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

Danqing Ji,[1] Jierui Jing,[1] Yi Wang,[1] Zisong Qi,[1] Fen Wang,[1] Yong Wang,[3*] Xingwei Li[1,2*]

[1]School of Chemistry and Chemical Engineering, Shaanxi Normal University, Xi'an 710062, China

[2]Institute of Molecular Science and Engineering, Institute of Frontier and Interdisciplinary Sciences, Shandong University, Qingdao 266237, China Correspondence: lixw@snnu.edu.cn; lixw@sdu.edu.cn*

[3]Institute of Drug Discovery Technology, Ningbo University, Ningbo 315211, China. E-mail: yong@nbu.edu.

Abstract: Palladium-catalyzed unprecedented 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

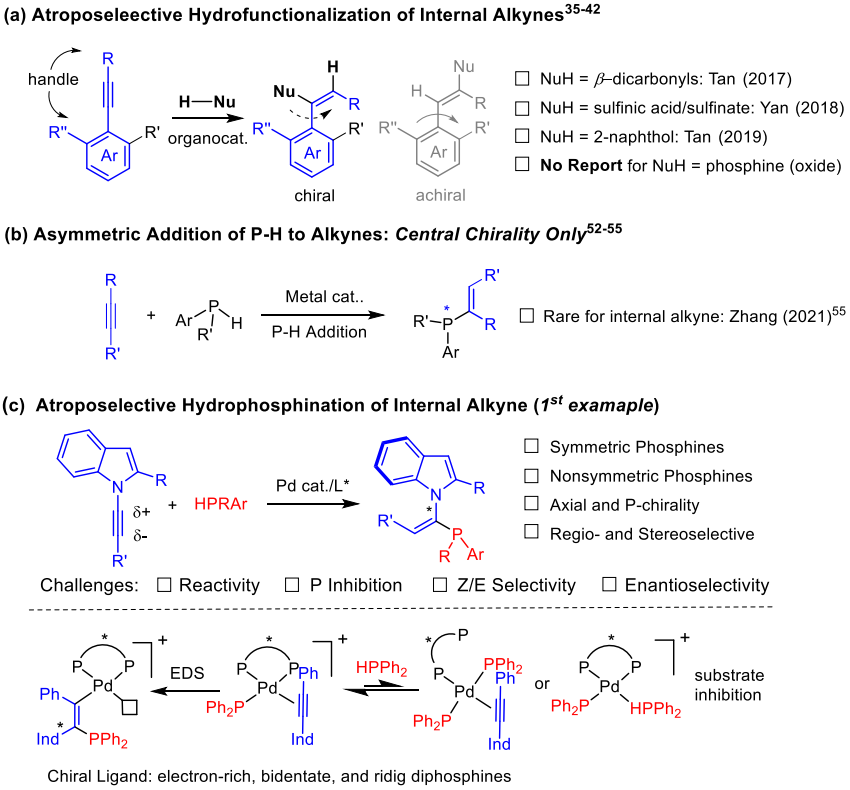
Development of novel synthetic methods that utilizes simple and abundant reagents is highly desirable toward selective construction of value-added organics. The catalytic hydrofunctionalization[1-6] of alkynes is intriguing for achieving these goals in that both substrates are widely available and readily 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[7-9] of the prochiral alkyne or functionalizing reagent, formation of chiral allylic compounds[10,11] or exhaustive hydrofunctionalization to C-C single bonds.[12-14]

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.[15-20] The majority of axially chiral molecules that have been extensively studied are biaryls.[21-23] In contrast, axially chiral olefins[24-28] 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 availablity 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,[29,30] [4+2] annulation,[31] or C-H bond activation,[32-34] but the products are typically (hetero)aromatics. Nevertheless, organocatalysis plays a pivotal role in atroposelective hydrofunctionalization of alkynes (Scheme 1a). In 2017, Tan elegantly realized hydroalkylation of alkynals using β-diketones toward construction of trisubstituted acroleins via intermediacy of reactive allene species.[35] Yan[36,37]and others[38-40] 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.[41] Recently, Chi described NHC-catalyzed atroposelective synthesis of axially chiral styrenes involving involve selective 1,4-

addition of sulfinic anion to acetylenic acylazolium intermediate as the key step.[42] In these cases, sterically hindered alkynes bearing a functional handle at the alkynyl position[35] or in the naphthol ring are employed.[36-42] 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 as ib 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.[43-51] Asymmetric hydrophosphination of alkynes has been developed mostly using terminal alkynes as the substrates (Scheme 1b),[52-55] 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,[56,57] Leung,[58] and Yin,[59,60] Zhang,[61] Harutyunyan and Ge,[62,63] and others using Pd, Ni, Cu, and Mn catalysts.[64-67] Chi recently also developed NHC-catalyzed hydrophsophination of α-bromoenals.[68] Besides, enantioselective addition of P(V)-H to diverse π-bonds has been accomplished by Dong[69] and others.[70-75] In addition to unsaturated substrates, carbon and hetero electrophiles also effectively coupled with P(III)-H and P(V)-H reagents.[76-85] 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.[52,53,55,59] 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 (Scheme 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.

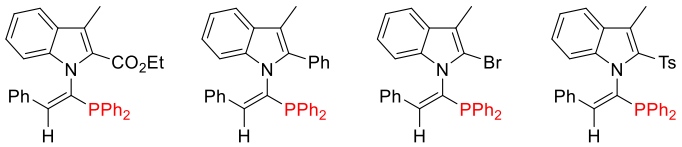
Scheme 1. Asymmetric Alkyne Hydrofunctionalization



RESULTS AND DISCUSSION

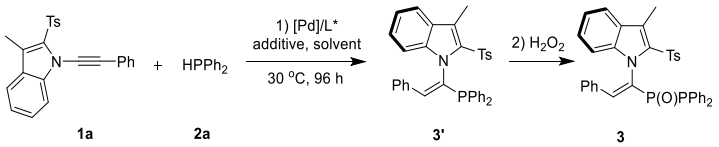
We initially screened four 1-indolylalkynes bearing a variable 2-substituent by DFT analysis of the atropostability of the corresponding hydrophsophinated products (Scheme 2). Moderate or low atropostability was identified for products **A**-**C**, and the presence of a bulky 2-Ts group increased the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

Scheme 2. Initial Screening of Alkyne Substrates via DFT Studies of the Racemerization Barrier ($\Delta G^{\neq}_{rac}$) of Their Hydrophosphinated Products.



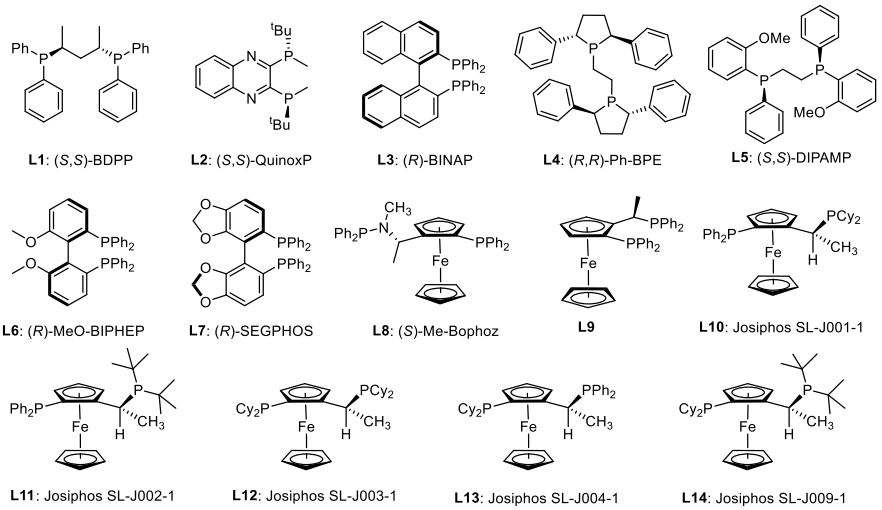
We next conducted experimental optimization studies using alkyne **1a** and Ph_2PH as substrates under palladium catalysis (Table 1 and Supplemental Information). A large set of chiral bidentate ligands were screened at 30 °C. In many cases, decay of the enantioselectivity was observed as the reaction 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 (S_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.

Table 1. Optimization of Reaction Conditions[a]



Entry	[Pd]	L*	Additive	Solvent	Yield (%)	Ee (%)
1	$Pd(acac)_2$	**L1**	-	PhMe	61	81
2	$Pd(acac)_2$	**L2**	-	PhMe	85	91
3	$Pd(acac)_2$	**L3**	-	PhMe	59	<5
4	$Pd(acac)_2$	**L4**	-	PhMe	82	79
5	$Pd(acac)_2$	**L5**	-	PhMe	58	46

6	$Pd(acac)_2$	**L6**	-	PhMe	56	33
7	$Pd(acac)_2$	**L7**	-	PhMe	63	57
8	$Pd(acac)_2$	**L8**	-	PhMe	46	38
9	$Pd(acac)_2$	**L9**	-	PhMe	46	62
10	$Pd(acac)_2$	**L10**	-	PhMe	54	18
11	$Pd(acac)_2$	**L11**	-	PhMe	61	39
12	$Pd(acac)_2$	**L12**	-	PhMe	88	92
13	$Pd(acac)_2$	**L13**	-	PhMe	89	85
14	$Pd(acac)_2$	**L14**	-	PhMe	56	20
15	$Pd(NO_3)_2 \cdot H_2O$	**L12**	-	PhMe	80	87
16	$Pd(OH)_2$	**L12**	-	PhMe	71	88
17	$Pd(OAc)_2$	**L12**	-	PhMe	81	92
18	$Pd(acac)_2$	**L12**	-	THF	64	75
19	$Pd(acac)_2$	**L12**	-	EtOAc	75	92
20	$Pd(acac)_2$	**L12**	-	PhCl	63	92
21	$Pd(acac)_2$	**L12**	AgOAc	PhMe	89	88
22	$Pd(acac)_2$	**L12**	CsOAc	PhMe	93	94
23	$Pd(acac)_2$	**L12**	HOAc	PhMe	85	93
24	$Pd(acac)_2$	**L12**	$Zn(OAc)_2$	PhMe	77	93



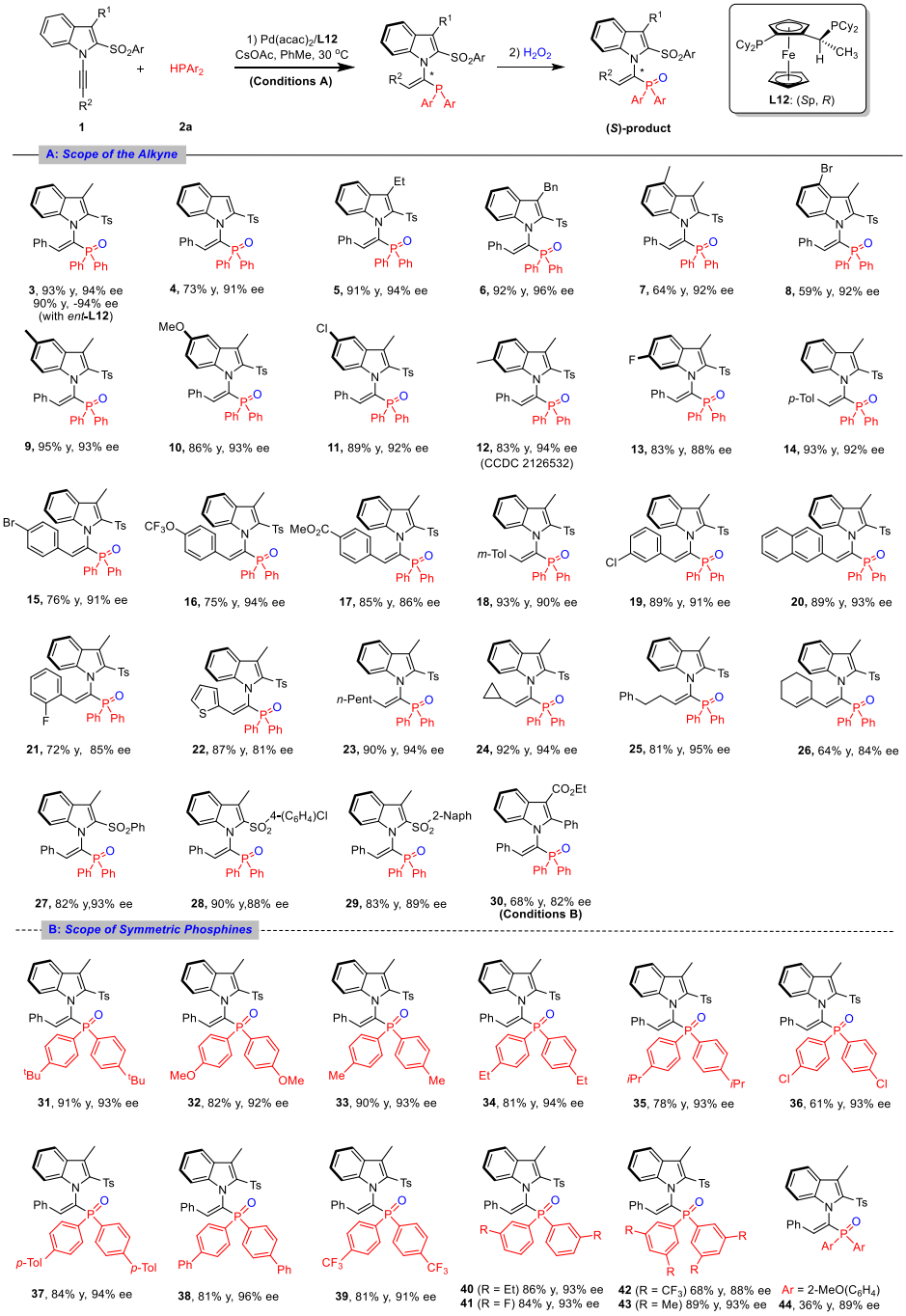
[a]Reaction conditions: **1a** (0.1 mmol), **2a** (0.2 mmol), Pd catalyst (6 mol%), chiral ligand (9 mol%), and additive (0.3 equiv) in PhMe (2 mL), 30 °C, 96 h; then H_2O_2 at 0 °C for 20 min. Isolated yield. The ee was determined by HPLC analysis using a chiral stationary phase.

Having established of the optimal reaction conditions, we next explored the scope and generality of this coupling system (Scheme 3A). Under the standard conditions, a broad scope of 1-indolylalkynes 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 ^{o}C afforded the product **30** in good yield and in 82% ee. The atropostability of product **3** has been examined, from which $\Delta G^{\neq}_{rac}$ = 33.4 kcal/mol was estimated (100 ^{o}C).

The scope of the symmetric diarylphosphines was next explored in the coupling with alkyne **1a** (Scheme 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).

Scheme 3. Substrate Scope in Enantioselective Hydrophosphination Using Symmetric Secondary Phosphines.



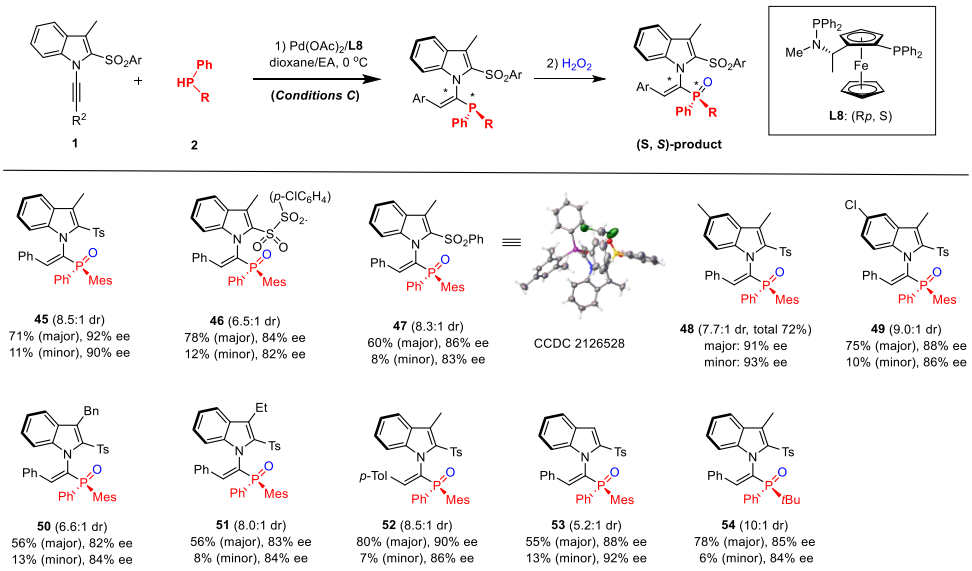
[a]Reaction conditions A: **1** (0.1 mmol), **2a** (0.2 mmol), $Pd(acac)_2$ (6 mol%), CsOAc (30 mol%), and **L12** (9 mol%) in toluene (2 mL), 30 °C, 96 h. Isolated yield. The ee was determined by HPLC analysis.

[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.

Having established the scope of symmetrical phosphines, we next moved to coupling using nonsymmetrical secondary phosphines, which will generate both axial and P chirality (Scheme 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 (*Rp*,*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.

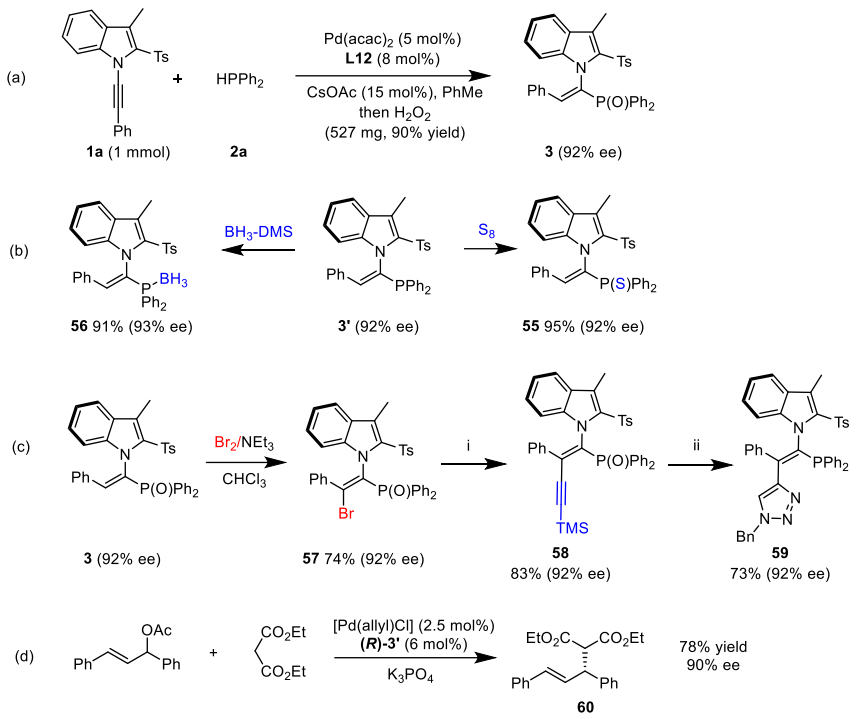
Scheme 4. Scope of Substrates in Enantioselective Hydrophosphination Using Nonsymmetric Secondary Phosphines.



[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.

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 (Scheme 5a). In addition to the protection in the oxide form, the initial hydrosphosphination product **3'** could also be protected upon treatment with S_8 (**55**) or BH_3-DMS (**56**, Scheme 5b). The olefin unit in product **3** is somewhat electronically activated. Treatment of **3** with Br_2 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, Scheme 5c). Phosphine **3'** was then designated as a chiral ligand in palladium-catalyzed asymmetric allylic alkylation, affording products **60** in high enantioselectivity (Scheme 5d).

Scheme 5. Synthetic Applications



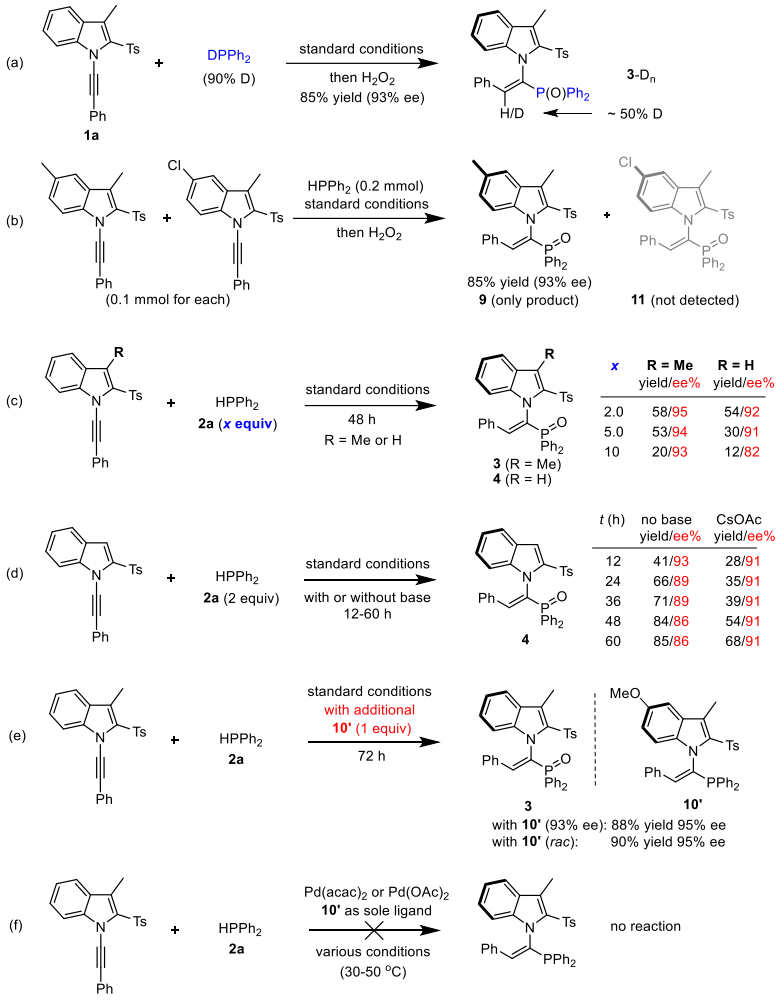
[i]TMSC≡CH, $Pd(PPh_3)_2Cl_2$ (2 mol%), CuI, PPh_3, NEt_3, 100 °C.

[ii] a) TBAF, b) CuTc, BnN_3, c) DIBAL-H.

Preliminary experimental studies have been conducted to explore the reaction mechanism (Scheme 6). The coupling of **1a** with $DPPh_2$ afforded the product **3**-D_n with H/D exchange (~ 50% D) at the olefinic position (Scheme 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 $HPPh_2$. NMR analysis indicated that the 5-methyl substrate completely overrode its 5-Cl analogue, affording the product **9** in excellent yield (Scheme 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 $HPPh_2$ afforded the product with negligible variations of the enantioselectivity with up to 10 equiv of $PHPh_2$ (48 h, Scheme 6c). In contrast, appreciable decrease of the enantioselectivity was detected for alkyne **1a'** only in the presence of a large amount (10 equiv) of $PHPh_2$. In both cases, the reaction was significantly inhibited by 10 equiv of $PHPh_2$, 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 Scheme 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 **1a'** 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 (Scheme 6d). The presence of the base additive probably facilitated formation of more coordinating PPh2 ligand and fine-tuned the enantioselectivity. To further explore the possible product inhibition, the coupling of **1a** was conducted in the presence of an enantioenriched or racemic phosphine product **10'** at the

beginning (Scheme 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 **1a** and $PHPh_2$, but only starting materials were recovered under various conditions (Scheme 6f). These observations verified irrelevance of autocatalysis in this coupling system, and the chiral phosphine product cannot outcompete the $PHPh_2$ substrate.

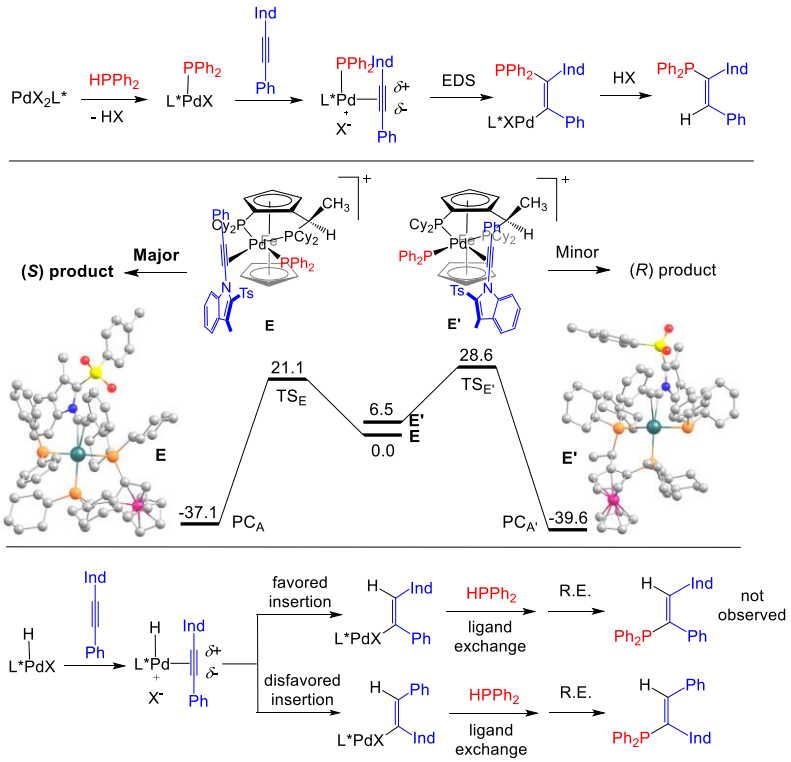
Scheme 6. Mechanistic Studies



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 (Scheme 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 Scheme 6) 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 π-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 (Scheme 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 π-π 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 π-π 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 $P(O)H(OMe)_2$ or $HP(O)Ph_2$ is unlikely because the opposite regioselectivity is expected (Scheme 6, 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.

Scheme 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/Lanl2tz (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-substitited 1-indolyl. The anion was omitted. EDS = enantiodetermining step.

CONCLUSION

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.

Further information and requests for resources should be directed to and will be fulfilled by the lead contact Xingwei Li (lixw@snnu.edu.cn).

Materials availability

All materials generated in this study are available from the lead contact without restriction

Data and code availability

The date of the X-ray crystallographic structures of **12** and **47** have been deposited in the Cambridge Crystallographic Data Center under accession numbers CCDC: 2126532 and 2126528.

Methods

Full experimental procedures are provided in the supplemental information.

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://chemrxiv.org

ACKNOWLEDGMENTS

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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.

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