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Ligand-controlled regiodivergent and enantioselective hydrophosphorylation of styrenes by palladium

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Chun Ma[1], Xinyue Wang[1], Tibor Soós[2], Junliang Zhang[1,3,4] & Junfeng Yang[1,3,4]

Asymmetric hydrophosphorylation of unsaturated compounds is a straightforward and atom-economic approach to obtain chiral organophosphorus compounds. Herein, we describe a ligand-controlled regiodivergent and enantioselective hydrophosphorylation of styrenes facilitated by Pd catalysis and a PC-Phos ligand. This methodology enables the facile synthesis of both Markovnikov and *anti*-Markovnikov alkyl phosphorus compounds with high to excellent regio- and enantioselectivity, achieving up to >95:5 *rr* and 92% *ee*. Deuterium-labeling experiment and computational mechanistic studies unveil that the migratory insertion is the enatio-determining step, in which the O···H hydrogen bonding between the H-phosphonate and the ligand is identified as a crucial factor. Furthermore, our investigations demonstrate that both migratory insertion and reductive elimination contribute to achieving high regioselectivity and enantioselectivity. These findings not only advance the field of asymmetric hydrophosphorylation of simple styrenes, but also deepen our understanding of noncovalent interactions in ligand design.

Enantioenriched organophosphorus compounds have garnered substantial attention in recent decades owing to their frequent occurrence in bioactive molecules and functional materials[1–5]. Among the numerous chiral organophosphorus compounds, α-chiral alkyl phosphorus compounds have received significant attention owing to their biological activities[6–11] and application as chiral ligands and catalysts in asymmetric catalysis (Fig. 1a)[12–15]. Conventional methods to access these compounds always involve various chiral auxiliaries and multiple steps[16–19]. Therefore, the pursuit of novel methods for synthesizing these enantioenriched phosphorus-containing compounds has been a subject of considerable interest. The predominate routine to access these compounds is asymmetric hydrogenation of α-substituted vinylphosphonates with Rh[20–22], Ir[23,24] and Ru[25–27]. Notably, Zhang and coworkers recently reported an elegant nickel-catalyzed asymmetric hydrogenation of α-substituted vinylphosphonates[28]. Besides the asymmetric hydrogenation, C-P bond coupling reactions also provide a convenient routine for α-chiral alkyl phosphorus compounds. For instance, Liu and coworkers presented an enantioconvergent radical Michaelis-Becker-type C-P bond coupling between H-phosphonates with alkyl halides via Cu catalysis (Fig. 1b)[29,30].

Apart from the hydrogenation and C-P coupling, the past few decades also witnessed great development on asymmetric addition of phosphorus nucleophiles to unsaturated bonds, including alkynes[31–38], dienes[39,40], allenes[41,42], and alkenes[43–59]. It is regarded as one of the most economical and straightforward methods to access enantioenriched organophosphorus compounds. In this regards, Duan and Leung pioneerly developed the asymmetric asymmetric Michael addition of diarylphosphines to enones. Later, Dong and coworkers reported a seminal work of enantioselective coupling of terminal 1,3-dienes and phosphine oxides to afford allylic phosphine oxides by palladium

[1]Department of Chemistry, Fudan University, 2005 Songhu Road, Shanghai 200438, China. [2]Institute of Organic Chemistry, Research Centre for Natural Sciences, Magyar tudósok körútja 2, H-1117 5, Budapest, Hungary. [3]School of Chemistry and Chemical Engineering, Henan Normal University, Xinxiang, Henan 453007, China. [4]School of Chemistry & Chemical Engineering, Yangzhou University, Yangzhou 225002, China. e-mail: junliangzhang@fudan.edu.cn; yangjf@fudan.edu.cn

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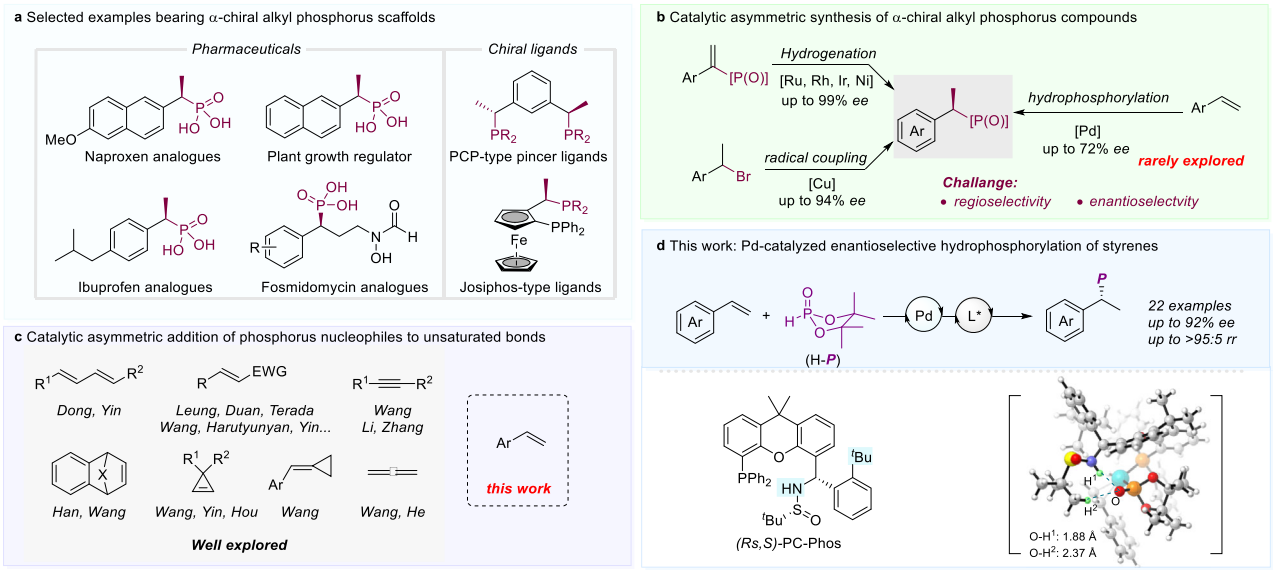

Fig. 1 | Background and project synopsis. a Representative example of α-chiral alkyl phosphorus compounds. **b** Current strategies of catalytic access α-chiral alkyl phosphorus. **c** Previous work: catalytic asymmetric addition of phosphorus nucleophiles to unsaturated bonds. **d** Our design: enantioselective hydrophosphorylation of styrenes by Pd catalysis.

catalysis. Meanwhile, this protocol was also applied to bicyclic alkenes and other active alkene substrate. Despite these advances, the alkene partner involved in the asymmetric addition is still confined to electro-biased Michael acceptors[43–53], or other activated alkenes (Fig. 1c)[54–59]. Since the initial report of hydrophosphorylation of alkenes by Han and Tanaka[60], sporadic efforts have been devoted to the enantioselective hydrophosphorylation of alkenes, particularly styrenes[61,62], which represent one of the most straightforward ways to access α-chiral alkyl phosphorus compounds. However, these attempts have been plagued by poor regioselectivity or enantioselectivity, which is known to be challenging to control. The primary difficulty arises from the lack of coordination site and low reactivity of styrenes compared with Michael acceptors and other activated alkenes. Moreover, the potential regioselectivity issue further complicates the situation[63]. Additionally, the facile tautomerism of the hydrogen phosphoryl compounds between the P(V) and P(III) forms, allows them to act as ligands to transition metal, potentially deactivating the catalyst[64–68]. Nevertheless, we believe that the particular ligand is pivotal in overcoming these challenges.

Recently, our groups have become increasingly intrigued by the formation of P-C bonds through the Pd-catalyzed P-C cross coupling reactions[69,70] and the atom-economical hydrophosphinylation of alkynes[33]. Building on our continuous interest in the synthesis of P-containing enantioenriched compounds, herein we present our work on the Pd-catalyzed enantioselective hydrophosphorylation of styrenes. Notably, it enables facile access to different α and β-arylphosphonic acid derivatives by simply switching the ligands (Fig. 1d).

Results

Optimization of the reaction conditions

At the outset, the asymmetric hydrophosphorylation reaction was carried out using 4-phenylstyrene (**1a**) with pinacol H-phosphonate (4,4,5,5-tetramethyl-1,3,2-dioxaphospholane 2-oxide, **2a**)[60] as the model reaction to verify the feasibility. As shown in Table 1, a range of commercially available chiral phosphine ligands, including bidentate P, P-ligands (**L1**-**L3, L5**-**L6**), N, P-ligands **L7**, and monodentate ligand (**L4**), were initially examined. Unfortunately, most of the commercial ligands did not yield good results. Although the bisphosphine ligands (**L1, L2, L5**) are promising in facilitating the reaction, it predominantly produced the *anti*-Markovnikov product. In contrast, when monophosphine ligands (**L4**) or N, P-ligands (**L6, L7**) were used, the reaction was dominated by Markovnikov products, but the reactivity and enantioselectivity of the reaction were suboptimal. These observations underscore the critical role of the ligand in influencing the reactivity, regioselectivity and enantioselectivity. Our recently developed Sadphos, known for their excellent performance in hydrophosphinylation of alkynes[33], prompted further investigation of their efficacy in the hydrophosphorylation reaction. Xu-Phos, Xiang-Phos and TY-Phos, like the other commercially available ligands, exhibit unsatisfactory catalytic performance. However, our exploration revealed intriguing insight: Wei-Phos ligands demonstrated good reactivity, albeit suffering from poor enantioselectivity, as observed with Segphos (**L1**). The use of Xiao-Phos improved reactivity, but shared similar regioselectivity control as Ming-Phos and PC-Phos. Notably, **PC1**, in contrast to **Ming1**, exhibited a slight improvement in enantioselectivity (Table 1, Entry 1). Therefore, we selected PC-Phos as the ligand backbone for the reaction modification. Initial modifications involved replacing the aryl group with the alkyl group, such as ^{t}Bu (**PC2**) and Ad (**PC3**), resulting in significantly increased reactivity, but a minor decrease in the enantioselectivity control (Table 1, Entries 3–4). Subsequent modifications fine-tuned the substituents on aryl group of the PC-Phos (Table 1, Entries 4–10). Remarkably, the enantioselectivity (44%–78% *ee*) was progressively improved with increasing aryl-neighboring site hindrance (Me, ^{i}Pr, ^{t}Bu) on PC-Phos (Table 1, Entries 8–10). Upon identifying **PC10** as the optimal ligand, we investigated the catalyst precursor for the reaction. Using $[Pd(allyl)Cl]_2$ as a catalyst further improved the reaction yield and enantioselectivity without compromising regioselectivity (Table 1, Entry 11). We also fine-tuned other parameters, such as solvents, additives, and catalyst loading, to enhance yield and enantioselectivity (see pages S6-S8 of the Supplementary information). Notably, the reaction could not proceed without the addition of $(PhO)_2P(O)OH$ (Table 1, Entry 15). Other H-P reagents, such as H-phoshpine oxide, H-phosphinates and other acylic H-phosphonates showed relatively low reactivity than **2a** (See Supplementary Fig. 1 for details). Ultimately, under the optimal reaction conditions, product **3aa** from the hydrophosphorylation reaction was obtained in high yield (87%) with high enantioselectivity (90% *ee*) and excellent regioselectivity (>95:5 *rr*) (Table 1, Entry 16).

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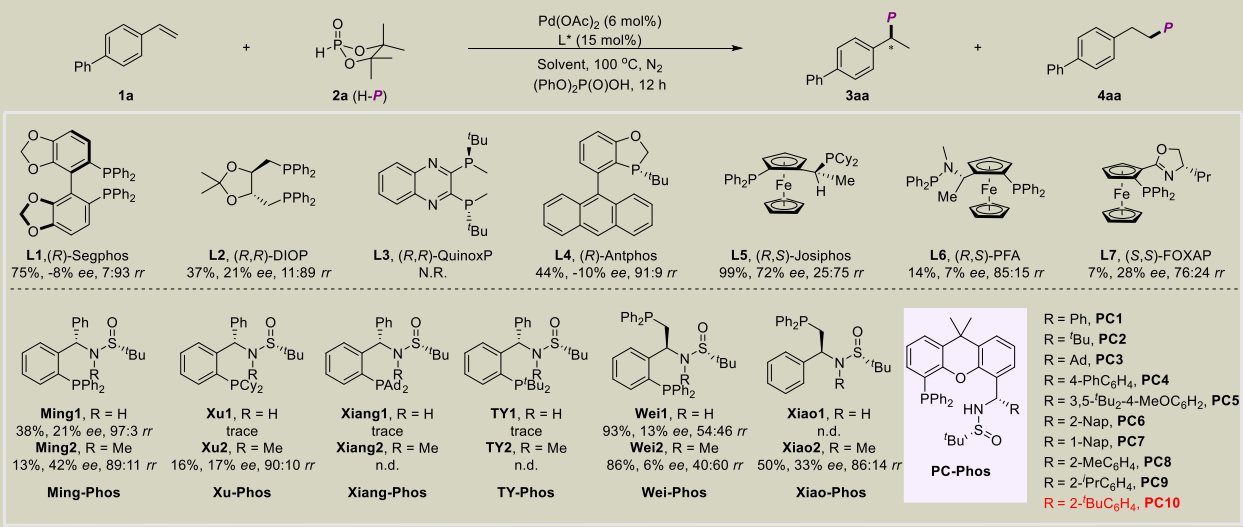
Table 1 | Optimization of reaction conditions



Entry[a]	L*	Solvent	Yield [%][b]	*Ee* [%][c]	*rr*[c]
1	**PC1**	Dioxane	36	24	96:4
2	**PC2**	Dioxane	68	−16	97:3
3	**PC3**	Dioxane	66	22	96:4
4	**PC4**	Dioxane	47	21	96:4
5	**PC5**	Dioxane	42	48	91:9
6	**PC6**	Dioxane	37	23	96:4
7	**PC7**	Dioxane	47	33	98:2
8	**PC8**	Dioxane	66	44	98:2
9	**PC9**	Dioxane	62	60	97:3
10	**PC10**	Dioxane	66	78	95:5
11[d]	**PC10**	Dioxane	89	87	91:9
12[d]	**PC10**	THF	91	84	90:10
13[d]	**PC10**	CH_3CN	69	75	81:19
14[d]	**PC10**	DCM	99	88	92:8
15[d,e]	**PC10**	DCM	Trace	-	-
16[d,f]	**PC10**	DCM	99(87)[g]	90	96:4

[a]Reaction conditions: **1a** (0.11 mmol), **2a** (0.1 mmol), $Pd(OAc)_2$ (6 mol%), **L*** (15 mol%), $(PhO)_2P(O)OH$ (30 mol%), solvent (0.3 mL), 100 °C, 12 h. [b]Yield was determined by ^{31}P NMR using PPh_3 as an internal standard. [c]Enantiomeric excess (*ee*) values and regiomeric ratios (*rr*) were determined by HPLC using a chiral stationary phase. [d]Using 3 mol% $[Pd(allyl)Cl]_2$. [e]Without $(PhO)_2P(O)OH$. [f]Using 0.5 ml DCM and 25 mol% $(PhO)_2P(O)OH$. [g]The yield of isolated product was shown within the parentheses. THF = tetrahydrofuran. DCM = dichloromethane. n.d. = not detected.

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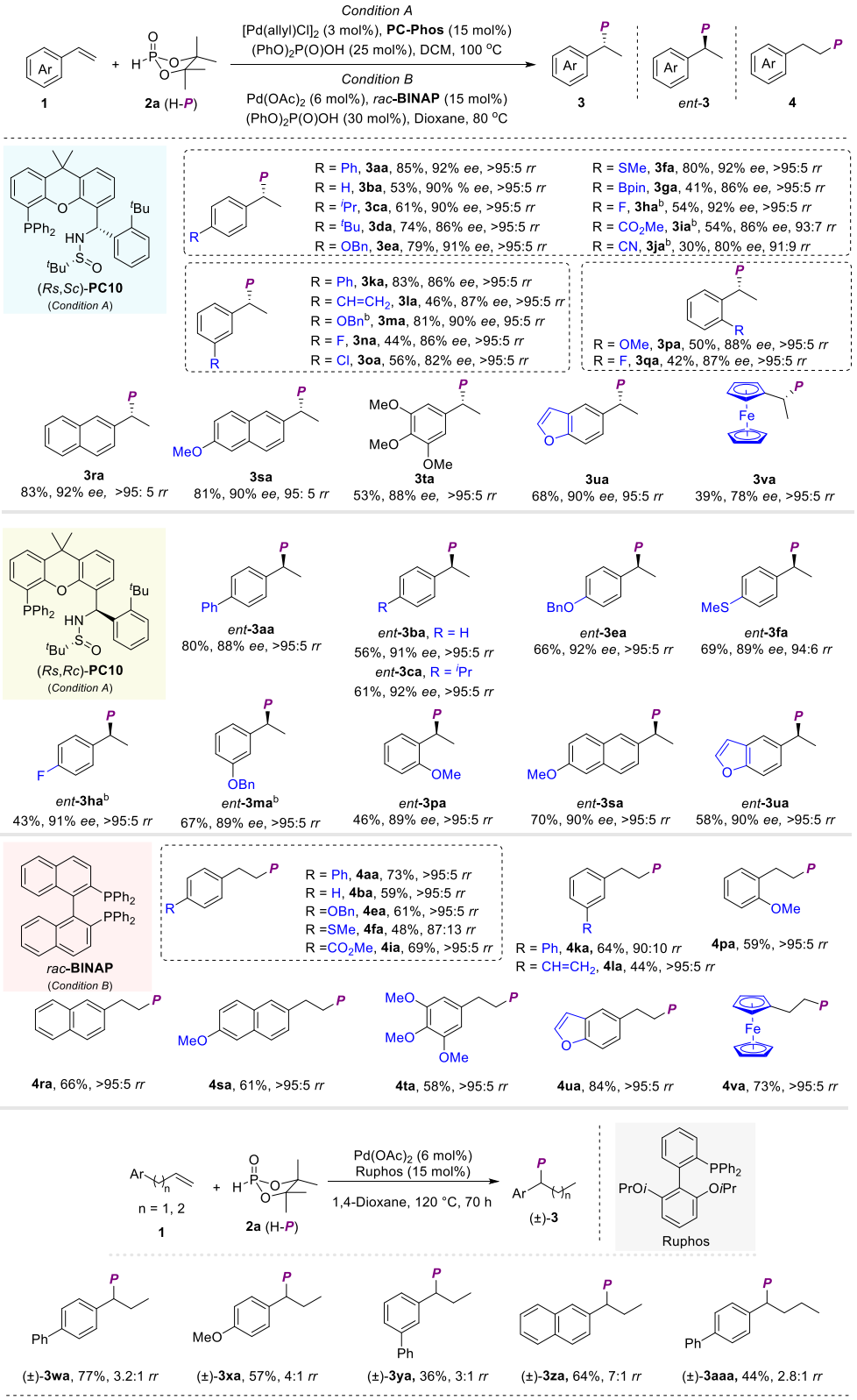

Fig. 2 | Exploration of substrate scope 1. [a]Reaction condition A: [a] **1** (0.22 mmol), **2a** (0.2 mmol), $(PhO)_2P(O)OH$ (25 mol%), $[Pd(allyl)Cl]_2$ (3 mol%) and **PC10** (15 mol%) in DCM (1 ml) at 100 °C for 24 h. [b] 15 mol% $TsOH{\cdot}H_2O$ was used instead of $(PhO)_2P(O)OH$. Reaction condition B: **1** (0.22 mmol), **2a** (0.2 mmol), $(PhO)_2P(O)OH$ (30 mol%), $Pd(OAc)_2$ (6 mol%) and *rac*-BINAP (15 mol%) in dioxane (0.6 ml) at 80 °C for 24 h.

Reaction scope study

Subsequently, the scope of substrates for vinylarenes **1** was examined under optimal conditions. As shown in Fig. 2, vinylarenes with electron-donating and electron-withdrawing substituents at the *para*-, *meta*-, or *ortho*-positions furnished the desired products (**3aa**-**3qa**) in moderate to good yields with excellent regioselectivities (up to >95:5 *rr*) and good enantioselectivities (up to 92% *ee*). The reaction displayed good tolerance of functional groups, including fluoro (**3ha, 3na, 3qa**), chloro (**3oa**), ester

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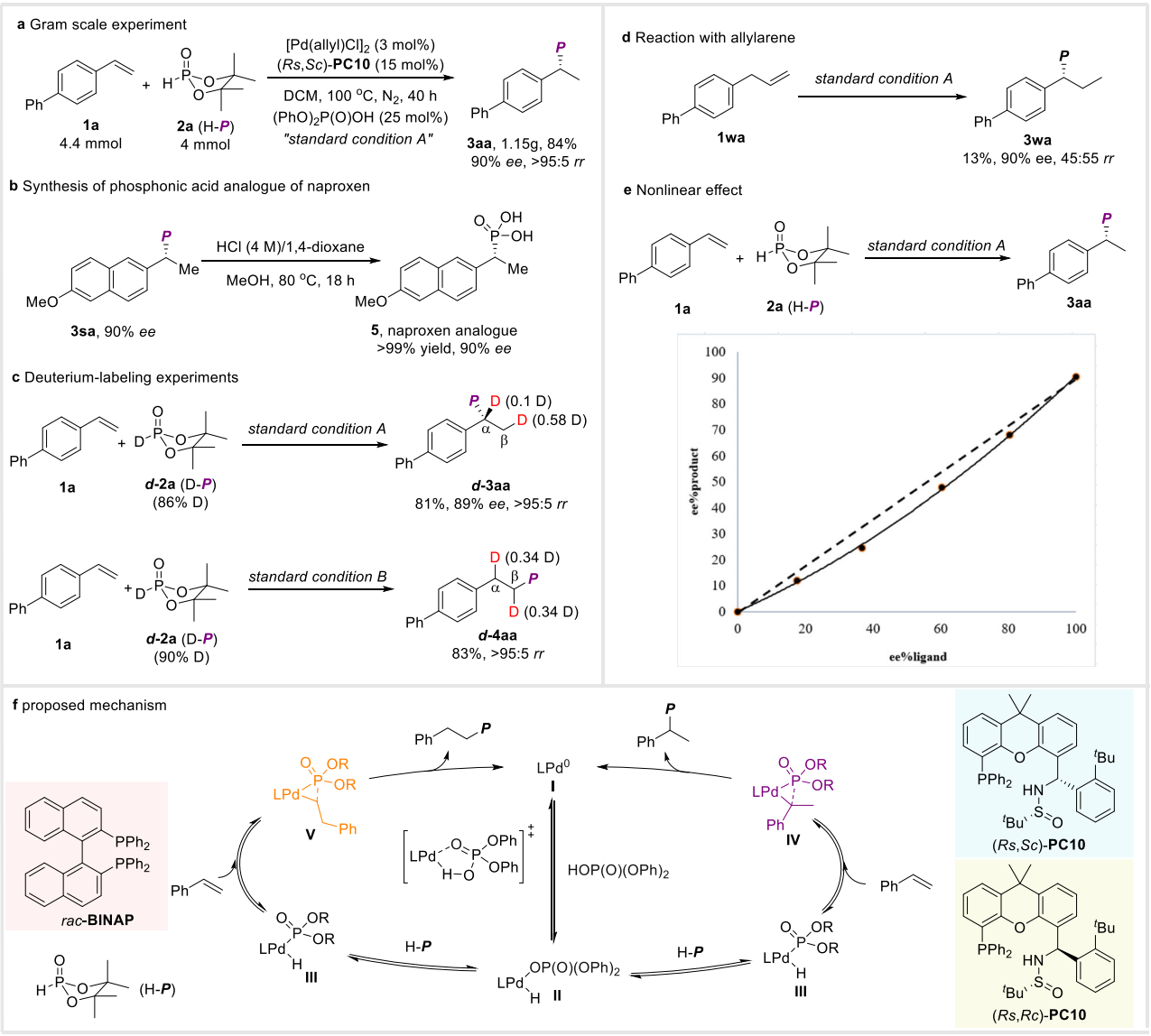

Fig. 3 | Gram-scale synthesis, transformations and preliminary mechanistic study. a Gram scale reaction. **b** Synthetic transformations. **c** Deuterium-labeling experiments. **d** Reaction with allylarene. **e** nonlinear effect study. **f** proposed mechanism.

(**3ia**), cyano (**3ja**), alkyl (3**ca, 3da**), alkoxy (**3ea, 3ma, 3pa**) and aryl (**3aa**) or alkenyl (**3la**) groups. It highlighted that substrates containing thioethers (**1f**) and boron esters (**1g**), which were typically incompatible in metal-catalyzed coupling reactions, delivered the desired products (**3fa, 3ga**) in good yields with excellent regioselectivities and enantioselectivities. Similarly, polysubstituted aryl (**3ta**) and naphthyl groups (**3ra, 3sa**) exhibited favourable results in asymmetric hydrophosphorylation reactions. Additionally, heteroaryl (**1u**) and ferrocene-substituted substrates (**1v**) proved suitable for this reaction system, though the enantioselectivity of the ferrocene-substituted product (**3va**) was slightly lower. The absolute configuration of **3aa** was confirmed by X-ray crystallography analysis, and those of the others were assigned analogously.

During the screening of the conditions, it came to our attention that enantioselective synthesis of *ent*-**3aa** could be achieved by employing diastereoisomers of Ming-Phos and PC-Phos-like ligands (see pages S4-S5 of the Supplementary information). Subsequently, we initiate trials using the diastereoisomer of the best ligand (R_S,S_C)-**PC10**. The result indicated that the reaction performance was comparable when (R_S,R_C)-**PC10** was used instead of (R_S,S_C)-**PC10**. Therefore, (R_S,R_C)-**PC10** was used as ligand for the synthesis of *ent*-**3** and the reactions consistently delivered the corresponding enantiomer products *ent*-**3** in good yields (up to 80%), regioselectivities (up to >95:5 *rr*), and enantioselectivities (up to 92% *ee*). This result highlights a novel approach for the rapid synthesis of product enantiomers, especially considering that the two diastereomers of the ligand were easily accessible by varying the organometallic reagent RLi or RMgX[71].

Likewise, in our ligand screening, we observed that bisphosphine ligands had the capacity to modulate the regioselectivity of the hydrophosphorylation reaction, favoring the *anti*-Markovnikov product. To delve deeper into this phenomenon, common bisphosphine ligands were subsequently screened. It was ultimately discovered that using *rac*-BINAP enabled the reaction to favor the *anti*-Markovnikov product **4aa** in high yield with excellent regioselectivity (see pages S8-S9 of the Supplementary information). As illustrated in Fig. 2, we systematically investigated the substrate scope of the reaction, which demonstrated good compatibility of functional groups and furnished the corresponding target products **4** in good yields (up to 84%) with excellent regioselectivities (up to >95:5 *rr*). Alkyl substituted alkenes were also examined and proved to be not compatible in current system, resulting in poor reactivity. Extensive exploration of ligands was

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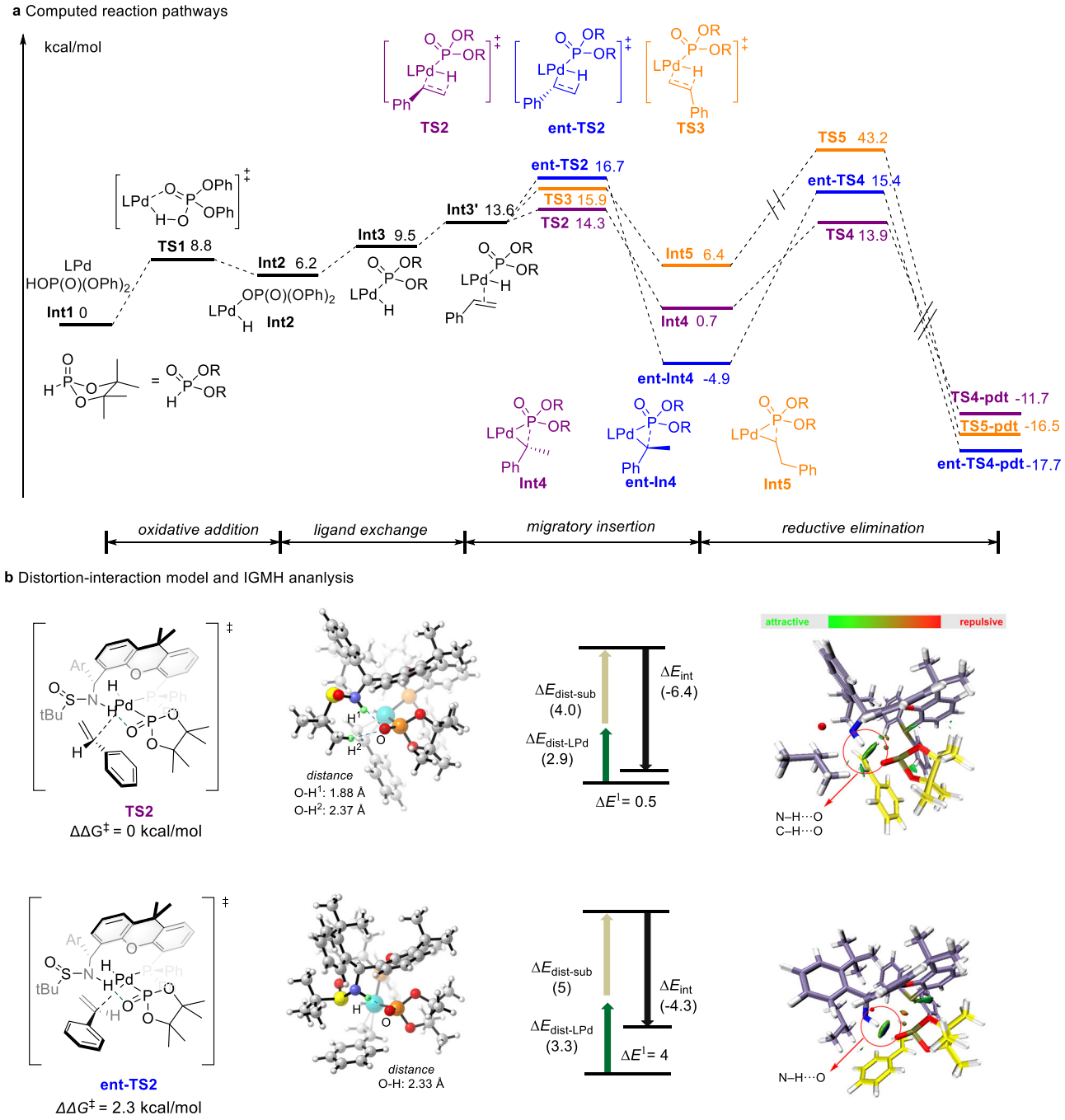

Fig. 4 | Proposed catalytic cycle. a Calculated reaction pathway. **b** Distortion/interaction and independent gradient model based on Hirshfeld partition (IGMH) analysis.

conducted using allylarene **1w**-**1aa** as the substrate. It is pleasing to detect the chain-walking hydrophosphorylation products **3wa**-**3aaa**, though the regioselectivity is relatively poor.

To investigate the mechanism, a series of control experiments were conducted as outlined in Fig. 3. Initially, deuterium-labeled pinacol H-phosphonate *d*–**2a** was subjected to the standard reaction conditions (Fig. 3c). In this experiment, deuterium incorporation was observed at both the α (0.10 D) and β (0.58 D) positions of *d*–**3aa**. Similarly, deuterium incorporation was also observed at both the α (0.34 D) and β (0.34 D) positions of *d*–**4aa** under standard condition B. An attempt to extend the current asymmetric hydrophosphinylation to the alkyl substituted alkene proved to be unsuccessful. As shown in Fig. 3d, the reaction with allylarene **1wa** afforded the chain-walking product **3wa** in poor yield and regioselectivitivity, albeit with good enantioselectivity. Additionally, a slight negative linear relationship between the ee values of the **PC10** and product 3aa was observed, suggesting that minor oligomeric aggregates of catalyst may play a role in influencing the stereochemistry of the asymmetric hydrophosphorylation reaction (Fig. 4e)[72–74]. Based on literature precedence[37] and our observations, we propose a plausible mechanism depicted in Fig. 3f. The Pd(0) precatalyst I undergoes oxidative addition to diphenylphosphoric acid ($(PhO)_2P(O)OH$) to form PdH species II. Notably, a significant loss of yield was observed in the absence of the acid additive ($(PhO)_2P(O)OH$). A related oxidative addition has been implicated as a key step in the hydrophosphinylation of terminal alkynes[35,36]. Following this, the ligand exchange and two distinct modes of migratory insertion lead to the formation of species V and IV. Subsequent reductive elimination furnishes the product and regenerates the catalyst.

To probe the origin of the enantioselectivity and regioselectivity control, we performed DFT calculations on the reaction pathway (Fig. 4a). Following the oxidative addition of diphenylphosphinic acid and subsequent ligand exchange, the migratory insertion of **Int3** with styrene occurs, leading to the major benzyl-Pd intermediate **Int4** with an energy barrier of 4.8 kcal/mol and the minor benzyl-Pd intermediate **ent-Int4** with an energy barrier of 7.1 kcal/mol. While, the energy barrier to generate the linear alkyl-Pd intermediate **Int5** is 6.3 kcal/mol. As the energy of the following reductive elimination from **TS4** and **ent-TS4** is relatively lower than the corresponding **TS2** and **ent-TS2**. Therefore, we speculate the migratory insertion is the enantio-determining step.c The high regioselectivity is attributed to the elevated energy barrier of reductive elimination (**TS5**: 33.7 kcal/mol) to afford the *anti*-Markovnikov product (The possibility of the migratory insertion occurring before the ligand exchange cannot be completely excluded). The energy of the following reductive elimination from **TS4** and **ent-TS4** is relatively lower than the corresponding **TS2** and **ent-TS2**. According to our DFT calculations, migratory insertion is considered to be the enantio-determining transition state. The comparison of **TS2** and **ent-TS2** is shown in Fig. 4b. The $\Delta\Delta G^{\neq}$(2.3 kcal/mol) was well consistent with the experimental enantioselectivity. Steric environment analysis of the transition state indicated that **TS2** possessed a stronger hydrogen bonding interaction between the phosphonate P = O and the NH, as well as the *tert*-butyl CH on the ligand. This weak hydrogen bonding interaction may contribute to the energy difference of migratory insertion. Control experiment showed a significantly decrease in enantioselectivity and reactivity when the reaction was conducted in high polarity solvent, such as DMF and EtOH, or when the NH is absent (see Supplementary Fig. 3 for details). Furthermore, distortion/interaction model analysis[75–77] suggested that the barrier differences between **TS2** and **ent-TS2** originate primarily from the much greater interaction between the substrate and catalyst (Fig. 4b). An independent gradient model based on Hirshfeld partition (IGMH)[77–81] indicated a significant interaction between the *tert*-butyl group of the ligand and the aromatic ring of styrene (the green region implied attractive interactions).

Subsequently, the origin of the regioselectivity control to obtain the *anti*-Markovnikov product while using *rac*-BINAP is also probed by DFT calculation. Similarly, the calculations revealed that migrataroy is the regio-determining step. Again, the hydrogen bonding interaction between the phosphonate P = O and the aryl CH on the ligand is observed to be stronger in the *anti*-Markovnikov transition state (see Supplementary Fig. 4 for details).

Discussion

We presented a ligand-controlled palladium-catalyzed asymmetric hydrophosphorylation of simple styrenes, enabling regio- and stereoselective access to both branched and linear alkyl phosphorus compounds by simply switching the ligands. Mechanistic studies and DFT calculation have provided valuable insights into the reaction process, revealing the reversibility of the migratory insertion and underscoring the importance of noncovalent interactions (O···H hydrogen bonding, *ect*) between the phosphonate P = O and the ligand. These findings not only advance the field of asymmetric hydrophosphorylation but also deepen our understanding of the noncovalent interactions in ligand design. Given the high importance and broad synthetic application of enantioenriched organophosphorus compounds, we believe that this protocol will pave the way for future developments of hydrophosphorylation.

Methods

Typical procedure for ligand-controlled regiodivergent and enantioselective hydrophosphorylation of styrenes by palladium

Under a nitrogen atmosphere, vinylarenes **1** (0.22 mmol), **2a** (0.2 mmol), $[Pd(allyl)Cl]_2$ (3 mol%), **PC10** (15 mol%) and $(PhO)_2P(O)OH$ (25 mol%) were added to a dry 10 mL sealed tube. Then, DCM (1.0 mL) was added to the reaction tube under a nitrogen atmosphere. The resulting mixture was stirred with 1000 rpm at 100 °C in an oil bath. After the reaction was complete as monitored by TLC, the reaction mixture was filtered to remove insoluble and further purified by flash column chromatography on silica gel (Petroleum ether: Ethyl acetate) to afford the desired product **3** or *ent*-**3**.

Under a nitrogen atmosphere, vinylarenes **1** (0.22 mmol), **2a** (0.2 mmol), $Pd(OAc)_2$ (6 mol%), *rac*-**BINAP** (15 mol%) and $(PhO)_2P(O)OH$ (30 mol%) were added to a dry 10 mL sealed tube. Then, dioxane (0.6 mL) was added to the reaction tube under a nitrogen atmosphere. The resulting mixture was stirred with 1000 rpm at 80 °C in an oil bath. After the reaction was complete as monitored by TLC, the reaction mixture was filtered to remove insoluble and further purified by flash column chromatography on silica gel (Petroleum ether: Ethyl acetate) to afford the desired product **4**.

Data availability

We declare that all the data supporting this study, including the experimental details, data analysis, and spectra for all unknown compounds, are available within the article and its Supplementary Information Files. Source Data are provided with this paper. The X-ray crystallographic coordinates for structures reported in this study have been deposited at the Cambridge Crystallographic Data Centre (CCDC), under deposition numbers 2248216 ((*R*)-**3aa**)). These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. Source data are provided with this paper.

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Author contributions

J.Y. and J.Z. conceived the project, analyzed the data and wrote the manuscript. C.M. performed the most of experiments. X.W. and T.S. participated in some of the experiments. J.Y. did the DFT calculations. All authors discussed the results and commented on the manuscript.

Competing interests

The authors declare no competing interests.

Additional information

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Correspondence and requests for materials should be addressed to Junliang Zhang or Junfeng Yang.

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