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A Ni-catalyzed asymmetric C(sp)–P cross-coupling reaction for the synthesis of P-stereogenic alkynylphosphines†

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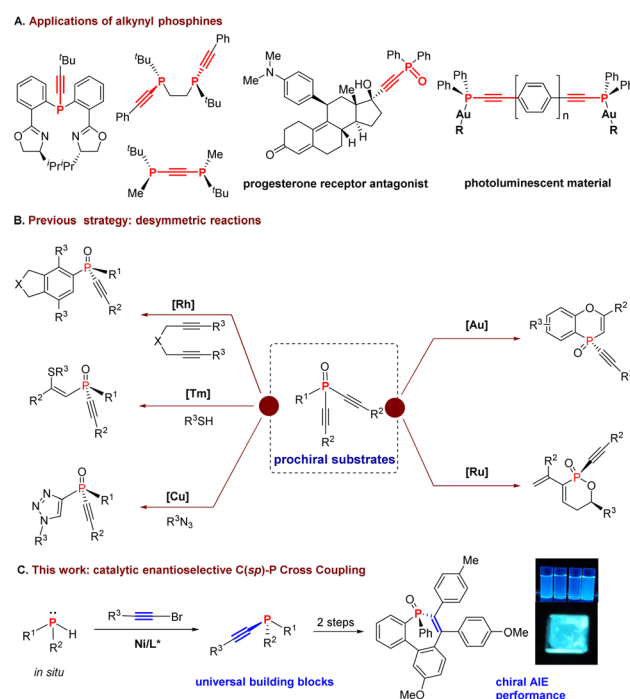
Due to the high reactivity of the triple bond, P-stereogenic alkynylphosphines could be easily derivatized, serving as universal building blocks for structurally diverse phosphine compounds. However, the synthesis of alkynylphosphines *via* direct P–C bond formation was unprecedented. Here, we report an efficient method for the synthesis of P-stereogenic alkynylphosphines with high enantioselectivity *via* a Ni-catalyzed asymmetric cross-coupling reaction. The reaction could tolerate a variety of functional groups, affording products that can be converted into useful phosphine derivatives.

Introduction

Enantioenriched P-stereogenic phosphines have been applied to a wide range of asymmetric transformations as ligands for metal catalysts or directly as organocatalysts.¹ Compared with phosphine ligands with backbone stereogenicities, P-stereogenic phosphines may exhibit a unique enantioselective induction because the stereogenic center of the catalyst is closer to the active site. In particular, P-stereogenic ligands with large differences in the bulkiness of the substituents on the phosphorus atom have been introduced as a key motif into ligands because of their ability to induce high enantioselectivity in asymmetric catalysis. And the best among them is *t*-butyl-substituted P-stereogenic ligands,² such as QuinoxP,^{2a} DuanPhos,^{2b} Buchwald ligand,^{2c} and WingPhos,^{2d} which have found broad applications in both academic investigations and industrial applications.

Alkynyl groups are considered to have the minimum stereobulkiness due to their linear topology. Therefore, the incorporation of both the small alkynyl and the large *tert*-butyl groups on the phosphorus atom would create the largest bulkiness differentiation and presumably exhibit profound stereogenic discrimination. In this regard, several interesting alkynyl chiral phosphine ligands have been developed, showing enhanced catalytic excellent performance in reactions, such as catalytic asymmetric hydrogenation and allylic substitution reactions (Scheme 1A).^{3,4} Furthermore, alkynylphosphine oxides have been found to have attractive biological activities in medicinal chemistry,⁵ as well as photoluminescent materials.⁶

However, the strategy for the synthesis of P-stereogenic alkynylphosphines is limited.⁷ Generally, most P-stereogenic alkynylphosphines were synthesized from stoichiometric amounts of chiral substrates *via* nucleophilic substitution reactions.^{3,8} And transition metal-catalyzed dehydrogenative coupling of stereogenic secondary phosphine oxides or secondary phosphine boranes with terminal alkynes provided an alternative method with retention of the P-stereogenicity.^{9,10} Despite better atom economy, stoichiometric stereogenic

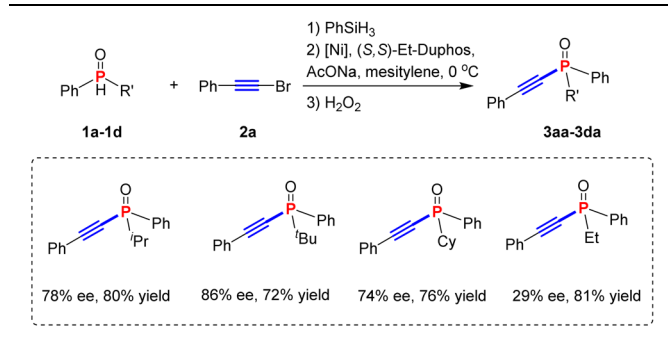


Scheme 1 P-stereogenic alkynylphosphines.

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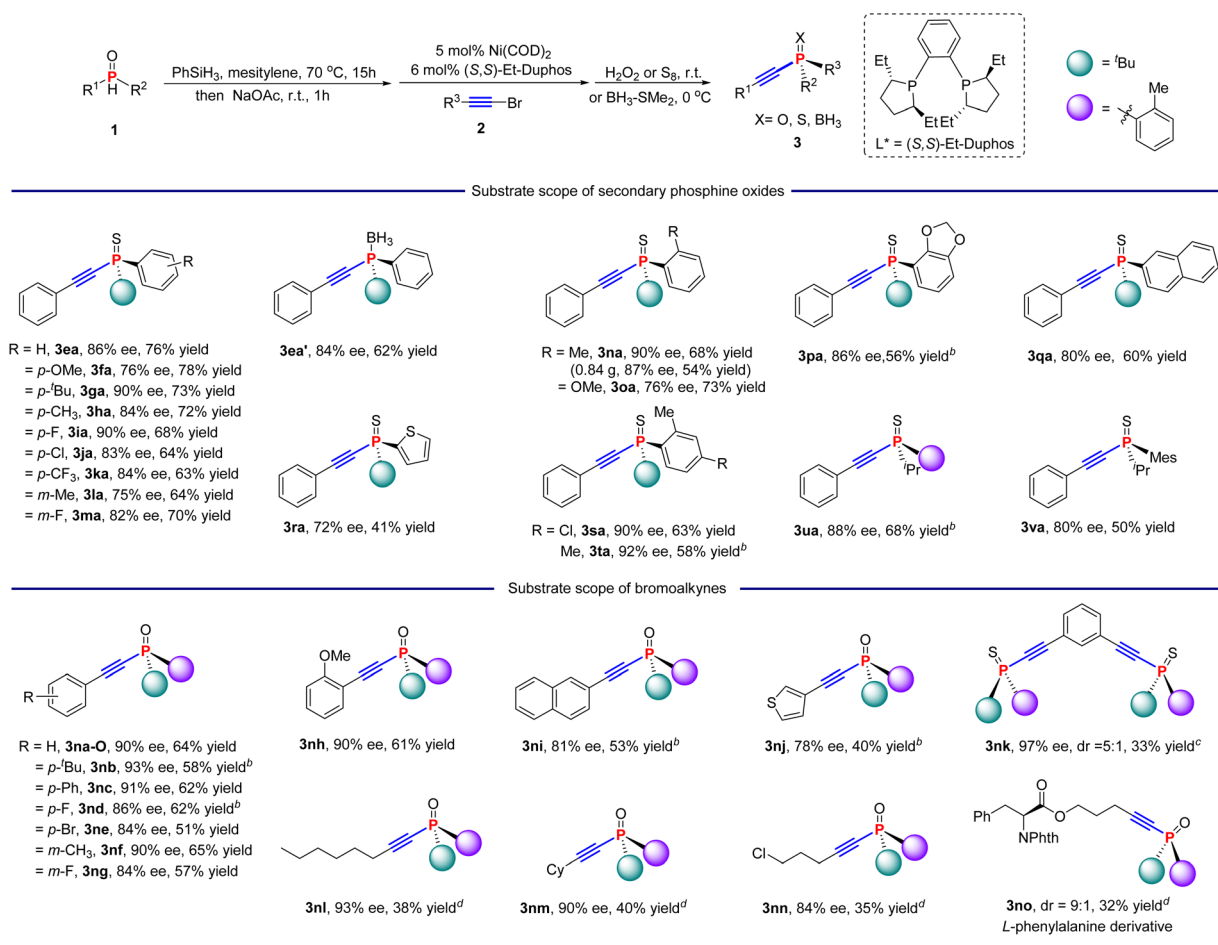
Table 1 Initial evaluation of the cross-coupling reaction



phosphine starting materials were still required in this method. As a more efficient strategy, a plethora of catalytic desymmetrization reactions have been reported recently with prostereogenic dialkynylphosphines through [2 + 2 + 2] cycloaddition, 1,4-addition reactions, *etc.* (Scheme 1B).¹¹ In

brief, previous methods suffer from limited substrate scope or tedious preparation of starting materials and are thus lacking in broad applications of the products. The development of catalytic asymmetric reactions by direct P–C bond formation to prepare P-stereogenic alkynylphosphines remains unexplored.

Recently, a transition metal-catalyzed enantioselective C(sp²)–P and C(sp³)–P coupling reaction was reported as an effective strategy for the construction of P-stereogenic centers.¹² However, enantioselective C(sp)–P coupling has not been reported. In addition, the synthesis of chiral P(III) phosphines is challenging in transition metal catalyzed asymmetric reactions because of the strong poisoning effect of both the P(III) starting material and the product.^{12j,t-v} Besides, the previously reported Ni-catalyzed asymmetric syntheses of P-stereogenic phosphines do not work for bulky P-nucleophiles, *e.g.* phosphines with a *tert*-butyl or mesityl substituent.^{12m-o} Herein, we disclosed our finding in the catalytic asymmetric cross-coupling reaction of secondary phosphines with bromoalkynes, in which excellent

Table 2 Substrate scope^a

^a 1 (0.2 mmol), PhSiH₃ (0.2 mmol), NaOAc (0.25 mmol), 2 (0.1 mmol), Ni(COD)₂ (5 mol%), (S,S)-Et-Duphos (6 mol%), 1 mL mesitylene, 0 °C, and 72 h. Isolated yields. dr was determined by ³¹P NMR analyses of crude reaction mixtures. ^b –10 °C and 96 h. ^c 1 (0.4 mmol), PhSiH₃ (0.4 mmol), NaOAc (0.5 mmol), Ni(COD)₂ (10 mol%), (S,S)-Et-Duphos (12 mol%), 0 °C, and 120 h. dr was determined by HPLC analyses. ^d Ni(COD)₂ (10 mol%), (S,S)-Et-Duphos (12 mol%), 10 °C, and 96 h.



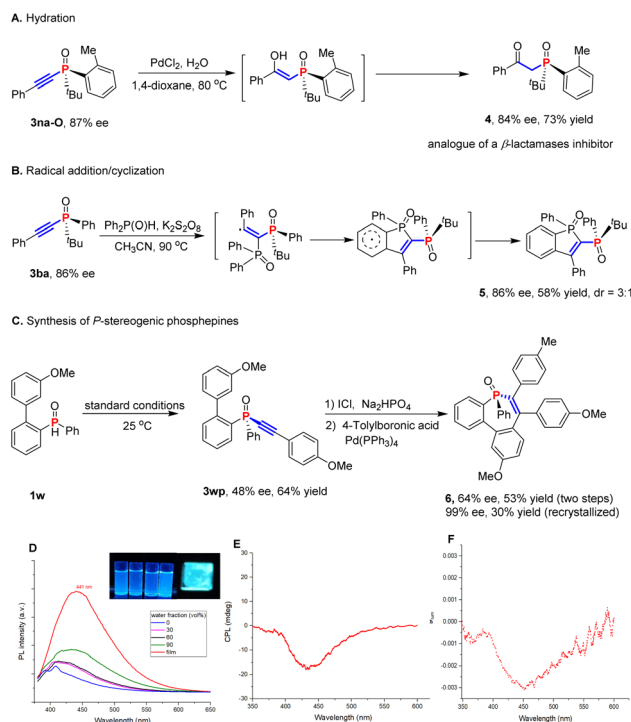


Fig. 1 (A) Hydration. (B) Radical addition cyclization. (C) Synthesis of P-stereogenic phosphine. (D) PL spectra of **6** in THF/water mixtures with different water fractions and **6** films under 365 nm. (E) CPL spectra of **6** films. (F) g_{lum} value spectra of **6** films.

results could be obtained with bulky secondary phosphines (Scheme 1C).

Results and discussion

The cross-coupling reaction was carried out with secondary phosphine **1a**, which was reduced *in situ* from bench-stable secondary phosphine oxides and (bromoethynyl)benzene **2a** (Table 1). At the outset of the investigation, we were aware that the high reactivity of the bromoalkyne may lead to an uncatalyzed background reaction, resulting in diminished ee. As expected, when the reaction was performed without a catalyst, a significant background reaction occurred to afford the desired product **3aa** in 20% yield (please see the ESI†). Therefore, a highly active catalyst is required to alleviate such a problem. Low temperature is beneficial to reduce the background reaction, although a long reaction time is required for the completion of the reaction.

After extensive evaluation of the reaction parameters, we were able to obtain the optimal conditions as follows. The secondary phosphine was formed *in situ* from **1** (0.2 mmol) and PhSiH_3 (0.2 mmol) followed by the addition of substrate **2a** (0.1 mmol), $\text{Ni}(\text{COD})_2$ (5 mol%), (*S,S*)-Et-Duphos (6 mol%), NaOAc (0.25 mmol), and mesitylene (1 mL) at 0 °C. Preliminary evaluation suggested that the steric hindrance of the substituents on the P atom also showed a profound effect on the enantioselectivity (Table 1). The bulky *t*-butyl phenyl secondary phosphine gave the best results with 86% ee and 72% overall

isolated yield of product **3ba**, whose absolute configuration was determined to be *sp* by comparison with known compounds (please see the ESI†).

The scope of the Ni-catalysed asymmetric C(sp)–P cross coupling reaction was investigated with respect to both the P-substituents and the bromoalkynes under the optimized conditions obtained above (Table 2). For the convenience of isolation and purification, the tertiary alkynylphosphine products were protected either as a borane derivative (**3ea'**), sulfides or oxides. The method could tolerate a broad range of secondary phosphines with various substituents at the aryl group. Products with substituents at the *para* position of the P-aryl group were obtained in 63–78% overall yields and 76–90% ee (**3fa–3ka**). Substrates with *meta*-substituents (**1l**, **1m**) also reacted smoothly, affording products **3la** and **3ma** in 75% ee and 64% yield and 82% ee and 70% yield, respectively. In addition, substrate **1n**, bearing an *o*-methylphenyl group, could give the desired product with better enantioselectivity (**3na**, 90% ee) than substrates **1o** and **1p** (**3oa**, 76% ee and **3pa**, 86% ee).

The current process was highly reliable and scalable, as demonstrated by the gram-scale reaction where **1n** (5 mmol, 0.98 g) and **2a** proceeded smoothly to generate **3na** with 87% ee and 54% yield. Furthermore, secondary phosphines with other aromatic groups were also competent substrates, generating the corresponding products with 80% ee and 60% yield, and 72% ee and 41% yield (**3qa** and **3ra**). To verify the effect of the *o*-methylphenyl group on the enantioselectivity, substrates **1s** and **1t** were tested. Both substrates gave corresponding products **3sa** and **3ta** in 90% ee and 92% ee. Notably, isopropyl-substituted (**1u**) and mesityl isopropyl (**1v**) secondary phosphines were also amenable to the protocol to give the desired products with 88% ee and 68% yield and 80% ee and 50% yield, respectively.

The scope of bromoalkynes was then examined (Table 2). Aromatic bromoalkynes with a variety of functional groups (**2a–2i**) were all amenable to the reaction, affording phosphine oxides in 84–93% ee and 51–64% yields (**3na–O–3ni**). Substrates with electron-donating groups at the *para* position gave better enantioselectivities than substrates with electron-withdrawing groups (**3nb** vs. **3nc**, **3nd**, and **3ne**). A similar trend was observed for *meta*-substituted aryl groups (**3nf** vs. **3ng**). This result may be due to the lower electrophilicity of electron-rich bromoalkynes, which results in minimal background reactions. In addition, substrates with electron-donating groups (OMe) at the *ortho* position also gave high enantioselectivity in 90% ee (**3nh**). The reactions of bromoalkynes bearing naphthyl and thienyl groups also gave the products with high ee (81% and 78%) and moderate yield (**3ni** and **3nj**). Notably, the reaction of 1,3-bis(bromoethynyl) benzene **2k** with **1n** gave the double cross-coupling product **3nk** in 97% ee, 5:1 dr and 33% overall yield. Then, the reaction of alkyl bromoalkynes was tested. Thus, substrate **1n** was selected to react with three representative alkyl bromoalkynes. All these substrates gave the corresponding products in 93%, 90% and 84% ee, respectively, albeit with diminished overall yields (**3nl–3nn**). The application of this reaction in a biologically relevant molecule was then investigated. And L-phenylalanine derivative **2o** gave corresponding products **3no** in 9:1 dr and 32% yield under standard conditions.



In addition, the P-stereogenic alkynylphosphine products could be easily elaborated to structurally diverse P-stereogenic molecules through simple transformations. P-stereogenic alkynylphosphine oxide **3na-O** could undergo a hydration reaction under palladium catalysis to give β -keto-phosphine derivative **4**, an analog of β -lactamase inhibitors^{13a,b} in 84% ee and 73% yield (Fig. 1A). In addition, **3ba** could also be transformed into π -conjugated benzo[*b*]phosphole oxides **5** in 86% ee, 58% yield and 3 : 1 dr by a radical-initiated tandem addition/cyclization reaction (Fig. 1B).^{13c} Phosphine derivatives have recently attracted broad attention in photoluminescent materials; however, the chiroptical properties of these materials with a P-stereogenic center have rarely been reported.¹⁴ To probe the potential value of enantioenriched P-stereogenic phosphines in luminescent materials, seven-membered phosphepine **6** was synthesized from **3wp** (64% ee and 53% yield) in two steps (99% ee after recrystallization, Fig. 1C).¹⁵ And the compound exhibited promising CPL photoluminescent properties in addition to the originally reported AIE effect of racemic **6** (Fig. 1D and E). The compound also represents a rare example of a CPL material with a single P-stereogenic centre stereogenicity, which merits in-depth investigation.

Conclusions

In summary, we developed an efficient method for the synthesis of P-stereogenic alkynylphosphines *via* a Ni-catalyzed asymmetric cross coupling reaction. The P-stereogenic alkynylphosphines could be converted to structurally diverse P-stereogenic compounds *via* simple transformations. The discovery may inspire new applications of alkynylphosphines in asymmetric catalysis and materials chemistry.

Data availability

The experimental details, characterization data, NMR spectra, and HPLC chromatograms associated with this article are provided in the ESI.†

Author contributions

Q. Z. conceived the project and B. Z. initiated the optimization studies and conducted the experiments. W. Z., X. L. and Y. S. helped with a part of the substrate scope. B. Z. and Q. Z. wrote the manuscript together. All authors have given approval to the final version of the manuscript.

Conflicts of interest

There are no conflicts to declare.

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