Palladium Catalyzed Asymmetric Hydrophosphinination of Internal Alkynes: Access to Phosphine-Functionalized Axially Chiral Olefins

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Abstract

Palladium-catalyzed atroposelective hydrophosphination of sterically hindered internal alkynes with secondary phosphines has been realized, affording C-N axially chiral trisubstituted olefins (vinylphosphines) in excellent regioselectivity, (E)-selectivity, and enantioselectivity. The axial chirality was constructed via integration of hydrophosphination and dynamic kinetic transformation of the alkynes, with both symmetrical and nonsymmetrical secondary phosphines being applicable.

Introduction

Development of novel synthetic methods that utilizes simple and abundant reagents is highly desirable toward selective construction of value-added organics. The catalytic hydrofunctionalization of alkynes is intriguing for achieving these goals in that both substrates are widely available and readily accessible, and this transformation also features high atom-economy. While diverse mechanistic pathways have allowed development of numerous synthetic methods of alkyne hydrofunctionalization, the functionalized products are mostly achiral since this reaction does not directly generate a chiral carbon center. In case of asymmetric alkyne hydrofunctionalization, enantioenriched products are often afforded via desymmetrization of the prochiral alkyne or functionalizing reagent, formation of chiral allylic compounds or exhaustive hydrofunctionalization to C-C single bonds.

On the other hand, axial chirality represents a large family of chiral platforms that are widely found in chiral ligands or catalysts, synthetic building blocks, and pharmaceuticals. The majority of axially chiral molecules that have been extensively studied are biaryls. In contrast, axially chiral olefins have been much less explored likely due to their synthetic challenges associated with their reduced atropostability since the bonds around the open-chain C=C bond may undergo deformation to minimize steric repulsion. The ready availability of substrates renders alkyne hyrofunctionalization an attractive strategy to address such synthetic challenges provided that sterically internal alkynes are used and the reaction also occurs with the correct regioselectivity. However, sterically hindered alkynes generally exhibited limited reactivity. Consequently, atroposelective hydrofunctionalization of alkynes that affords trisubstituted chiral olefins remains a drastic challenge. In fact, to evade this challenge, annulative difunctionalization of alkynes have often been explored instead via well-known metal catalyzed [2+2+2] cycloaddition, [4+2] annulation, or C-H bond activation but the products are typically (hetero)aromatics. Nevertheless, organocatalysis plays a pivotal role in atroposelective hydrofunctionalization of alkynes (Fig. 1a). In 2017, Tan elegantly realized hydroalkylation of alkynals using b-diketones toward construction of trisubstituted acroleins via intermediacy of reactive allene species. Yan and others developed novel organocatalyzed hydrofunctionalization of 1-alkynyl-2-naphthol analogues by taking advantage of the vinylidene ortho-quinone methide intermediate. In this regime, Tan also extended the nucleophile to 2-naphthols for efficient hydroarylation. Recently, Chi described NHC-catalyzed atroposelective synthesis of axially chiral styrenes involving selective 1,4-addition of sulfinic anion to acetylenic acylazolium intermediate as the key step. In these cases,
sterically hindered alkynes bearing a functional handle at the alkynyl position or in the naphthol ring are employed. Despite the progress, the hydrofunctionalization is limited in reaction patterns governed by the specific organocatalytic modes with a handle in the sterically hindered alkyne. Thus, introduction of new heteroatoms such as phosphorus via hydrofunctionalization that delivers functional molecules is under great demand.

The significance of chiral phosphines as ligands or catalysts has called for new asymmetric synthetic methods. Asymmetric hydrophosphination of alkynes has been developed mostly using terminal alkynes as the substrates (Fig. 1b), and the products are restricted to chirality at the P atom. Besides alkynes, asymmetric hydrophosphination of activated olefins has been extensively studied since 2010 by Duan, Leung, and Yin, Zhang, Harutyunyan and Ge, and others using Pd, Ni, Cu, and Mn catalysts. Chi recently also developed NHC-catalyzed hydrophosphination of α-bromoenals. In addition to unsaturated substrates, carbon and hetero electrophiles also effectively coupled with P(III)-H and P(V)-H reagents. In all these reports, the reactions are limited to generation of C- or P-chiral centers. Of note, synthesis of the large family of axially chiral phosphines remains largely untouched via hydrophosphination. In atroposelective hydrophosphination of alkynes, the reactivity, regioselectivity, and enantioselectivity are major concerns. We reasoned that the reactivity and the regioselectivity may be partially addressed using an electronically biased and sterically hindered alkyne such as 1-alkynylindole. Nevertheless, the substrate inhibition should be fully addressed since in many cases the PH substrate may competitively bind to the catalyst. We rationalized that the substrate inhibition and the enantioselectivity may be collectively addressed using a proper electron-rich chiral bidentate phosphine ligand that can suppress the PH binding while rendering chiral induction (Fig. 1c). We now report our proof-of-concept studies on palladium-catalyzed atroposelective hydrophosphination of internal alkynes for generation of axial and central chirality using symmetrical and nonsymmetrical secondary phosphines.

**Results And Discussion**

We initially screened four 1-indolylalkynes bearing a variable 2-substituent by DFT analysis of the atropostability of the corresponding hydrophosphinated products (Fig. 2). Moderate or low atropostability was identified for products A-C, and the presence of a bulky 2-Ts group increased the barrier of racemization. Therefore, 2-sulfonyl-substituted alkynylindole (1a) was selected as our model substrate for further optimization.

We next conducted experimental optimization studies using alkyne 1a and Ph2PH as substrates under palladium catalysis (Table 1 and Supplemental Information). A large set of chiral bidentate ligands were screened at 30 °C. In many cases, decay of the enantioselectivity was observed as the reaction time was prolonged. Among the chiral ligands surveyed, (S, S)-BDPP, QuinoxP, and selected Josiphos ligands outperformed others and offered good enantioselectivity (entries 1, 2, 12). As expected, generally higher
enantioselectivity was obtained when an electron-rich ($R_P, R$)-Josiphos SL-J003-1 (L12) was used (entry 12). Screening of the palladium source indicated that Pd(acac)$_2$ was superior in terms of enantioselectivity (entries 15-17). Evaluation of solvents returned PhMe or PhCl as the more suitable one (entries 18-20). Introduction of CsOAc further improved the enantioselectivity to 94%, and the product was isolated in excellent yield (entry 22). Other acid or base additives tended to give inferior results (entries 21, 23, and 24). The direct hydrophosphination product 3' turned out to be moderately stable under air at ambient temperature, and it was converted to the oxide for convenience of characterization.

Having established of the optimal reaction conditions, we next explored the scope and generality of this coupling system (Fig. 3A). Under the standard conditions, a broad scope of 1-indolyalkynes has been defined. The 3-unsubstituted indolyl substrate also reacted efficiently with slightly reduced enantioselectivity (4, 90% ee). Variation of the 3-substituent to benzyl or ethyl group was also successful (5, 6). Various substituents such as alkyl, halogen, and methoxy at the 3-, 4-, and 5- positions of the indole ring were compatible (7-13, 88-94% ee). The absolute configuration of the product 12 was determined to be (S) by X-ray crystallographic analysis (CCDC 2126532). Extension of the alkyne terminus to phenyl groups bearing various electron-donating, withdrawing, and halogen substituents at the meta and para positions and to a 2-naphthyl group proved successful (14-20, 86-93% ee). A 2-fluorophenyl group was also compatible, affording the expected product 21 in 85% ee. The presence of a 2-thienyl group gave the product 22 in high yield albeit with lower enantioselectivity (81% ee). Significantly, extension of the substituent to alkyl (23 and 25) and cyclopropyl group (24) met with no difficulty, and the products were all isolated in excellent enantioselectivities, suggesting tolerance of the electronic effect of the alkyne. As expected, the coupling of a cyclohexenyl-substituted alkyne with PHPh$_2$ afforded product 26 in high enantioselectivity. The 2-sulfonyl group in the indole functions as an activating group as well as a bulky group to ensure axial chirality. Extension of the Ts group to other arenesulfonyls was successful (27-29, 88-93% ee). Extension of the 2-sulfonyl group to an ester met with failure under the standard reaction conditions, under which the ee of the coupled product decayed significantly versus reaction time. Moving the chiral ligand to ($R, R$)-Ph-BPE 0 °C afforded the product 30 in good yield and in 82% ee. The atropostability of product 3 has been examined, from which $D G_{rac}^\circ = 33.4$ kcal/mol was estimated (100 °C).

The scope of the symmetric diarylphosphines was next explored in the coupling with alkyne 1a (Fig. 3B). Diarylacetylenes bearing diverse electron-donating and withdrawing groups at the para position all reacted smoothly under the standard conditions (31-39, 91-96% ee). Phosphines bearing different meta substituted and 1,3-disubstituted phenyls also reacted in excellent enantioselectivity (40-43, 88-93% ee). Sluggish reaction was found for ortho substituted diarylphosphines due to the steric effect. Nevertheless, ortho-methoxy substituted diphenylphosphine coupled in acceptable yield with high enantioselectivity (44, 89% ee).

Having established the scope of symmetrical phosphines, we next moved to coupling using nonsymmetrical secondary phosphines, which will generate both axial and P chirality (Fig. 4). The
HPPHMes bearing two sterically biased groups was evaluated, and its coupling with alkyne 1a was extensively screened. Our previous catalyst system turned out to be inapplicable. After various studies, a bidentate (Sp, S)-Bophoz (L8) was identified as a superior ligand at 0 °C. Thus, the coupling with 1a afforded the product 45 in good dr (8.5:1) and in excellent enantioselectivity (92% ee). The scope of the alkyne was also briefly explored. It turned out that indolylalkyne bearing different substituents at the 2- and 4-positions or bearing a different sulfonyl substituent generally underwent smooth coupling in 6.5 to 9.0:1 dr and in 82-92% ee for the major product (46-52), and similar enantioselectivity was consistently observed for both the major and minor diastereomeric products. The major product of 47 was determined to be (S, S) configuration by X-ray crystallography (CCDC 2126528) and the rest products were assigned by analogy. A comparable diastereoselectivity was observed when the indole ring is 3-unsubstituted (53, 88% ee). All the above initially hydrophosphinated products are reasonably air-stable, but the diastereomeric products cannot be chromatographically separated unless they were oxidized. Extension of the sterically biased phosphine to phenyl-tert-butylphosphine was also successful, affording the product 54 in 10:1 dr and 85% ee.

Synthetic applications of representative products were next performed. The coupling of 1a and 2a was easily scaled up, affording product 3 in excellent yield with only slightly lower enantioselectivity (Fig. 5a). In addition to the protection in the oxide form, the initial hydrosphosphination product 3' could also be protected upon treatment with S8 (55) or BH3-DMS (56, Fig. 5b). The olefin unit in product 3 is somewhat electronically activated. Treatment of 3 with Br2 led to electrophilic bromination at the olefinic site, and tetrasubstituted olefin 57 was obtained in 92% ee. Alkynylation followed by dysilylation, Click reaction, and standard reduction afforded a triazole-functionalized phosphine 59 that is a potential bidentate ligand (92% ee, Fig. 5c). Phosphine 3' was then designated as a chiral ligand in palladium-catalyzed asymmetric allylic alkylation, affording products 60 in high enantioselectivity (Fig. 5d).

Preliminary experimental studies have been conducted to explore the reaction mechanism (Fig. 6). The coupling of 1a with DPPh2 afforded the product 3-Dn with H/D exchange (~ 50% D) at the olefinic position (Fig. 6a). This observation is consistent with a reaction pathway that involves protonolysis or sigma-bond metathesis of a palladium alkenyl intermediate. In a competitive experiment, two electronically distinguishable indolylalkynes bearing different groups at the 5-position were allowed to competitively couple with HPPH2. NMR analysis indicated that the 5-methyl substrate completely overrode its 5-Cl analogue, affording the product 9 in excellent yield (Fig. 6b). This may suggest that a more electron-rich indole ring facilitated the coupling with more pronounced substrate activation or with stronger alkyne coordination. To explore possible phosphine inhibition, control experiments have been conducted. The employment of alkyne 1a as a substrate for coupling with different amounts of HPPH2 afforded the product with negligible variations of the enantioselectivity with up to 10 equiv of PHPh2 (48 h, Fig. 6c). In contrast, appreciable decrease of the enantioselectivity was detected for alkyne 1a' only in the presence of a large amount (10 equiv) of PHPh2. In both cases, the reaction was significantly inhibited by 10 equiv of PHPh2, suggesting substrate inhibition but probably with dechelation of the chiral ligand only in the case of 1a', which is less sterically hindered and less electron-rich and consequently
more prone to ligand substitution-dechelation (see Fig. 1c). These results highlighted the subtle steric and electronic differences of the alkyne and the importance of proper choice of a chiral bidentate ligand. The role of the base additive was then examined. It was found that the enantioselectivity of the coupling of alkyne $1\text{a}'$ slightly decayed as the reaction proceeded in the absence any base additive. Control experiments indicated that the decay was not caused by post-coupling interaction of the product with the catalyst. Introduction of CsOAc afforded a constant ee although the reaction was somewhat retarded (Fig. 6d). The presence of the base additive probably facilitated formation of more coordinating PPh$_2$ ligand and fine-tuned the enantioselectivity. To further explore the possible product inhibition, the coupling of $1\text{a}$ was conducted in the presence of an enantioenriched or racemic phosphine product $10'$ at the beginning (Fig. 6e). Neither the coupling efficiency nor the enantioselectivity was essentially affected in either case, indicative of negligible phosphine product inhibition. We also attempted to apply $10'$ as the sole chiral ligand for the coupling of $1\text{a}$ and PHPh$_2$, but only starting materials were recovered under various conditions (Fig. 6f). These observations verified irrelevance of autocatalysis in this coupling system, and the chiral phosphine product cannot outcompete the PHPh$_2$ substrate.

The mechanism of this coupling reaction likely involves the initial deprotonation-ligand substitution between HPPh$_2$ and L*PdX$_2$ to give a Pd(II)PPh$_2$ species (Fig. 7). The alkyne coordination is then followed by an enantio-determining migratory insertion of the PPh$_2$ group into the alkyne. This insertion is also regioselective as dictated by both the electronic and steric effects of the 1-indolyl group which functioned toward the same direction. Indeed, the metal tends to end up at the vinyl site that is distal to the bulky aryl group on the basis of our previous studies.$^{32-34}$ Protonolysis of the C-Pd bond eventually furnished the coupled product. In the enantio-determining migratory insertion, the more hindered indole moiety of the alkyne tends to be placed downward and two orientations (E and E' shown in Fig. 7) of the alkyne versus the PPh$_2$ group can be visioned. In the intermediate E, minimal repulsion between the alkyne-attached phenyl group and the alkylphosphino group is experienced. In addition, the p-acidic alkyne is favorably trans to the more donating alkylphosphino group, which eventually affords the observed (S) selectivity.

Density functional theory (DFT) calculations support this proposal (Fig. 7, middle). The intermediate E lies 6.5 kcal/mol lower than the E' in free energy. Accordingly, the transition state of the major route (TS$_E$) was also found to be lower in free energy than the TS$_{E'}$ by 7.5 kcal/mol. By investigation of the geometries (see Supplemental Information), it was found that the interaction between the biased chelating ligand and the alkyne plays an important role. In E' strong p-p interaction was observed between the PPh$_2$ and the alkyne-attached phenyl group. Meanwhile, the Ts side-chain of the alkyne is oriented on top of the bulky alkylphosphino group, which exerts steric effect toward ligation of the alkyne unit. While in intermediate E, one of the phenyl rings of the PPh$_2$ group forms a T-shape orientation with the phenyl of the alkyne, and this causes the other phenyl group in the PPh$_2$ to lie between the phenyl and indole rings to avoid steric interactions, which keeps the Ts side-chain away from the bulky alkylphosphino group. These different phenyl-phenyl orientations (the p-p stacking versus the T-shape) along with the different orientation of the Ts side-chain affects the coordination of the alkyne carbons (in E, Pd-C1:
2.243 Å, Pd-C2: 2.333 Å; in $E'$, Pd-C1: 2.331 Å, Pd-C2: 2.369 Å.) Of note, the hydropalladation pathway,$^{69,86,87}$ that has been suggested in alkyne hydrophosphorylation using $\text{P(O)H(OMe)}_2$ or $\text{HP(O)Ph}_2$ is unlikely because the opposite regioselectivity is expected (Fig. 7, bottom). Indeed, our DFT studies verified that this opposite regioselectivity of insertion is more kinetically favorable by at least 13 kcal/mol (see Supplementary Information). This is caused by the weaker interaction between the Pd and the C(Indolyl) akynyl carbon (Pd-C(ind): ~ 2.8 angstrom) than between the Pd-C(Ph) (Pd-C: ~2.3 angstrom) in the staring palladium hydride intermediate, which is consistent with the higher nucleophilicity/coordinating ability of the C(Ph) site. This different binding affinity causes drastically different shapes of the corresponding transition states. For hydride insertion into the C(Ph) site, a triangle shape of the H-C-C-Pd moiety with large tension is observed in the transition state, while for hydride addition to the C(Ind), a favorable, regular quadrangle-like Pd-C-C-H transition state was located.

Conclusions

In summary, we have realized palladium-catalyzed atroposelective hydrophosphination of sterically hindered internal alkynes using diverse secondary phosphines. The coupling system overcomes the low reactivity of internal alkynes via substrate activation using a sterically bulky but electron-donating 1-indolyl group, affording C-N axially chiral trisubstituted olefins (vinylphosphines) in excellent regioselectivity, E-selectivity, and enantioselectivity under mild reaction conditions. The axial chirality was established via integration of hydrophosphination and dynamic kinetic transformation of the alkynes, with both symmetrical and nonsymmetrical secondary phosphines being applicable. In the latter case, additional P-central chirality has been constructed in good diastereoselectivity as well as high enantioselectivity. The observed enantioselectivity has been rationalized by DFT studies. This hydrophosphination reaction offers a new approach to access underexplored chiral open-chain olefins and may provide new insight into direct atroposelective functionalization of alkynes.

Methods

**General procedure for the synthesis of 3-29 and 31-44 from symmetrical phosphines.** To a sealable tube (15 mL) were charged with 1-indolylalkyne (0.1 mmol), Pd(acac)$_2$ (6 mol%), L$_{12}$ (9 mol%), CsOAc (0.3 equiv) and anhydrous toluene (2.0 mL) under argon. Then symmetrical diarylphosphine (0.2 mmol) was added and the mixture was stirred at 30 °C for 96 h. After that, H$_2$O$_2$ (30%, 0.5 mL) was added at 0 °C and the resulting solution was stirred for another 20 min. The reaction mixture was quenched with H$_2$O and the mixture was concentrated under vacuum. The residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc = 5/1 to 1/1) to afford the desired product 3-29 and 31-44. The enantiomeric excess was determined by chiral HPLC analysis.

**General procedure for the synthesis of 45-54 from nonsymmetrical secondary phosphines.** To a sealable tube (15 mL) were charged with 1-indolylalkyne (0.1 mmol), Pd(OAc)$_2$ (6 mol%), L$_8$ (9 mol%) and dioxane (1.0 mL)/EtOAc (1.0 mL) under argon. Then secondary phosphate 2 (0.2 mmol) was added at 0 °C and
the mixture was stirred for 96 h. After that, H$_2$O$_2$ (30%, 0.5 mL) was added at 0 °C and the resulting solution was stirred for another 20 min. The reaction mixture was quenched with H$_2$O and the mixture was concentrated under vacuum. The residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc = 3/1 to 1/1) to afford the desired products 45-54. The enantiomeric excess was determined by chiral HPLC analysis.

References


**Declarations**
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Author contributions

X.L. conceived the concept and directed the project. D.J., J.J., Y.W., Z.Q., and F.W. conducted the experiments and data analysis. Y.W. conducted the DFT studies. X.L. and Z.Q. wrote the paper with feedback from all other authors.

Competing interests

The authors declare no competing financial interests.

Additional information

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Tables

Table 1 is in the supplementary files section.

Figures
(a) Atroposelective Hydrofunctionalization of Internal Alkynes\textsuperscript{35-42}

\[
\begin{align*}
&\text{handle} \quad \begin{array}{c}
\text{R''} \\
\text{Ar} \\
\text{R'}
\end{array} \quad \begin{array}{c}
\text{H} \\
\text{Nu}
\end{array} \quad \text{organocat.} \quad \begin{array}{c}
\text{R''} \\
\text{Ar} \\
\text{R'}
\end{array} \\
&\text{chiral} \quad \text{achiral}
\end{align*}
\]

- NuH = β-dicarbonyls: Tan (2017)
- NuH = sulfinic acid/sulfinate: Yan (2018)
- NuH = 2-naphthol: Tan (2019)
- No Report for NuH = phosphine (oxide)

(b) Asymmetric Addition of P-H to Alkynes: \textit{Central Chirality Only}\textsuperscript{52-55}

\[
\begin{align*}
&\text{R'} \\
&\text{R''} \\
&\text{Ar} \\
&\text{P-H Addition} \\
&\text{Metal cat.}
\end{align*}
\]

- Rare for internal alkyne: Zhang (2021)\textsuperscript{55}

(c) Atroposelective Hydrophosphinination of Internal Alkyne (1\textsuperscript{st} example)

\[
\begin{align*}
&\text{R} \\
&\text{δ+} \\
&\text{δ-} \\
&\text{R'} \\
&\text{HPRAr} \\
&\text{Pd cat./L*}
\end{align*}
\]

- Symmetric Phosphines
- Nonsymmetric Phosphines
- Axial and P-chirality
- Regio- and Stereoselective

Challenges: □ Reactivity □ P Inhibition □ Z/E Selectivity □ Enantioselectivity

Chiral Ligand: electron-rich, bidentate, and rigid diphosphines

Figure 1

Asymmetric Alkyne Hydrofunctionalization
Figure 2

Initial Screening of Substrates via DFT Studies of the Racemization Barrier (DG$^i_{\text{rac}}$) of Their Products.
Figure 3

Substrate Scope in Enantioselective Hydrophosphination Using Symmetric Secondary Phosphines. (a) Reaction conditions A: 1 (0.1 mmol), 2a (0.2 mmol), Pd(acac)$_2$ (6 mol%), CsOAc (30 mol%), and L12 (9 mol%) in toluene (2 mL), 30 °C, 96 h. Isolated yield. The ee was determined by HPLC analysis. (b)
Conditions B: indolylphenylacetylene (0.1 mmol), 2a (0.2 mmol), Pd(acac)$_2$ (6 mol%) and (R, R)-Ph-BPE (9 mol%) in toluene (2 mL), 0 °C, 96 h.

Figure 4

Scope of Substrates in Enantioselective Hydrophosphination Using Nonsymmetric Secondary Phosphines. (c) Reactions Conditions C: alkyne (0.1 mmol), nonsymmetric phosphine (0.2 mmol), Pd(OAc)$_2$ (6 mol%) and L8 (9 mol%) in dioxane (1 mL)/EtOAc (1 mL) at 0 °C, 96 h.
Figure 5

**Synthetic Applications.** i) TMSCOCH, Pd(PPh_3)_2Cl_2 (2 mol%), Cul, PPh_3, NEt_3, 100 °C. ii) TBAF, b) CuTc, BnN_3, c) DIBAL-H.
Figure 6

Mechanistic Studies.
Figure 7

Proposed Reaction Mechanism and DFT rationalization of the enantioselectivity. (a) The energy profiles (in kcal/mol) for the C-P bond formation at the UB3LYP/Lanl2dz(Pd,Fe)-6-31+G**(the rest)//Lanl2dz(Pd,Fe)-6-31G*(the rest) computational level are presented. Hydrogen atoms of the calculated geometries of E and E' were omitted for clarity. Ind = 2-substituted 1-indolyl. The anion was omitted. EDS = enantiodetermining step.

Supplementary Files
This is a list of supplementary files associated with this preprint. Click to download.

- SI0318.pdf
- Table1.docx