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Copper-Catalyzed Enantioselective Hydrophosphorylation of Unactivated Alkynes

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This work is dedicated to John F. Hartwig on the occasion of his 60th birthday.

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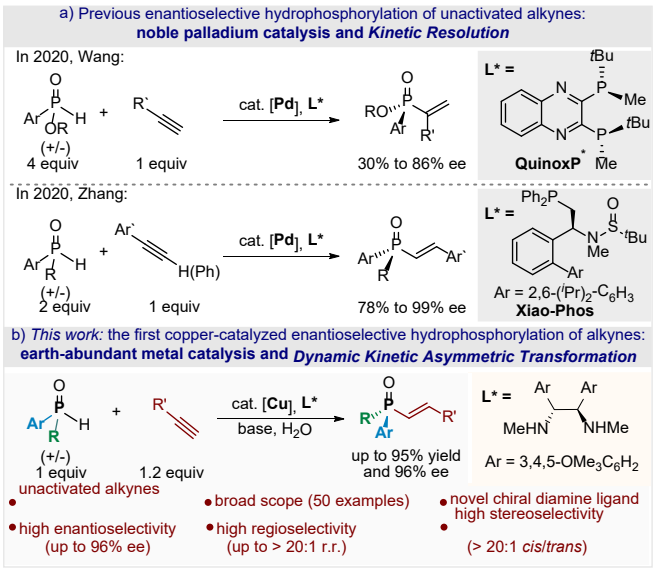
Abstract: P-stereogenic phosphorus compounds are essential across various fields, yet their synthesis *via* enantioselective P-C bond formation remains both challenging and underdeveloped. We report the first copper-catalyzed enantioselective hydrophosphorylation of alkynes, facilitated by a newly designed chiral 1,2-diamine ligand. Unlike previous methods that rely on kinetic resolution with less than 50% conversion, our approach employs a distinct dynamic kinetic asymmetric transformation mechanism, achieving complete conversion of racemic starting materials. This reaction is compatible with a broad range of aromatic and aliphatic terminal alkynes, producing products with high yields (up to 95%), exclusive *cis* selectivity, and exceptional regio- and enantioselectivity (> 20:1 r.r. and up to 96% ee). The resulting products were further transformed into a diverse array of enantioenriched P-stereogenic scaffolds. Preliminary mechanistic studies were conducted to elucidate the reaction details.

P-chiral phosphorus compounds play pivotal roles across various fields,[1] including agrochemicals, pharmaceuticals,[2] material sciences, and asymmetric catalysis.[3] Their broad utility has sustained significant interest in their synthesis, making this a vibrant and enduring area of research.[4] Traditionally, these compounds have been synthesized using chiral auxiliary-based diastereoselective methods,[5],[6] which require stoichiometric amounts of chiral reagents and involve multiple synthetic steps. Although catalytic approaches, such as the desymmetrization of prochiral phosphorus compounds[7] and enantioselective transformations of secondary phosphines (SPs; H-PR^{1}R^2),[6b, 7i, 8] have been developed, these methods often face limitations, including the need for structurally constrained substrates and the use of highly toxic, volatile, and air- and moisture-sensitive P$^{(III)}$-reagents.

Racemic pentavalent hydrophosphoryl compounds (H-P$^{(V)}$(O)R^{1}R^2) have recently emerged as highly attractive substrates for enantioselective P-C bond-forming reactions due to their ready availability, non-toxicity, bench stability, and ease of handling.[4f] Notable progress has been made in the transition metal-catalyzed enantioselective P-C cross-coupling of these compounds with aryl and alkyl (pseudo) halides,[9],[10] as well as in their asymmetric conjugate addition to activated alkenes, such as *α*,*β*-unsaturated carbonyl compounds, using both transition-metal catalysis or organocatalysis.[9d, 11] Despite these promising developments, enantioselective P-C bond-forming reactions with H-P(O)R^{1}R^2 remains limited, highlighting the need for further exploration and innovations in this field.

The enantioselective addition of racemic H-P(O)R^{1}R^2 across alkynes—generally termed hydrophosphorylation—provides a direct and atom-economical route to P-stereogenic compounds. Although Tanaka and Han first reported the hydrophosphorylation of alkynes in 1996,[12] the development of enantioselective variants has been impeded by significant challenges.[13] These challenges include limited reactivity[14] and the need to simultaneously control multiple selectivities, such as regioselectivity,[15] stereoselectivity (*cis vs trans*),[16] and enantioselectivity. It wasn`t until 2020 that Wang and co-workers reported the first enantioselective addition of H-P(O)Ph(OR) to aromatic alkynes using palladium complexes with QuinoxP*, achieving Markovnikov adducts with moderate to good enantioselectivity (30-86% ee) (Scheme 1a, top).[15a] In the same year, the Zhang group achieved the *anti*-Markovnikov, highly enantioselective addition of H-P(O)RPh to alkynes using a



Scheme 1. Enantioselective hydrophosphorylation of unactivated alkynes

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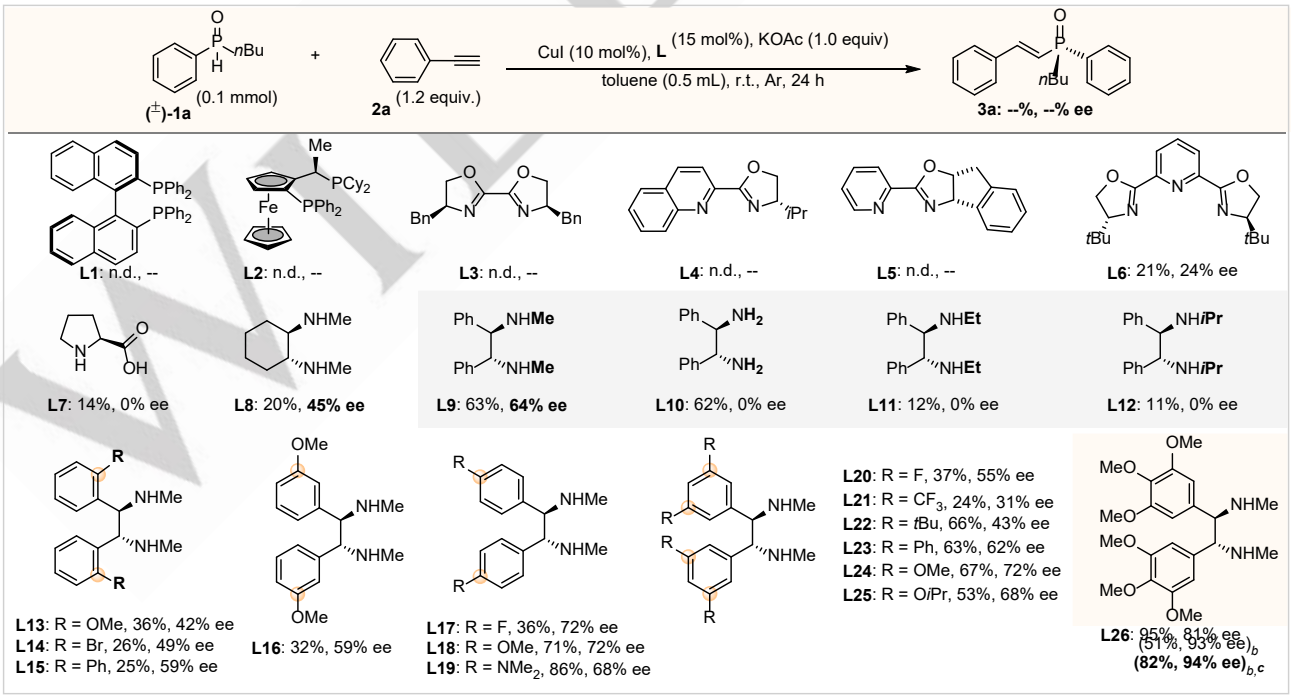
palladium catalyst derived from their chiral sulfinamide phosphine ligand, Xiao-Phos (Scheme 1a, bottom).[15b] To date, these remain the only two examples of enantioselective hydrophosphorylation of unactivated alkynes, both relying on noble palladium catalysts.[15] Therefore, developing catalyst systems based on inexpensive, earth-abundant metals for these reactions remains a highly desirable and significant goal.

Beyond the challenges of reactivity and selectivity, another significant obstacle in developing practical enantioselective hydrophosphorylations is the difficulty in racemizing hydrophosphoryl compounds due to the high energy barrier required for interconversion between their two enantiomers. Consequently, this limitation restricts the reported hydrophosphorylations to proceed *via* kinetic resolution,[15],[17] only forming P-stereogenic products in less than 50% yield, as the hydrophosphoryl substrates act as the limiting reagents. In contrast, dynamic kinetic asymmetric transformation (DYKAT)[18] of hydrophosphoryl compounds can theoretically achieve up to 100% yield,[19],[20] making it a more efficient and attractive strategy. However, DYKAT processes are significantly more complex and rare, as they require a catalyst capable of not only delievering high reactivity and selectivity but also promoting the racemization.[18],[21] Although various transition metal catalysts have been developed for P-C bond-forming reactions, only two catalyst systems—nickel[9a] and copper[10g, 10i] [10d, 10e, 10j]—have been shown to facilitate racemization, and both have been exclusively applied to P-C cross-coupling reactions. Besides the catalyst, other reaction parameters, such as base, solvent, temperature, and substituent variations of phosphorus substrate,[9c] also play crucial roles in developing such DYKATs.[19b, 20] For instance, while the nickel catalyst system with KOAc could promote the dynamic kinetic asymmetric allylation of hydrophosphoryl compounds, the same system with K_3PO_4 failed to do so;[9a] similarly, nickel catalysts were ineffective in catalyzing enantioselective arylation and benzylation under dynamic kinetic conditions.[9f, 10f] Moreover, side-reactions associated with hydrophosphoryl substrates often present additional obstacles to achieving DYKATs with these compounds.[10a] These factors collectively render the development of a novel DYKAT with hydrophosphoryl compounds highly complex and elusive.

Building on our ongoing work in developing enantioselective P-C bond-forming reactions,[10g, 10i] we report here the first earth-abundant copper-catalyzed hydrophosphorylation of unactivated terminal alkynes (Scheme 1b), which also represents the inaugural dynamic kinetic asymmetric hydrophosphorylation of unsaturated C-C bonds. By utilizing a newly developed chiral 1,2-diamine ligand, this hydrophosphorylation of terminal aryl and alkyl alkynes produces P-stereogenic products with high yields, exclusive *cis*- and *anti*-Markovnikov selectivity, and excellent enantioselectivity (up to 96% ee).

We initiated our investigation by examining various chiral ligands for the reaction between racemic **1a** and phenylacetylene **2a**, using CuI as the precatalyst and KOAc as the base in toluene (0.2 M) at room temperature for 24 hours (Table 1). Several commercially available ligands were tested, including bisphosphines **L1** and **L2**, bisoxazoline **L3**, pyridyl oxazolines **L4** and **L5,** pyridyl bisoxazoline **L6**, amino acid **L7**, and cyclic and acyclic 1,2-diamines **L8** and **L9**. Among these, 1,2-diphenyl-ethylene-1,2-diamine **L9** led to the *anti*-Markovnikov hydrophosphorylated product **3a** with a 63% yield and 64% ee.

Table 1. Condition optimization.[a]



[a]The yield refers to NMR yield with 2,4,6-trimethoxybenzene as internal standard; [b]Reaction was conducted in 2 mL of xylene at -20 °C for 96 h. [c]5 equiv of degassed water was added.

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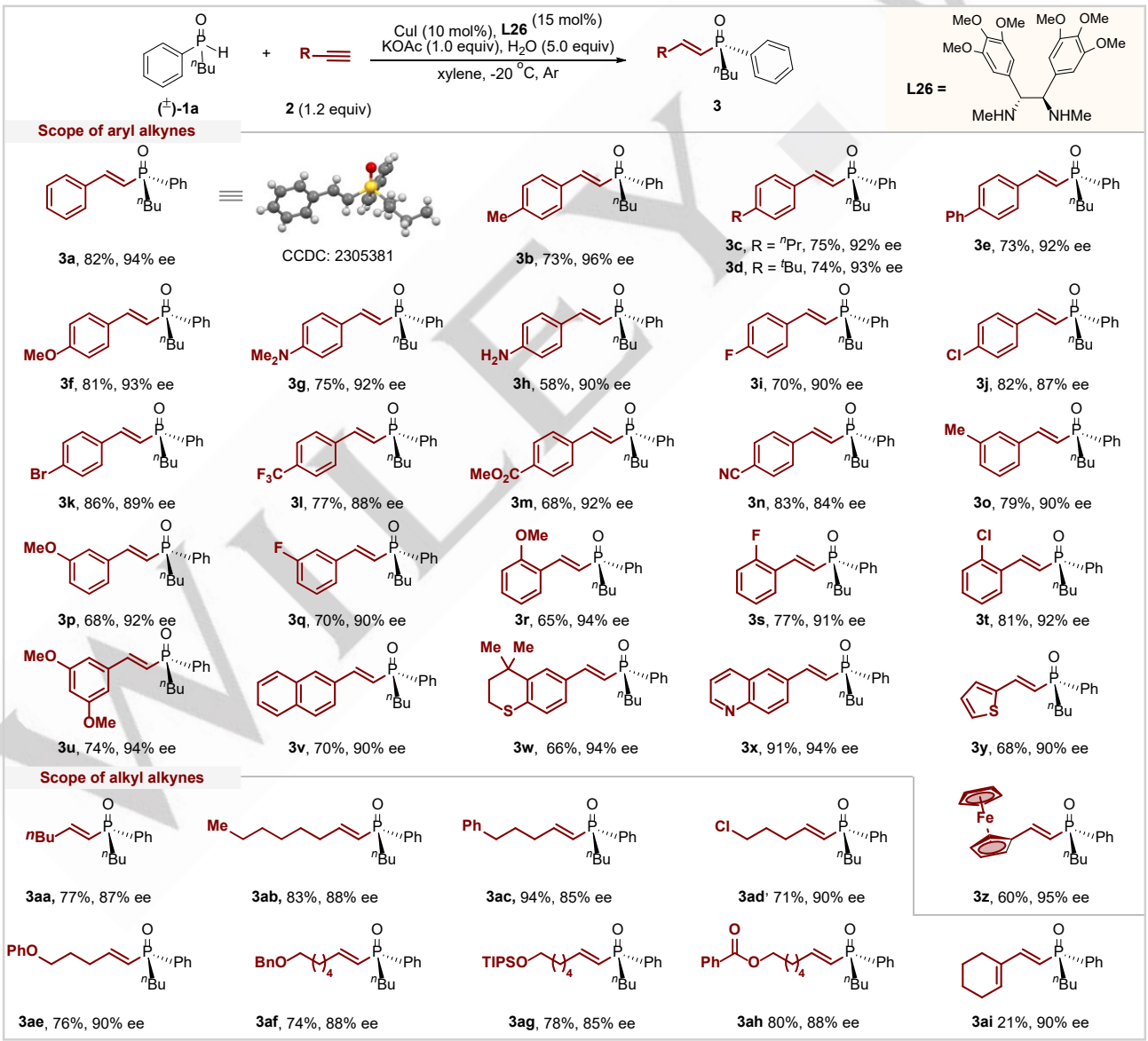
To improve enantioselectivity, we systematically modified the structure of **L9**. Removing the methyl groups from the nitrogen atoms (**L10**) or replacing them with a bulkier ethyl or isopropyl groups (**L11** and **L12**) resulted in no detectable ee, highlighting the importance of the *N*HMe groups in **L9** for stereocontrol. We then explored electronic and steric effects by introducing substituents on the phenyl groups of **L9**. While *ortho*- and *meta*-substituents (**L13** to **L16**) slightly reduced enantioselectivity, *para*-substituents (**L17** to **L19**) increased it. Further modifications at the 3,5-positions of the aryl groups (**L20** to **L26**) significantly increased both yield and enantioselectivity, with **L26**, bearing 3,4,5-OMe_3-substituted aryl groups, providing the best results (95% yield and 81% ee).

We further optimized other conditions, including base, solvent, concentration, and temperature (see SI for details). Conducting the reaction in xylene at a lower concentration (0.05 M) and temperature (-20 °C) increased the enantioselectivity to 93%, but the yield dropped to 51%, even after 96 hours. We attributed this low yield partially to the poor solubility of KOAc in xylene and therefore added 5 equivalents of water to the reaction. Gratifyingly, this adjustment led to a practical yield (82%) with high ee (94%) for product **3a**.

Having established conditions to form tertiary phosphine oxide (TPO) **3a** with high yield and enantioselectivity, we explored the scope of the alkyne component (Table 2). Both aromatic and aliphatic alkynes underwent hydrophosphorylation exclusively in a *cis*- and *anti*-Markovnikov fashion, yielding structurally diverse TPO products with high yields and enantioselectivity (up to 96% ee). The absolute configuration of **3a** was determined to be *S* by X-ray single-crystal diffraction analysis,[22] and other products were assigned by analogy.

Table 2. Scope of alkynes for the copper-catalyzed enantioselective hydrophosphorylation[a]



[a]Reactions were conducted with **1a** (0.1 mmol), **2a** (0.12 mmol) for 96 h, the yields refer to isolated yields, and the ee was determined by HPLC analysis.

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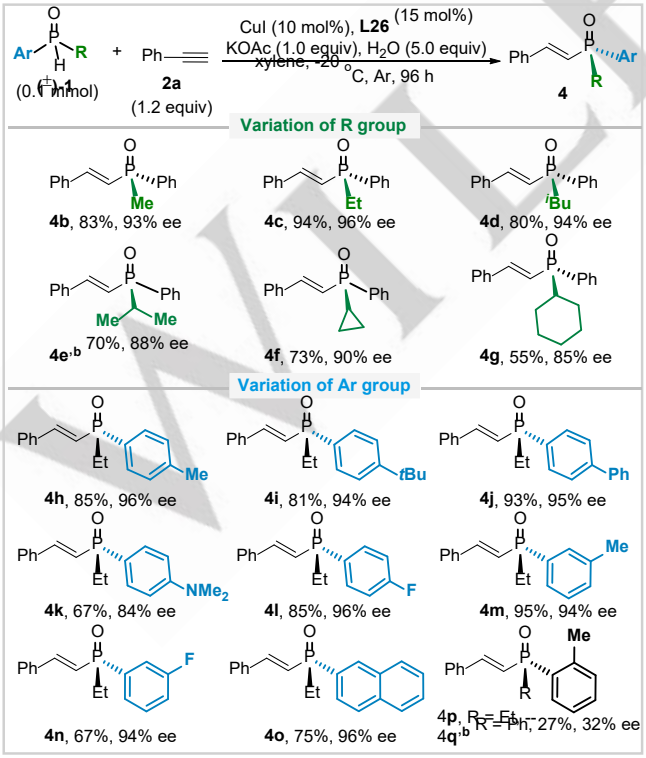
We first investigated aromatic alkynes with various *para*-substituents, including alkyl (**2b-2d**), phenyl (**2e**), halides (F, Cl, Br; **2i-2k**), electron-donating methoxyl (**2f**) and amino groups (**2g** and **2h**), and electron-withdrawing trifluoromethyl (**2l**), ester (**2m**) and nitrile (**2n**). These alkynes efficiently reacted with SPO **1a**, producing TPOs (**3b-3n**) with high enantioselectivity. Notably, the reaction tolerated a free amine (**2h**), yielding product **3h** with 90% ee and a moderate yield (58%). *Meta*- and *ortho*-substituted aryl alkynes also performed well, affording TPOs **3o-3u** with excellent enantioselectivities (≥ 90% ee). Additionally, naphthyl acetylene (**2v**) and heteroaryl-containing alkynes (**2w** to **2z**) were suitable substrates, leading to highly selective products.

We then studied aliphatic alkynes with various functionalities, including alkyl (**2aa** and **2ab**), phenyl (**2ac**), alkyl chloride (**2ad**), ethers (**2ae** to **2ag**), and ester (**2ah**). These alkynes reacted smoothly and selectively, yielding TPOs in high yields and ee values comparable to those from aromatic alkynes. When enyne **2ai** was used, hydrophosphorylation chemo- and regioselectively occurred at the alkyne moiety, producing TPO **3ai** with 90% ee, albeit in a low yield (21%). Internal alkynes, such as diphenylacetylene and 1-butynylbenzene, did not react under the standard conditions.

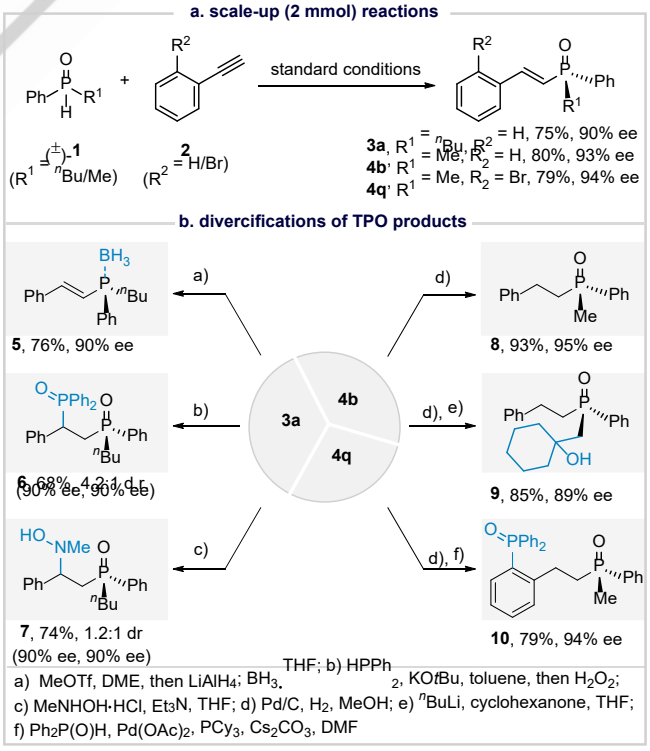
Next, we explored the scope of the SPO component for the enantioselective hydrophosphorylation reaction (Table 3). Both alkyl and aryl groups in SPOs were varied. SPOs with either primary (**1b-1d**) or secondary (**1e-1g**) alkyl groups reacted regio- and stereoselectively with phenylacetylene, yielding TPOs (**4b-4g**) with 85%-96% ee. Reactions with SPOs bearing bulkier secondary alkyl groups showed decreased reactivity, as seen with the slow formation of **4e** (120 hours, 70% yield). SPOs with either *para*- or *meta*-substituted aryl groups (**1h-1o**) were also compatible. However, SPOs with *para*-methyl substituted aryl group (**1p** and **1q**) or with *tert*-butyl and methyl groups (structure not shown) did not undergo hydrophosphorylation under standard conditions. While these sterically hindered SPOs could react at elevated temperatures, both the yield and enantioselectivity decreased significantly (**1q**: 27% yield, 32% ee at 0 °C). Additionally, SPO bearing an ethoxyl group (ethyl phenylphosphinate) exhibited lower reactivity, yielding the desired product in 15% yield with 57% ee at room temperature.

To showcase the synthetic utility of the newly developed enantioselective hydrophosphorylation, we conducted scaled-up reactions and transformed the resulting enantioenriched products into structurally diverse P-chiral scaffolds (Scheme 2). Hydrophosphorylation reactions with SPOs **1a** and **1b** on a 2 mmol scale formed products with yields and ee values comparable to those obtained on a 0.1 mmol scale (Scheme 2a). We then explored transformations to further diversify the alkenyl-substituted TPO products (Scheme 2b). The $P^{(V)}$-**3a** was stereoinversely reduced under conditions with MeOTf and $LiAlH_4$,[23] followed by boron complexation, producing $P^{(III)}$-**5** in 76% yield and 90% enantiopurity. The electron-withdrawing phosphoryl functionality enabled the C-C double bonds in the alkenyl-substituted TPO to act as Michael receptors.[24] For instance, TPO **3a** underwent 1,4-addition with nucleophilic diphenyl phosphine, followed by oxidation, forming 1,2-bisphosphine oxides **6** in 68% yield as a mixture of two diastereomers (d.r. = 4.2:1). Similarly, reaction with nucleophilic *N*-methylhydroxylamine produced 1,3-*N*, *P*-containing scaffold **7**. The alkenyl group in **4b** was efficiently reduced to an alkyl group *via* palladium-catalyzed hydrogenation, yielding dialkyl aryl TPO **8** in 93% yield while maintaining enantiopurity. Deprotonation of

Table 3. Scope of SPOs for the enantioselective hydrophosphorylation[a]



[a]Reactions were conducted with **1a** (0.1 mmol) and **2a** (0.12 mmol). [b]Reaction was conducted at 0 °C for 120 h.



Scheme 2. Scalability and diverse transformations

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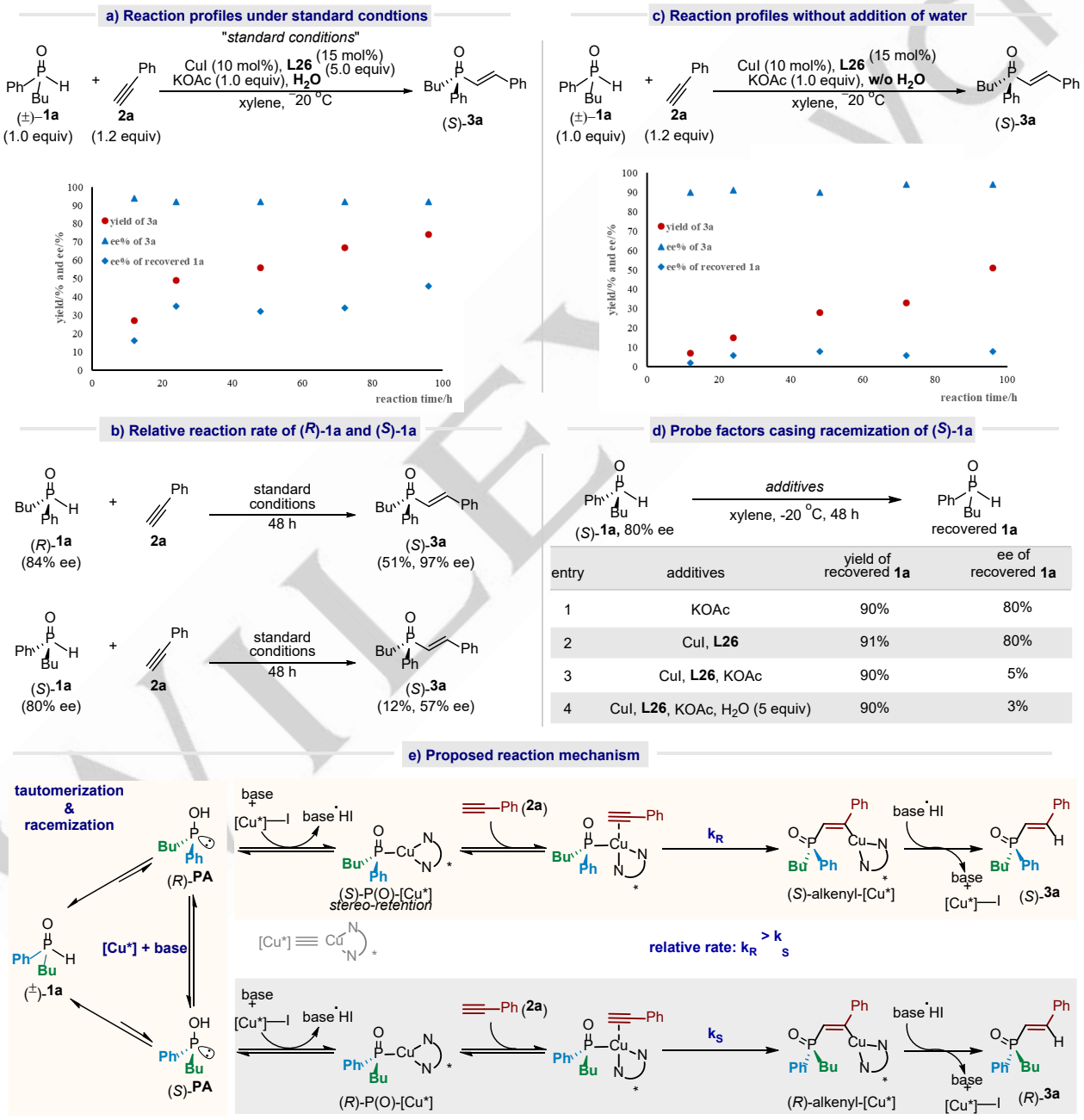
TPO **8** with ^{n}BuLi preferentially occurred at the methyl group, and subsequent trapping with cyclohexanone afforded TPO **9** in 85% yield and 89% ee. Bisphosphine oxide **10** was efficiently synthesized from TPO **4q** and diphenyl phosphine oxide using palladium-catalyzed C-P cross-coupling conditions. These transformations yield P-stereogenic compounds that are difficultto produce using conventional methods, making them valuable precursors for the development of novel chiral ligands or organocatalysts.[3a, 3b, 25]

We conducted various reactions to gain preliminary insights into the mechanism of this enantioselective hydrophosphorylation (Scheme 3). First, we examined the variations in enantiomeric excess (ee) of the resulting TPO **3a** and the unreacted SPO **1a** during the reaction. The ee of **3a** remained consistently high (92%-94%) throughout the reaction (Scheme 3a), indicating that racemic SPOs reacted *via* a dynamic kinetic asymmetric transformation mechanism. Meanwhile, the ee of the recovered unreacted **1a**, with (*S*)-**1a** as the major enantiomer, gradually increased up to 46%, suggesting that the interconversion between (*S*)-**1a** and (*R*)-**1a** (racemization) was slower than the formation of (*S*)-**3a**. Parallel reactions with (*R*)-**1a** and (*S*)-**1a** showed that both led to the formation of (*S*)-**3a** as the major component, but (*S*)-**1a** reacted much slower and significantly less enantioselectively than (*R*)-**1a** (Scheme 3b).[26] These results suggest that (*R*)-**1a** is the preferred enantiomer in the reaction and reacts in a stereoretentive fashion.

To understand to role of added water in the dynamic kinetic asymmetric hydrophosphorylation, we compared reactions with



entry	additives	yield of recovered **1a**	ee of recovered **1a**
1	KOAc	90%	80%
2	CuI, **L26**	91%	80%
3	CuI, **L26**, KOAc	90%	5%
4	CuI, **L26**, KOAc, H_2O (5 equiv)	90%	3%

Scheme 3. Mechanistic studies and proposed catalytic cycle

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and without added water (Scheme 3c *vs* Scheme 3a). In the reaction without water, product **3a** was also formed with consistently high ee values (90%-94% ee), and racemization of SPO **1a** occurred as well, indicating that water is not essential for the stereocontrol of the hydrophosphorylation and the racemization of SPOs. However, water significantly influenced the reaction rate: the reaction with water yielded product **3a** in 74% yield in 4 days, whereas the reaction without water only achieved 51% yield in the same period and less than 60% yield even after 7 days. This rate-accelerating effect of water is likely due to the increased solubility of KOAc in the reaction system.

We further investigated the factors causing SPO racemization by subjecting (*S*)-**1a** to various control conditions (Scheme 3d). (*S*)-**1a** did not racemize over 48 hours with either KOAc or copper complexes alone (Scheme 3d, entries 1 and 2). In contrast, nearly complete racemization occurred in the presence of both KOAc and copper complexes, regardless of the presence of water (Scheme 3d, entries 3 and 4). These results suggest that both the base and copper complexes are essential for SPO racemization. While the exact mechanism behind the racemization remains unclear, it is likely driven by a base-promoted pyramidal inversion of the trivalent phosphinous acid (the tautomer of SPO) or its conjugate base.[27] In this process, the copper complex is thought to coordinate with the oxygen of SPO, thereby increasing its acidity and facilitating the inversion.

Based on these preliminary results and related literature,[16],[28] we proposed a mechanism for the copper-catalyzed enantioselective hydrophosphorylation of alkynes, exemplified with reaction between **1a** and **2a** (Scheme 3e). Tautomerization of pentavalent racemic SPO (+/-)-**1a** leads to two trivalent enantiomers, phosphinous acids (*S*)-**PA** and (*R*)-**PA**. (*R*)-**PA** reacts with in situ generated chiral copper catalysts [Cu*]-I in the presence of base to form a phosphoryl copper intermediate (*S*)-P(O)-[Cu*], which then reacts with alkyne **2a** through coordination and *cis*-addition to yield (*S*)-alkenyl-[Cu*] species. This species subsequently forms the *anti*-Markovnikov product (*S*)-**3a** upon protonation. This process, forming (*S*)-**3a**, is significantly faster than the parallel formation of (*R*)-**3a** from (*S*)-**PA**.

In conclusion, we have successfully developed the first copper-catalyzed enantioselective hydrophosphorylation of alkynes, utilizing a newly designed chiral 1,2-diamine ligand. This work represents the first example of dynamic kinetic asymmetric hydrophosphorylation of unsaturated carbon-carbon bonds, driven by a unique copper catalyst capable of racemizing of SPOs. The reaction exhibits broad tolerance for unactivated terminal alkynes, consistently producing structurally diverse P-stereogenic phosphorus compounds with exclusive *cis*-selectivity and high regio- and enantioselectivity (up to >20:1 r.r. and 96% ee). Mechanistic studies further elucidate the pivotal roles of the copper catalyst and base in facilitating SPO racemization, while water acts as a rate-accelerating factor by improving the solubility of the inorganic base in the reaction medium.

Acknowledgements

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Keywords: *P*-stereogenic compounds • asymmetric synthesis • dynamic kinetic resolution • copper catalysis• transition metal catalysis

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[22] Deposition Number 2305381 (**3a**) contains the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.

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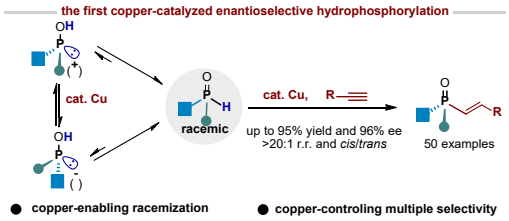

The first copper-catalyzed enantioselective hydrophosphorylation of alkynes is reported, marking the inaugural example of dynamic kinetic asymmetric hydrophosphorylation of unsaturated carbon-carbon bonds. The reaction exhibits a broad scope of unactivated alkynes, consistently yielding structurally diverse P-stereogenic phosphorus compounds with exclusive *cis*-selectivity and high regio- and enantioselectivity (up to >20:1 r.r. and 96% ee).

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