, Synthesis of metal-ligand complexes. **c**, Preliminary evaluation of chiral ligands. **d**, Derivation of the products. **e**, Antibacterial activity of selected vinyl phosphine derivatives.

il. Importantly, compound **42** exhibited the most potent anti-*Xoo* (Xanthomonas oryzae pv. oryzae) activity, with an EC_{50} value of 22 μg/mL, which was superior to that of thiodiazole copper (TC, EC_{50}: 283 μg/mL). Compound **3** displayed the best anti-*Xac* (Xanthomonas axonopodis pv. citri) activity, with an EC_{50} value of 12 μg/mL, outperforming thiazole zinc (TZ, EC_{50}: 374 μg/mL). Collectively, these results highlight the practical utility and broad potential of this methodology.

Mechanistic investigation. To verify the reaction mechanism, a series of mechanistic experiments was carried out (Fig. 5). Replacing *n*-butanol with 4-methoxybenzyl alcohol gave *p*-methoxybenzaldehyde (**97**) in 90% yield (based on (*R*)-BINAP), confirming that the alcohol serves as a hydrogen donor and is oxidized to the corresponding aldehyde (Fig. 5a). Deuterium-labeling experiments were next performed to probe the hydrogen transfer pathway (Fig. 5b). Using C_2H_5OD as the H donor, no deuterium was incorporated into the hydroarylation product **2**-d_1; however, the hydrophosphination product **3**-d_1 showed deuteration at both the vinylic (60% D) and allylic (38% D) positions. With C_2D_5OD, the vinylic double bond of **2**-d_2 incorporated 95% D. These results indicate that the hydroxy hydrogen and the α-hydrogen of the alcohol are transferred into the two products, respectively, consistent with the proposed catalytic cycle (Fig. 1c). Partial allylic deuteration (**3**-d_1 and **3**-d_2) further implies that the first migratory insertion is reversible, involving β-hydride elimination to release allene followed by re-addition.[49] An H/D competition experiment using a 1:1 (v/v) mixture of C_2H_5OD and C_2D_5OD gave 15% deuterium incorporation in **2**-d_3, corresponding to a KIE of 5.7, suggesting that either β-hydride elimination or the second alkyne insertion is involved in the turnover-limiting step (Fig. 5c).

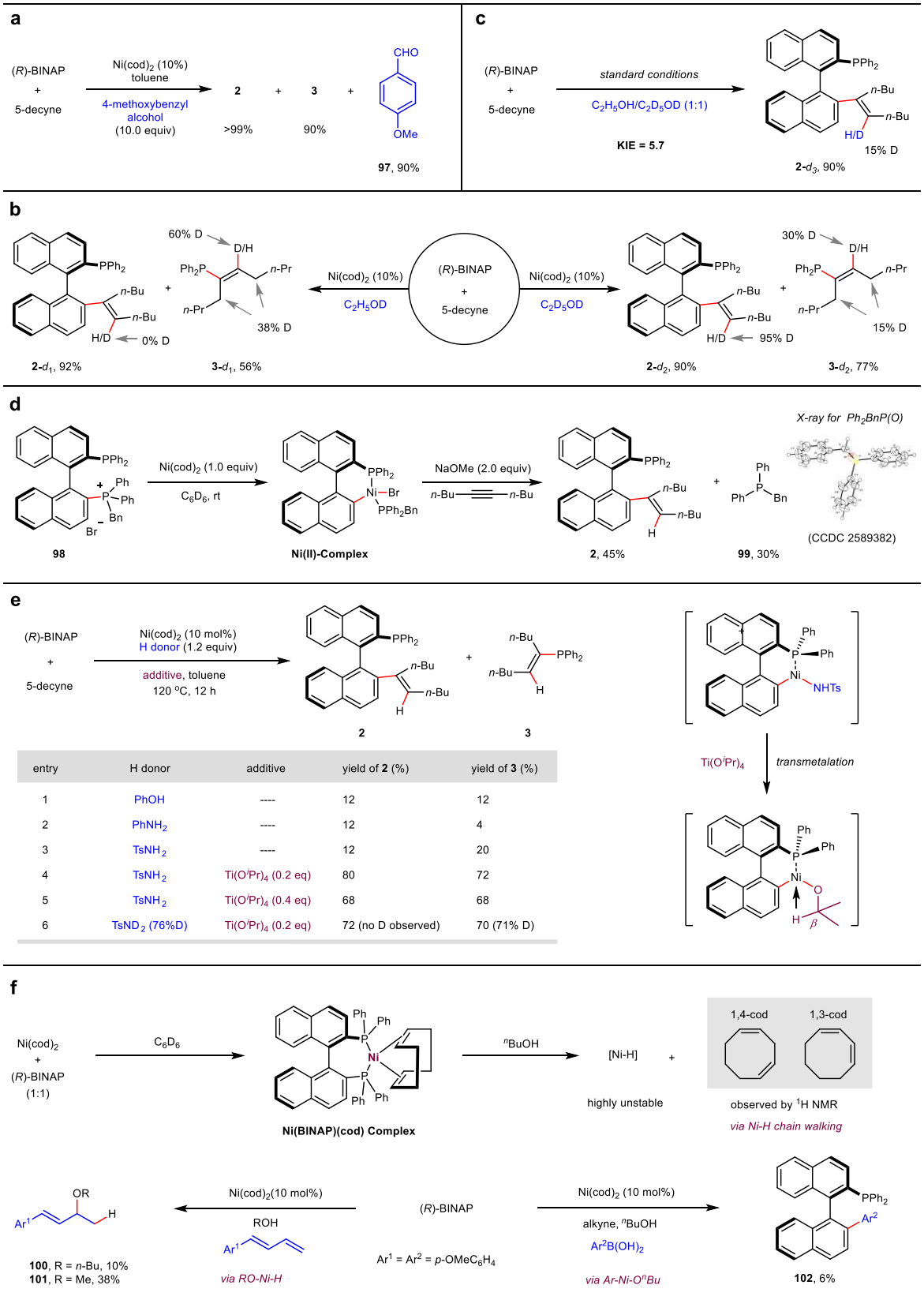


Fig. 5 Mechanistic experiments. a, Analysis and identification of byproducts. **b**, Deuterium labeling experiments. **c**, Kinetic isotope effect. **d**, Reactivity of quaternary phosphonium salt. **e**, Control experiments by using H donors without *β*-H. **f**, Observation and capture of possible intermediates.

In addition, under standard conditions using sodium methoxide as the hydride source via anion

exchange, the preformed Ni(II)-complex derived from quaternary phosphonium salt **98** delivered product **2** in 45% yield, along with benzyldiphenylphosphane **99** (30% yield; Fig. 5d), hinting at the possible involvement of a quaternary phosphonium intermediate. When Brønsted acids lacking β-hydrogens (phenol, aniline, and 4-methylbenzenesulfonamide) were employed as hydrogen donors, unexpectedly, a small amount of **2** was detected (entries 1–3, 12% yield; Fig. 5e), along with the formation of a trace amount of H-MOP, revealing an alternative pathway for the intermolecular C–P bond reorganization. We hypothesized that, under nickel catalysis, decomposition of intermediate **INT-3** generates H-MOP, which subsequently undergoes P-directed C–H alkenylation.[53] However, using H-MOP as the substrate afforded only trace amounts of the alkenylated product (see Supplementary Information for further details), ruling out this tandem sequence as the major pathway. Notably, addition of $Ti(O^iPr)_4$, which can supply a β-hydrogen via transmetalation (Fig. 5e, right),[54] significantly enhanced the yield (entries 4 and 5). Further deuterium-labeling experiments confirmed that the hydrogen transfer with $TsNH_2/Ti(O^iPr)_4$ follows the same pathway as with alcohols (entry 6). Despite extensive efforts, direct observation of the proposed Ni–H species proved unsuccessful, indicative of its high instability. Nevertheless, stoichiometric experiments effected the isomerization of 1,5-COD to 1,4- and 1,3-COD (Fig. 5f), implying the formation of a Ni–H species. Supporting this, the putative Ni–H intermediate (Fig. 1c, **INT-1**) was efficiently trapped by dienes to give hydroalkoxylation products **100** and **101**.[55] Finally, the possible alkoxy-Ni species (**INT-4**) could be intercepted by an arylboronic acid, affording dephosphinative arylation product **102**. Collectively, these mechanistic experiments unambiguously support our initial research hypothesis (Fig. 1c).

Discussion

In summary, we have reported the first nickel-catalyzed, one-step, intermolecular, enantiospecific

reductive C–P reorganization of atropisomeric diphosphines with alkynes, using alcohols as the hydrogen donors. This method converts chiral bisphosphines such as (*R*)-BINAP into diverse chiral P/olefin hybrid ligands with high yields and complete stereospecificity, while also enabling rapid hydrophosphination of alkynes using stable biaryl bisphosphines as the phosphorus source. Mechanistic investigations demonstrate that the alcohol serves as a key hydrogen donor in the reaction system by generating Ni–H intermediates, which promote C–P bond activation and reorganization through sequential alkyne insertion. In the future, this late-stage C–P bond editing strategy should find broader applications in catalyst development and ligand design, as well as in the synthesis of complex phosphorus-containing bioactive molecules.

Methods

General procedure for C-P reorganization. In a nitrogen-filled glovebox, $Ni(cod)_2$ (5.5 mg, 0.02 mmol, 10 mol%), biaryl diphosphines (0.2 mmol, 1.0 equiv), dry degassed *n*-BuOH (2.0 mL; for arylalkynes, *n*-BuOH/toluene 1:1 v/v, 2.0 mL total), and alkyne (0.5 mmol, 2.5 equiv) were placed successively into a 15 mL oven-dried tube. After sealing, the tube was removed from the glovebox and heated at 110 °C in a preheated dry-block heater for 12 h. The mixture was cooled to room temperature, treated with aqueous H_2O_2 (30 wt%, 2 h, rt), and then quenched with brine (20 mL). The aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered through a short silica gel plug (eluted with EA), and concentrated in vacuo. The crude product was purified by flash chromatography (silica gel, EtOAc/petroleum ether) to afford the pure compound.

Data availability

The authors declare that all data supporting the findings of this study are available in the article and its Supplementary Information. Experimental procedures, NMR data, and HPLC data are given in the Supplementary Methods in the Supplementary Information. The X-ray crystallographic coordinates for structures reported in this study have been deposited at the Cambridge Crystallographic Data Centre (CCDC), under deposition number CCDC 2544512 and 2589382. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via https://www.ccdc.cam.ac.uk/structures/.

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Author contributions

R.-H.W. and B. L. discovered and developed the reactions. C.-M. Y., D.-Y. G. and X. K. performed part of synthetic experiments. Y.-N. L. and J. S. completed the bioactivity tests. L. T. and M. Y. participated in supervising the experiments and analyzing the data. R.-H. W. conceived, designed the investigations and wrote the manuscript. R.-H.W. wrote the Supplementary Information according to the feedback from all authors.

Competing interests

The authors declare no competing interests.

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