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P-Chiral Alkenylphosphine Oxides Enabled by Highly Chemo-, Regio- and Enantioselective Hydrophosphinylation of Alkynes

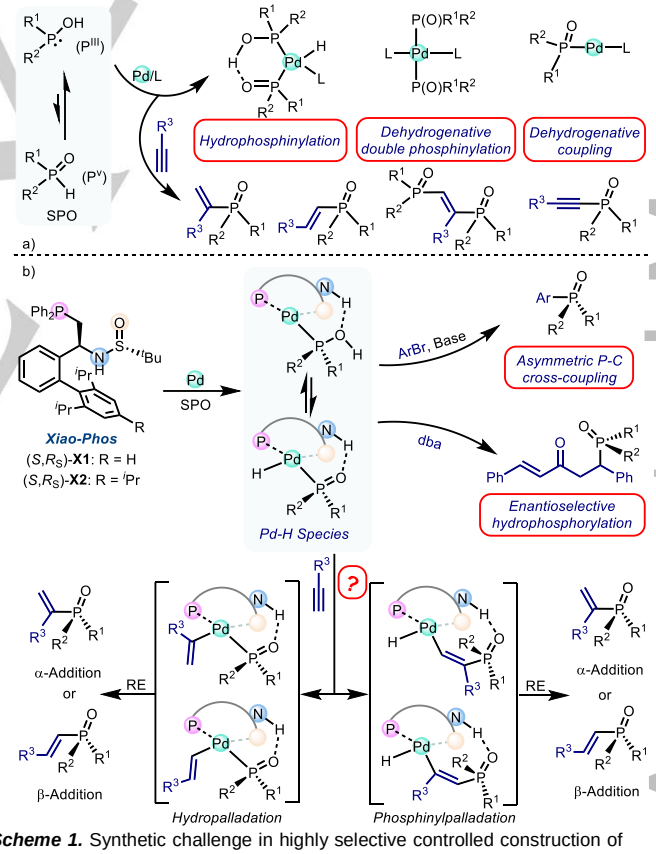
*Qiang Dai, Lu Liu, Yanyan Qian, Wenbo Li and Junliang Zhang**

Dedicated to 70th anniversary of Shanghai Institute of Organic Chemistry, CAS

Abstract: *Alkenylphosphine oxides have a wide spectrum of practical applications. However, high chemo-, regio- and enantio-controlled construction of this structural motif still constitutes a significant synthetic challenge. Here we show an efficient strategy that can be realized via the palladium/Xiao-Phos catalytic system, which lead to highly regioselective formation of the anti-Markovnikov adducts by addition of a secondary phosphine oxide to an alkyne. Diverse (hetero)aryl, alkyl alkynes and both terminal and internal alkynes can be employed as substrates. The kinetic resolution process makes it possible to produce alkenylphosphine oxide and recovered SPO both with high ees. Further transformations of these two P-chiral scaffolds confirm the high practicability and application prospect of our synthetic strategies. Initial mechanistic studies strongly suggested that the hydropalladation is more inclined for this conversion process.*

Introduction

P-Stereogenic phosphines represent a very important class of chiral phosphine compounds,[1] however, despite tremendous efforts have been devoted to develop asymmetric catalytic reactions for their preparation over the past decades, the catalytic enantioselective construction of P-stereogenic phosphines is a long standing goal that has only been partially achieved.[2] Beyond that, the biggest challenge lies in achieving this compounds with structure that are likely to be utilized in real applications.[1,2] Alkenylphosphine oxides belong to a class of significant building blocks in synthetic chemistry. The olefinic bond can be further modified by adding a number of heteroatom nucleophiles,[3] carbanion species[4] or carbon-centered radicals[5] to providing more practically bifunctional adducts. Accordingly, such compounds and their derivatives play critical roles in many fields, ranging from bioactive species[6] to material science[7] and also using as the key precursors for the preparation of valuable phosphine ligands.[8] Despite these diverse practical applications, however, synthetic methods available are quite limited. Common synthetic approaches to this type of molecules include transition-metal-catalyzed cross-coupling of P(O)H compounds with vinyl halides,[9] Heck-type coupling of vinylphosphonates with various aryl partners,[10] and radical conditions.[11] In an effort to pursue atom economy and straightforward pathways, the catalytic addition of H−P(O) across unsaturated systems, referred to as hydrophosphinylation, has been investigated in recent years.[12] Palladium and other transition metals have been used in catalytic hydrophosphinylation,[13] However, these reactions commonly lack chemo-, regio-, and stereoselectivity more or less[14] (Scheme 1a).



Scheme 1. Synthetic challenge in highly selective controlled construction of P-chiral alkenylphosphine oxide.

The unique tautomerism of the hydrogen phosphoryl compounds between the P(V) and P(III) forms [P(O)H=P(OH)], enables it to ligate, like phosphines R_3P, to transition metals,[15] which is the key to the hydrophosphinylation. On the other hand, the various coordination modes might exist in one system and the formed metal complexes bearing different reaction properties,[16] as

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such, makes the reaction more complicated and suppress the selectivity to some extent (Scheme 1a). Undoubtedly, much more difficulties and challenges would be encountered when considering the construction of P-stereocenter on this basis. Since the low availability of the catalytic asymmetric synthesis of P-stereogenic phosphines,[2] in the reported systems, highly selective construction of alkenylphosphine oxide while simultaneous formation of P-stereocenter has hardly been reported.[13e]

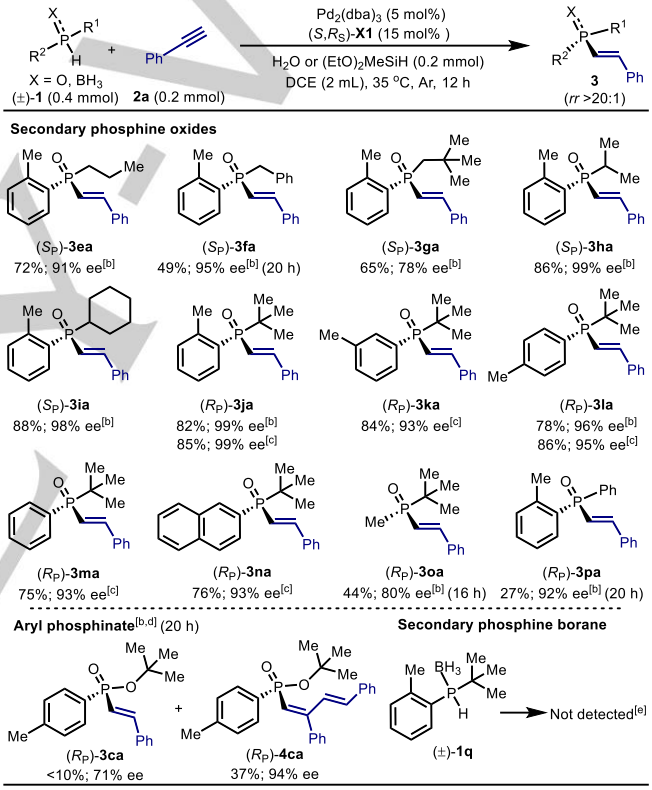
Recently, our groups became interested in the formation of P–C bonds by the metallo-catalysed P–C cross coupling reactions or by the atom-economical hydrophosphinylation reactions. Dealing with P–C cross coupling reactions, we have developed a robust Pd/Xiao-Phos-catalytic system for the efficient synthesis of highly enantioenriched P-stereogenic phosphine oxides (Scheme 1b).[17] Preliminary results indicated the chiral catalytic system could selectively identify the configuration of the secondary phosphine oxides (SPOs), referred to as kinetic resolution process, which plays the decisive role in the enantioselection step. Moreover, a more competitively enantioselective hydrophosphorylation process was observed as a side reaction,[17] which indicates the active intermediate may undergo the chiral palladium hydride species in the catalytic cycle. Probably, the proton might bind in equilibrium to the O atom of the SPO and directly to the palladium center. For further understanding this asymmetric introduction mode and expanding a new reactivity platform for P-chiral construction, we questioned whether certain chiral catalytic system could engage the hydrophosphinylation process to form adducts containing P-stereocenter selectively. To test this, we selected alkynes as suitable unsaturated system to construct a single P-stereocenter. Despite these, much more difficulties still need to be overcomed and we were quite uncertain whether these selectivities mentioned above would be compatible under a single catalytic system (Scheme 1b).

Results and Discussion

Our initial effort was focused on switching the preference of the previous catalytic system to facilitate the hydrophosphinylation process. Therefore, we expected the additional hydrogen source would enable the equilibrium favouring the formation of palladium hydride species. After extensive screening (for the conditional optimization processes, please see Supporting Information, Section 3), we were pleased to observe that silane or water is an additive suitable for different types of SPO, and that both promote the formation of the *anti*-Markovnikov hydrophosphinylation adduct with high chemo-, regio- and enantio-selectivity.

With the optimal conditions in hand, we investigated the scope of the enantioselective hydrophosphinylation reaction and found that a diverse array of alkynes and SPOs are viable in this transformation, providing P-chiral alkenylphosphine oxides in excellent regioselectivity (*rr* >20:1). We initially probed variations of alkyl substitution on the SPOs (Table 1). The reaction displayed good steric tolerance. As steric closely adjacent to the P atom increases, we observed the reaction all underwent smoothly to afford the desired products in moderate to good yield and excellent enantioselectivities (**3ea**−**3ja**, 49−88% yield, 91−99% ee). As an exception, the remote steric hindrance had great influence on the enantioselectivity, and only giving **3ga** in 78% ee.

Table 1: Scope of the secondary phosphine reagents.[a]



[a] Conditions: (±)-**1** (0.4 mmol), **2a** (0.2 mmol), $Pd_2(dba)_3$ (5 mol%), (*S*, R_S)-**X1** (15 mol%), the indicated additive (0.2 mmol), DCE (2 mL), Ar, 35 °C, 12 h. The ratio of regioselectivity of **3 : 3'** was determined by ^1H *NMR* analysis of the crude product. Isolated yield. Enantiomeric excesses were determined by HPLC. [b] Using $(EtO)_2MeSiH$ as the additive. [c] Using H_2O as the additive. [d] (±)-**1c** (0.4 mmol) and **2a** (0.4 mmol) was used. [e] No related hydrophosphination products were detected with or without additives.

With respect to the aryl group of SPOs, the phenyl group with different location of the methyl group, and the naphthyl group were also compatible with this protocol, furnishing **3ka**−**3na** with good yields and excellent enantioselectivity. Notably, the absolute stereochemistry of **3ma** was identified by X-ray crystallography analysis.[18] In addition, the comparable yield and ee value of **3ja** or **3la** in different hydrogen source showed that

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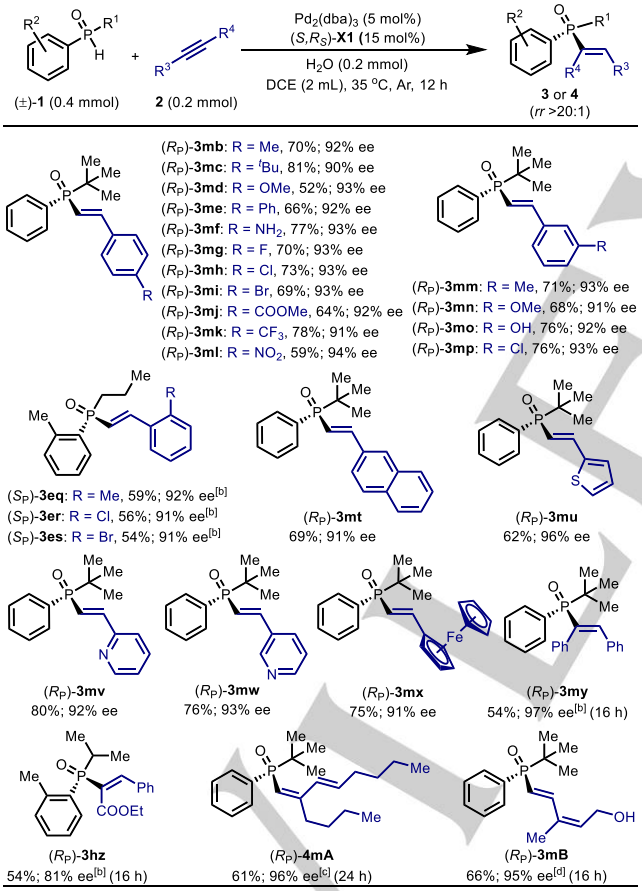
the $(EtO)_2MeSiH$ and water took the same efficiency in such *t*-butyl-, aryl-substituted SPOs at least. When dialkyl substituted SPO **1o** was subjected to the reaction conditions, the reaction suffered from low efficiency, yielding **3oa** only in 44% yield, 80% ee. Unfortunately, biaryl substituted SPO **1p** was less reactive and gave the hydrophosphinylation product **3pa** in 27% yield, albeit still in excellent enantioselectivity (92% ee). We also tried other types of secondary phosphine reagents in this catalytic system. For aryl phosphinate **1c**, the reaction was more inclined to produce the double alkyne addition product and maintain excellent enantioselectivity (**4ca**, 37% yield, 94% ee), while the obtained trace amount of the conventional single alkyne inserted product **3ca** only reached 71% ee value. In the condition with or without additives, the secondary phosphine borane adduct **1q** was not compatible with this system and no associated hydrophosphination products were detected.

Table 2: Scope of the alkynes.[a]



[a] Conditions: (±)-**1** (0.4 mmol), **2a** (0.2 mmol), $Pd_2(dba)_3$ (5 mol%), (S, R_S)-**X1** (15 mol%), H_2O (0.2 mmol), DCE (2 mL), Ar, 35 °C, 12 h. The ratio of regioselectivity of **3 : 3'** was determined by ^1H *NMR* analysis of the crude product. Isolated yield. Enantiomeric excesses were determined by HPLC. [b] H_2O was insteaded by $(EtO)_2MeSiH$ as the additive. [c] (±)-**1m** (0.4 mmol) and 1-hexyne (0.4 mmol) was used, less than 10% yield of single alkyne inserted product **3mA** was detected, and the ee value is 89%. [d] Alkyne **2B** = (*Z*)-3-Methylpent-2-en-4-yn-1-ol.

The scope with respect to different alkynes was examined next (Table 2). Good functional group compatibility was observed, most phenylacetylene derivatives with regular substituents as well as some reactive handles such as amine, halides, ester, alcohol, nitro could undergo the reaction smoothly to afford the corresponding linear P-chiral alkenylphosphine oxides in moderate to good yield and excellent enantioselectivities (**3mb**−**3es**, 54−81% yield, ≥90% ee). Regarding to the *ortho* position of phenylacetylene, it might be too close to the reactive center, and thus using a less steric SPO **1e** and accompanying $(EtO)_2MeSiH$ as additive could ensure the enantioselectivity. Moreover, heteroaryl groups such as naphthyl, thiophenyl, pyridinyl were all tolerated, and the ferrocenyl, which was commonly found in ligand backbones, could be incorporated into the desired product with equally high efficiency (**3mt**−**3mx**, 62−80% yield, 91−96% ee). Compared with terminal alkynes, diphenylacetylene resulted in similar yield and furnishing **3my** with better enantioselectivity (54% yield, 97% ee).

Significantly, the reaction with unsymmetrical phenylacetylenes like ethyl phenylpropiolate also exhibited high regioselectivity, the phosphinylation occurred selectively at the *α*-position of the ester group, converting into single isomer **3hz** with 54% yield, 81% ee. Of particular note is that when alkyl terminal alkyne was subjected to the standard reaction conditions, an unexpected double alkyne addition product **4mA** was afforded as the major product over the normal *mono*-alkyne inserted product **3mA**. In order to increase the selectivity to the product **4mA**, we increased the concentration of the reaction solution to increase the yield of **4mA** to 61% with 96% ee. We also tested the enantioselectivity of the less produced product **3mA**, interestingly, a relatively low ee value (89% ee) was provided. According to the structure analysis of **4mA**, it might not stem from the head-to-tail dimerization of 1-hexyne.[19] The most plausible pathway is that after the first alkyne inserted into the palladium hydride species, the formed alkenyl palladium complex did not undergo reductive elimination immediately, and then the second alkyne inserted competitively into the alkenyl palladium complex, followed by the reductive elimination, and eventually led to formation of the product **4mA**. It seems an extended conjugation could promote the reductive elimination rate, that is why the *mono*-alkenyl palladium complex is difficult to undergo reductive elimination before the second alkyne inserted, which might also account for the high regioselectivity of **3hz**. In support of this hypothesis, a separate reaction using conjugated enyne **2B** did efficiently produce **3mB** in high selectivity (66% yield, 95% ee). But for the alkyne insertion process, we thought that the ee value of **3mA** and **4mA** appeared to strongly suggest that 1-hexyne was inserted into the H–Pd bond (hydropalladation) rather than the Pd–P(O)R_2

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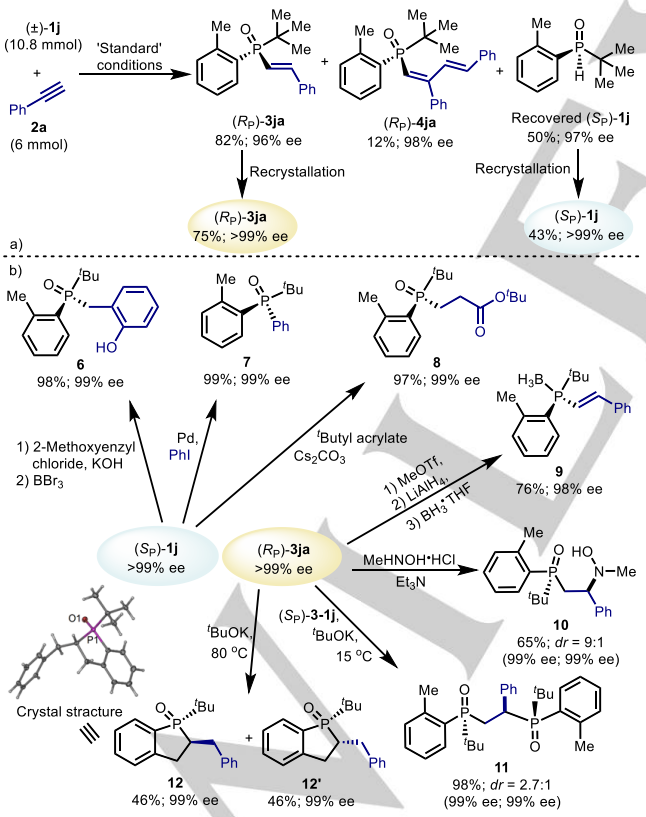
bond (phosphinylpalladation). Otherwise, the products **3mA** and **4mA** should have the same enantioselectivity level regardless of the second alkyne insertion, as the P-stereocenter has been constructed after the phosphinylpalladation.

To demonstrate the practicability of our method, gram-scale preparation was firstly conducted undergoing the kinetic resolution process to producing alkenylphosphine oxide **3ja** and recovering SPO **1j** both with excellent enantioselectivity, and both of which could be further elevated to enantiomerically pure level via the operable recrystallization process (Scheme 2a). A small amount of unconventional double alkyne inserted product **4ja** was produced within this large-scale condition (Scheme 2a). Further transformations of the two P-chiral scaffolds were investigated (Scheme 2b). We firstly managed to synthesize a potential P-chiral organocatalyst **6** in almost quantitative yield through two steps without loss of P-chirality. Its racemic version is widely used in catalytic Mitsunobu reaction,[20] and such transformation could double the utility of this catalyst and might enable the asymmetric catalysis form. In addition, cross coupling and Michael addition could also be used to install an aryl or alkyl group at the P atom to forming P-chiral phosphine oxides **7** and **8** (Scheme 2b).



Scheme 2. Gram-scale synthesis and practical synthetic transformations.

Although P-chiral TPOs are also effective ligands in a range of asymmetric reactions,[1c] the corresponding phosphines are more widely used in chemical synthesis. Therefore, we were pleased to find that reduction to the corresponding P-chiral phosphines can be achieved by treating the enantiopure TPOs with a combination of MeOTf and $LiAlH_4$, and forming the P-chiral phosphine−BH_3 adducts **9** after borane protection (Scheme 2b). The obtained P-chiral phosphines from reduction procedure provide potential opportunities for asymmetric metal-catalyzed transformations. As the known chemical reactions, the olefinic bond can be further functionalized by adding a number of heteroatom nucleophiles.[3] By using the *N*-methylhydroxylamine and the recovered (S_P)-**1j**, we successfully obtained the P,P-, P,N-compounds **10** and **11** in moderate to good yield as a mixture of diastereomers, and the P-chirality retained (Scheme 2b). Furthermore, besides the intermolecular additions, an intramolecular cyclization was achieved by the addition of *in-situ* generated benzyl carbanion species under basic condition, which provides a rapid synthesis of benzophospholane oxide compounds **12** and **12'** (Scheme 2b). Recently, phospholane oxides and their cyclic derivatives have emerged as effective precatalysts for an expanding new area of organocatalysis. Current areas of development include catalytic aza-Wittig,[21] Appel reactions,[22] and the most recent deoxygenative condensations.[23] The formed diastereomers (**12** and **12'**) could be easily separated by column chromatography and the absolute stereochemistry of **12** was identified by X-ray crystallography.[24] Their unique structure will certainly have potential applications in these and other asymmetric catalytic areas. Such P-, P,P-, P,O-, P,N-compounds, containing P-chirality and even both P,C-chirality, that are difficult to synthesize from conventional methods, which confirms the high practicability and application prospect of this synthetic strategy.

The reaction of (±)-**1m** and **2a** in the concentrated reaction solution did favored the formation of bialkyne inserted product **4ma** (Scheme 3a), its relatively higher ee value than **3ma** is in accordance with previous findings (**4ca**, **4mA** and **4ja**) and further verifies the reaction proceeds through the hydropalladation process. Matched/mismatched reactions also be conducted and both gave the S_P-enantiomer of product (Scheme 3b). We thought the reduced ee value of recovered **1j** in the matched conditions resulted from the enrichment phenomenon rather than the racemization of **1j** during the reaction. The amount of products generated beyond expectation in the mismatched conditions indicated another low active species might exist in the reaction. To probe the racemization ability of SPO **1j**, we conducted the enantioenriched **1j** under optimal conditions without addition alkyne, and found that in all cases the remaining **1j** fully maintained their original ee value, which means that the bulky SPO **1j** was unlikely to racemize in the reaction (Scheme 3c, for more basic data, please see Supporting Information, Section 7). We also showed that the *N*-

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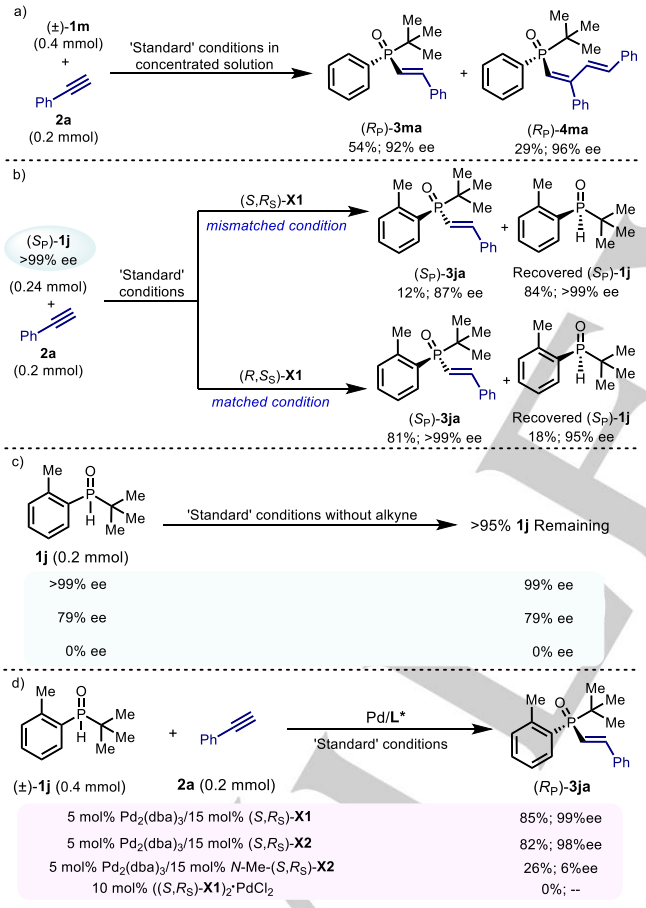
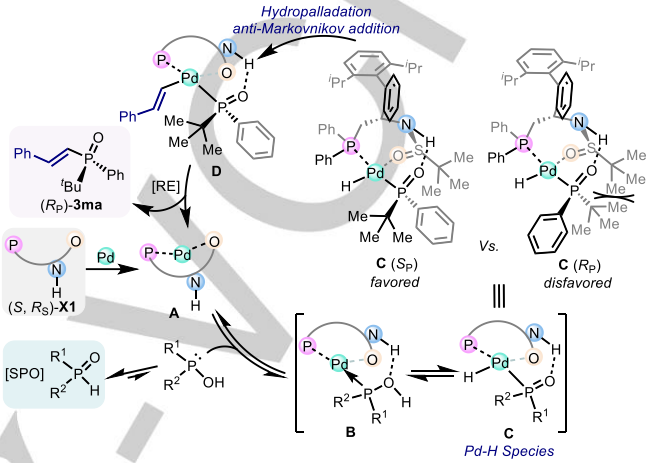
methylated ligand (*S*, R_S)-**X2** dramatically inhibited the yield and ee value of the product (Scheme 3d), from which we can rationalize the NH moiety of the ligand is crucial for the catalytic activity and enantioselectivity. The H-bond interaction between the sulfinamide NH and the oxygen of the SPO plays the key role for the chiral introduction (Scheme 4), similar to the previous work.[17] On the other hand, we can also infer the H-bond blocked ligand still has week catalytic activity from the poor performance of *N*-methylated ligand (*S*, R_S)-**X2**, and almost in a none enantioselective way. This existing catalytic pattern of non-hydrogen bond interactions might explain the higher than expected yield in the mismatched conditions (Scheme 3b). In addition, palladium complex [((*S*, R_S)-**X1**)$_2$·$PdCl_2$][25] has no catalytic activity, which is consistent with the catalytic results of Pd(II).

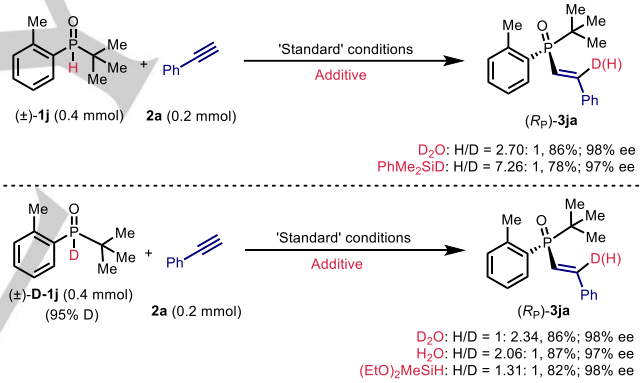


Scheme 3. Mechanistic Research Experiments.

Based on literature precedent and our own observations,[17] the Pd(0) precatalyst undergoes ligand substitution with the Xiao-Phos to form a chiral monomeric species **A**, and subsequent oxidative addition with trivalent phosphinic acid ($R_2P(OH)$) forms Pd−H species **C** (Scheme 4). The spatial repulsion between the *tert*-butyl of the sulfinyl group and the large alkyl group of the SPO might play the decisive role in the enantioselective discrimination step. It seems the chiral catalytic system could selectively identify the configuration of the SPOs through coordination and hydrogen bond interactions, and the more favored intermediate **C**(S_P) forms the *anti*-Markovnikov addition intermediate **D** through hydropalladation process. The final reductive elimination of **D** results in the target product (R_P)-**3ma**, which is in agreement with the formation of the major experimental enantiomer.



Scheme 4. Tentative mechanism.



Scheme 5. Deuterium incorporation experiments.

To further support the mechanistic hypothesis and demonstrate that water and silane as auxiliary hydrogen source could favor the palladium−H species, we conducted a series of deuterium incorporation experiments by using deuterium-labeled **D-1j**, D_2O and $PhMe_2SiD$ (98% D) (Scheme 5). Although the H-exchange is very easy between SPO and water, it is almost nonexistent with silane (for the stability test of $PhMe_2SiD$, please see Supporting Information, Section 7). In these experiments, we saw deuterium incorporation at the *β*-positions of the alkenylphosphine oxides (H/D = 7.26:1) when using $PhMe_2SiD$ as additive. We reason the H/D exchange or proton supply is only possible during the period of active Pd−H species. Water may also be a suitable hydrogen source, or it may have different mechanisms from silane, such as changing the H-bond stability through its own function as an H-bond Bridge. However, whether it stabilized or disordered the transition state in the reaction

process might largely relate to the steric hindrance of the substrate used.

Conclusion

In summary, we have developed a Pd/Xiao-phos-catalyzed enantioselective hydrophosphinylation of alkynes. Secondary phosphine oxides and alkynes can be coupled to furnish P-chiral alkenylphosphine oxides in high chemo-, regio-, and enantioselectivities. This protocol works with a wide range of substrates and tolerates a series of functional groups. Flexible synthetic elaboration for both the P-chiral alkenylphosphine oxides and recovered SPO renders this protocol highly practical. The strategy disclosed herein may serve as a general principle for achieving other synthetically or medicinally useful P-chiral phosphine derivatives.

Acknowledgements

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Conflict of interest

The authors declare no conflict of interest.

Keywords: P-Chiral Alkenylphosphine Oxides • Enantioselective hydrophosphinylation • palladium/Xiao-Phos • Pd−H species • hydropalladation

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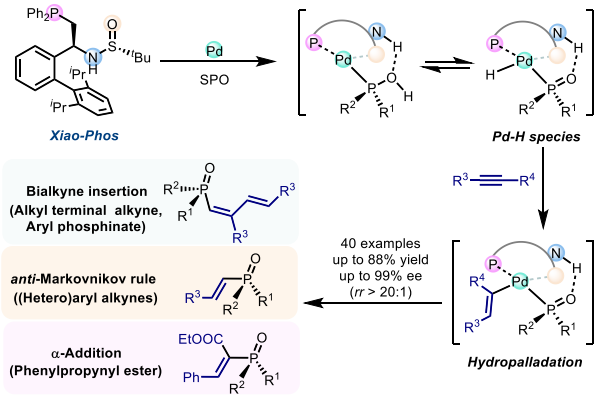

Highly chemo-, regio- and enantioselective hydrophosphinylation of alkynes was achieved by using the palladium/Xiao-Phos catalytic system. Providing enantioenriched P-chiral alkenylphosphine oxides with broad substrate scope.

*Q. Dai, L. Liu, Y. Qian, W. Li, J. Zhang**

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