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Catalytic Asymmetric Addition of Alkyl and Aryl Alkynes to *N*-(Diphenylphosphinoyl)imines

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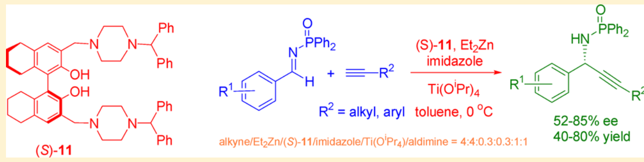
Supporting Information

ABSTRACT: A 3,3′-di(1-diphenylmethylpiperazinyl)methyl H_8BINOL compound, (*S*)-**11**, was prepared from the Mannich-type reaction of (*S*)-H_8BINOL with paraformaldehyde and 1-(diphenylmethyl)piperazine. This compound can catalyze the asymmetric reaction of alkyl and aryl alkynes with *N*-(diphenylphosphinoyl)imines in the presence of Et_2Zn and $Ti(O^iPr)_4$. It exhibits unprecedented high enantioselectivity (up to 85% ee) for a simple alkyl alkyne addition to the *N*-(diphenylphosphinoyl)imines. The easy removal of the *N*-(dipehenylphosphinoyl) protecting groups makes this method practically useful for the asymmetric synthesis of chiral propargyl amines.



1. INTRODUCTION

Chiral propargyl amines are important building blocks for the synthesis of numerous pharmaceuticals, biologically active compounds, and natural products.[1] The enantioselective alkyne addition to imines represents a very efficient process to produce chiral propargyl amines, and a number of highly enantioselective catalytic systems have been developed.[1−3] For example, extensive work has been conducted by using the Cu(I)-catalyzed reaction of terminal alkynes with *N*-arylimines that could be generated in situ from an aldehyde and an arylamine, and excellent enantioselectivity has been achieved for a number of substrates in the presence of various nitrogen-containing chiral ligands.[2] In many of these reactions, however, the N-protecting groups of the propargyl amine products, such as the aryl groups, are not easily removable for further transformation.

Among the imine substrates studied in the asymmetric alkyne additions to generate propargyl amines, the use of *N*-(diphenylphosphinoyl)imines is particularly interesting because the *N*-diphenylphosphinoyl activating/protecting group can be easily removed under very mild conditions after the reaction.[4−6] For example, when a methanol solution of an optically active *N*-(diphenylphosphinoyl) propargyl amine was treated with aqueous HCl at room temperature for 2 h, the resulting propargyl amine was obtained in 92% yield with retention of the enantiomeric purity.[6] Several reports have appeared for the catalytic asymmetric alkyne addition to the *N*-(diphenylphosphinoyl)imines, high enantioselectivity has been observed for certain substrates, but there are still limitations in these methods.[5,6] For example, no highly enantioselective reaction of *N*-(diphenylphosphinoyl)imines with simple *alkyl* alkynes was reported, although good results have been obtained for the additions of alkynes with aryl, $TMSOCH_2$, TMS, or 2-propenyl groups.[5,6] As shown in Scheme 1, although the 1,1′-bi-2-naphthol (BINOL) compound (*R*)-**1** showed high enantioselectivity for the reaction of *aryl* alkynes with *N*-(diphenylphosphinoyl)imines, it gave only 14% ee and 22% yield for the reaction of 1-hexyne with *N*-(diphenylphosphinoyl)benzaldimine (**2**).[6]

In our laboratory, we have discovered that the 3,3′-di(aminomethyl)-substituted partially hydrogenated BINOL (H_8BINOL) derivatives exhibit high enantioselectivity for the asymmetric alkyne, aryl, and vinyl additions to aldehydes.[7,8] This class of compounds can be synthesized in one step from the Mannich-type reaction of H_8BINOL with paraformaldehyde and a secondary amine (Scheme 2). We have also explored the use of these compounds in combination with Et_2Zn and $Ti(O^iPr)_4$ to catalyze the alkyne addition to *N*-(diphenylphosphinoyl)imines and have achieved high enantioselectivity for the reactions of both alkyl and aryl alkynes. Herein these results are reported.

2. RESULTS AND DISCUSSION

Previously, we reported the use of the 3,3′-di(morpholinylmethyl) H_8BINOL (*S*)-**3** (Figure 1) in combination with Et_2Zn and $Ti(O^iPr)_4$ to catalyze the phenylacetylene addition to aldehydes with high enantioselectivity.[7a] Therefore, we first tested the use of this compound to catalyze the reaction of phenylacetylene with **2** in the presence of Et_2Zn and $Ti(O^iPr)_4$, and the results are given in Table 1. As shown in entry 1 of Table 1, in the presence of 30 mol % (*S*)-**3**, the *N*-(diphenylphosphinoyl) propargyl amine product was obtained in 58% yield and 50% ee. We found that addition of pyridine (30 mol %) as an additive improved both the yield and ee of the product (entry 2). We have prepared the monomorpholinylmethyl-substituted H_8BINOL derivatives (*S*)-**4** and (*S*)-**5**, but these compounds gave much lower enantioselectivity (entries 3, 4). Especially, compound (*S*)-**5** with a bulky TBS group gave almost no enantioselectivity at all (entry 4). These results demonstrate that both of the 3,3′-aminomethyl groups are important for the chiral induction. Compound (*S*)-**6** is a sulfur-substituted analogue of

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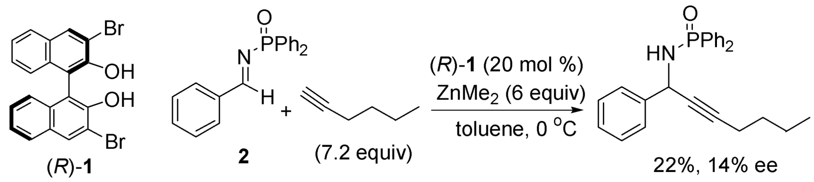
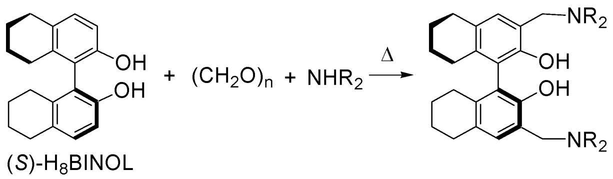
Scheme 1. An Aliphatic Alkyne Addition to *N*-(Diphenylphosphinoyl)imine 2



Scheme 2. Synthesis of 3,3′-Di(aminomethyl) H_8BINOLs



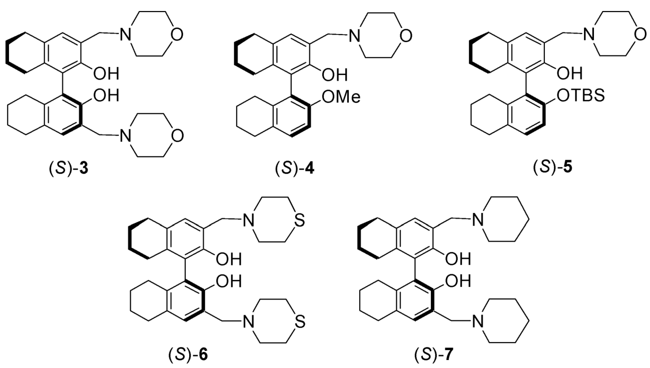
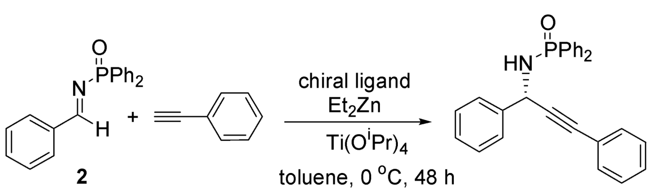


Figure 1. Chiral H_8BINOL derivatives containing 3-aminomethyl substitutents.

Table 1. Results for the Reaction of Phenylacetylene with 2 Catalyzed by (*S*)-3–(*S*)-7[a]

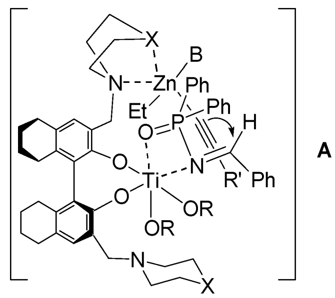


entry	chiral ligand	additive	yield (%)	ee (%)
1	(*S*)-**3**	none	58	50
2	(*S*)-**3**	pyridine	70	58 (*S*)
3	(*S*)-**4**	pyridine	62	43
4	(*S*)-**5**	pyridine	60	3
5	(*S*)-**6**	pyridine	58	59
6	(*S*)-**7**	pyridine	62	49

[a] Alkyne/Et_2Zn/ligand/Ti(O^iPr_4)/imine = 4:4:0.3:1:1. Pyridine (30 mol %) was added in entries 2–6. The reactions were conducted at 0 °C in toluene for 48 h. All the yields represent isolated product.

(*S*)-**3**, and it gave the same enantioselectivity as (*S*)-**3** (entry 5). However, when (*S*)-**7**, an analogue of (*S*)-**3** without the oxygen atom in the morpholinyl ring, was used, the enantioselectivity was significantly decreased (entry 6).

The study of (*S*)-**3**, (*S*)-**6**, and (*S*)-**7** indicates that the additional heteroatoms in the cyclic amine groups of these compounds should play a role in the asymmetric induction. The intermediate **A** is proposed to guide our exploration of this catalytic system. In **A**, the zinc acetylide is coordinated to the Lewis base additive (B) and the heterocyclic substituent of the H_8BINOL ligand. On the basis of this hypothesis, changing the heteroatom X and the additive B should allow us to tune the catalytic properties of this system.



We thus designed a new type of catalyst for this reaction by incorporating an additional nitrogen atom into the cyclic amine substituents to give (*S*)-**8** (Figure 2). This compound was prepared from the condensation of 1-methylpiperazine with H_8BINOL and paraformaldehyde. This compound represents an interesting class of H_8BINOL derivatives in which the terminal nitrogen atom could be easily modified by using various N-substituents. This should allow us to systematically modify the steric and electronic properties of the heteroatom X coordinated to the zinc acetylide as shown in the proposed intermediate **A**.

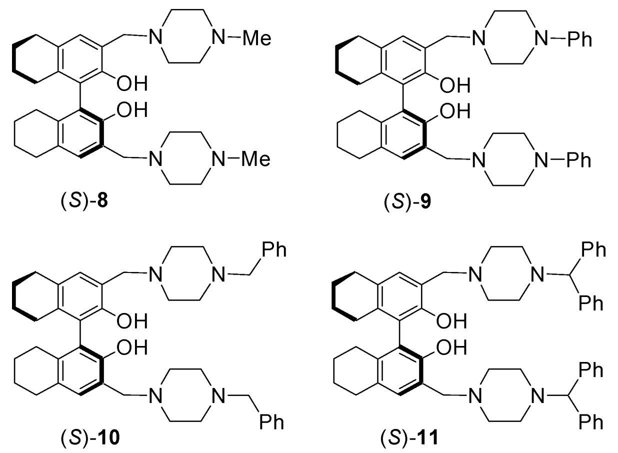


Figure 2. Chiral H_8BINOL derivatives containing 3,3′-piperazinyl substituents.

When (*S*)-**8** was used to catalyze the reaction of phenylacetylene with **2** under the same conditions as that used for (*S*)-**3**, it gave 47% ee for the addition product as shown in entry 1 of Table 2. To improve the enantioselectivity of this reaction, we have used various N-substituted piperazines to prepare compounds (*S*)-**9**–(*S*)-**11** and examined their catalytic properties. As shown in entries 2–4 of Table 2, among these compounds, (*S*)-**11** with a bulky 1-(diphenylmethyl) substituent on each piperazine ring gave the best enantioselectivity (64% ee, entry 4). When the solvent of the reaction was changed from

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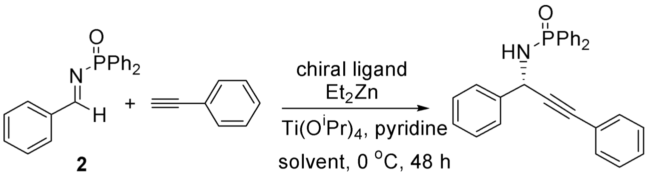
Table 2. Results for the Reaction of Phenylacetylene with 2 Catalyzed by the Piperazine Derivatives (*S*)-8–(*S*)-11[a]



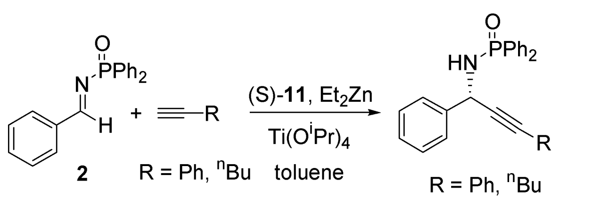
entry	chiral ligand	solvent	yield (%)	ee (%)
1	(*S*)-**8**	toluene	67	47
2	(*S*)-**9**	toluene	42	56
3	(*S*)-**10**	toluene	48	50
4	(*S*)-**11**	toluene	63	64
5	(*S*)-**11**	CH_2Cl_2	low	–
6	(*S*)-**11**	THF	45	35
7	(*S*)-**11**	Et_2O	60	51

[a]Alkyne/Et_2Zn/ligand/pyridine/$Ti(O^iPr_4)$/imine = 4:4:0.3:0.3:1:1. The reactions were conducted at 0 °C in toluene for 48 h. All the yields represent isolated product.

toluene to CH_2Cl_2, THF, and Et_2O, the yield and/or ee decreased (entries 5–7).

Because (*S*)-**11** shows improved enantioselectivity compared with the other H_8BINOL compounds, we further explored the reaction conditions for the use of this compound. The results are summarized in Table 3. As shown in entry 2, without the additive, the enantioselectivity significantly decreased for the reaction of phenylacetylene with **2**. We tested the use of imidazole in place of pyridine as the additive, and the enantioselectivity was improved to 72% ee (entry 3). Increasing the concentration of the reaction by reducing the solvent volume increased the enantioselectivity to 77% ee (entry 4). Lowering the reaction temperature to −20 °C greatly decreased the reaction yield and also slightly reduced the enantioselectivity (entry 5). Increasing the reaction temperature to room temperature increased the yield but greatly reduced the enantioselectivity (entry 6). At 0 °C, when the amount of Et_2Zn was increased to 6 equiv, the enantioselectivity was further enhanced to 81% ee (entry 7). In the absence of $Ti(O^iPr)_4$, there was significant reduction of ee (entry 8). When Et_2Zn was replaced with Me_2Zn, lower enantioselectivity was observed (entry 9). The configuration of the product was determined to be *S* by comparing the HPLC retention time with those in the literature.[5a,6] Besides imidazole, we also screened the use of a broad range of nitrogen-containing acyclic and cyclic bases as the additive, but they all gave lower enantioselectivity (52–70% ee) under the same conditions of entry 7.

Table 3. Results for the Reaction of Phenylacetylene with 2 Catalyzed by (*S*)-11[a]



entry	RC≡CH	additive	R_2Zn	yield (%)	ee (%)
1	Ph	pyridine	Et_2Zn (4 equiv)	63	64
2	Ph	none	Et_2Zn (4 equiv)	60	47 (*S*)
3	Ph	imidazole	Et_2Zn (4 equiv)	72	72
4	Ph	imidazole	Et_2Zn (4 equiv)	75	77
5[b]	Ph	imidazole	Et_2Zn (4 equiv)	24	74
6[c]	Ph	imidazole	Et_2Zn (4 equiv)	82	37
7[d]	Ph	imidazole	Et_2Zn (6 equiv)	80	81
8[e]	Ph	imidazole	Et_2Zn (4 equiv)	67	60
9[f]	Ph	imidazole	Me_2Zn (4 equiv)	70	68
10	^{n}Bu	imidazole	Et_2Zn (4 equiv)	52	85
11	^{n}Bu	imidazole	Et_2Zn (6 equiv)	55	74

[a]Unless noted otherwise, the following reagent ratio was used: Alkyne/Et_2Zn/(*S*)-**11**/additive/$Ti(O^iPr_4)$/**2** = 4:4:0.3:0.3:1:1, **2** (0.1 mmol), and toluene (1.0 mL for entries 1–3; 0.7 mL for entries 4–11). The reaction was allowed to proceed at 0 °C for 48 h. [b]At −20 °C. [c]At rt. [d]Alkyne/Et_2Zn/(*S*)-**11**/additive/$Ti(O^iPr_4)$/**2** = 7.2:6:0.3:0.3:1:1. [e]$Ti(O^iPr_4)$ was not added. [f]Me_2Zn was used in place of Et_2Zn. All the yields represent isolated product.

When the reaction conditions of entry 7 in Table 3 were applied to the reaction of 1-hexyne with **2**, we were pleased to observe a high enantioselectivity (85% ee) for this aliphatic alkyne addition (entry 10, Table 3). As described previously in Scheme 1, the previous catalytic system gave very low enantioselectivity for such an aliphatic alkyne addition. Increasing the amount of Et_2Zn from 4 equiv to 6 equiv reduced the enantioselectivity (entry 11, Table 3). We have conducted the background reaction in the absence of the chiral catalyst. After 48 h at 0 °C, there was only less than 20% conversion of the starting material to the product. That is, the chiral catalyst (*S*)-**11** promoted the reaction with good stereocontrol. The high enantioselectivity observed for the reaction of 1-hexyne with **2** catalyzed by (*S*)-**11** in entry 10 prompted us to apply these conditions for the reaction of various alkyl alkynes with various *N*-(diphenylphosphinoyl)imines. As the results summarized in Figure 3 show, when 1-hexyne was reacted with the aldimines

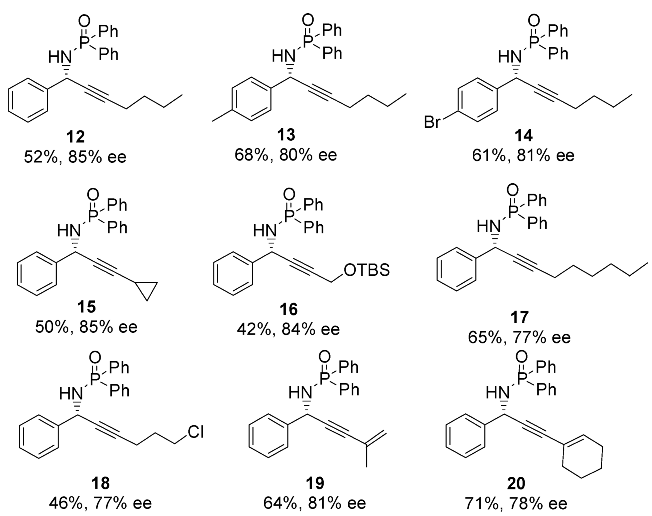


Figure 3. Products for the reaction of aliphatic alkynes with *N*-(diphenylphosphinoyl)imines catalyzed by (*S*)-**11**. Reagents: Alkyne/Et_2Zn/(*S*)-**11**/additive/$Ti(O^iPr_4)$/imidazole = 4:4:0.3:0.3:1:1, imine (0.1 mmol). All the yields represent isolated product.

containing the electron-donating Me group or the electron-withdrawing Br, the corresponding products **13** and **14** were obtained with good yields and ee's. The addition of other aliphatic alkynes to **2** also gave good enantioselectivities in the synthesis of compounds **15**–**18**. The lower yields in the isolation of compounds **15**, **16**, and **18** could be attributed to the sensitivity of the functional groups on the alkyl alkynes under the reaction conditions. The reaction of the conjugated enynes with

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2 was also studied which gave the products **19** and **20** with good results. We have treated an aliphatic imine with 1-hexyne under the same conditions, but no reaction was observed.

We applied the conditions of entry 7 in Table 3 for the asymmetric addition of aryl alkynes to *N*-(diphenylphosphinoyl)imines. The results are summarized in Figure 4. Similar enantioselectivity was observed for the phenylacetylene addition to *N*-(diphenylphosphinoyl) benzaldimines containing an electron-donating Me group or an electron-withdrawing Br for the formation of compounds **22** and **23**. Addition of other aryl alkynes to **2** was studied. It was found that the more electron-rich aryl alkynes gave higher enantioselectivity for the formation of products **24**−**26** compared with the more electron-deficient aryl alkynes which gave the products **27** and **28**. The lower yields of **27** and **28** could be attributed to their corresponding less nucleophilic zinc acetylides.

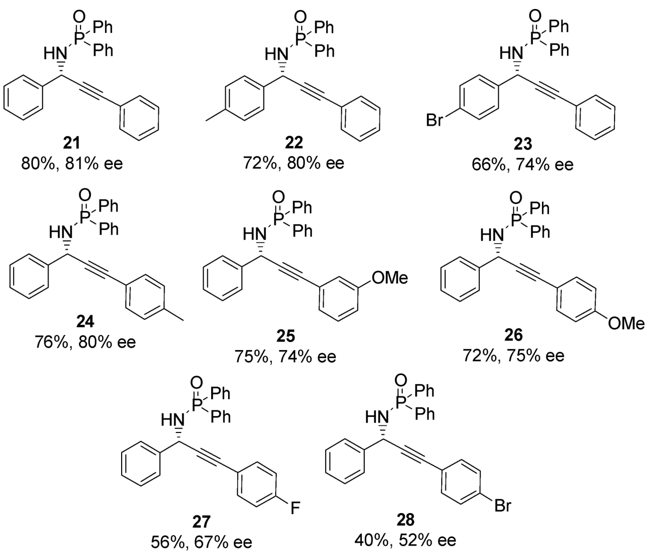

Figure 4. Products for the reaction of aromatic alkynes with *N*-(diphenylphosphinoyl)imines catalyzed by (*S*)-**11**. Reagents: Alkyne/Et_2Zn//(*S*)-**11**/additive/$Ti(O^iPr_4)$/imine = 7.2:6:0.3:0.3:1:1, imine (0.1 mmol). All the yields represent isolated product.

3. CONCLUSION

We have discovered that a 3,3′-di(1-diphenylmethylpiperazinyl)-methyl H_8BINOL compound can catalyze the asymmetric reaction of various alkynes with *N*-(diphenylphosphinoyl)imines in the presence of Et_2Zn and $Ti(O^iPr)_4$. It exhibits unprecedented high enantioselectivity for the reaction of *N*-(diphenylphosphinoyl)imines with simple and functional *alkyl* alkynes. The easy removal of the *N*-(diphenylphosphinoyl) protecting groups of the propargylic amine products makes this method useful for the synthesis of this class of important chiral compounds. Because this catalyst system utilizes two metallic reagents in combination with a multifunctional chiral ligand, more detailed study of the reaction mechanism is necessary to gain better understanding of this reaction and further improve the catalytic efficiency. Work along this line will be conducted.

4. EXPERIMENTAL SECTION

General Data. Reactions were carried out under nitrogen in vials. All commercial chemicals were used without further purification unless otherwise noted. Zinc reagents were purchased and stored in dry nitrogen atmosphere. Toluene was distilled over sodium and benzophenone under nitrogen. All the NMR spectra were obtained in $CDCl_3$ unless indicated otherwise. Compounds (*S*)-**3**,[7d] (*S*)-**6**,[7e] and (*S*)-**7**[7e] were known compounds, and their NMR spectra match those reported (see SI).

*Synthesis and Characterization of (S)-**4**.* (a) To a solution of (*S*)-H_8BINOL (2.04 mmol, 600 mg, 1 equiv) and K_2CO_3 (10.2 mmol, 1.4 g, 5 equiv) in 20 mL of THF was added MeI (2.04 mmol, 127.1 μL, 1 equiv) at room temperature under nitrogen. Then the reaction was heated to 50 °C and stirred for 24 h. After being cooled to room temperature, the mixture was quenched with water (10 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The organic layer was then dried over anhydrous Na_2SO_4 and concentrated by rotary evaporation. The crude mixture was purified by flash column chromatography on silica gel eluted with hexanes/CH_2Cl_2 (5/1) to give *O*-Me-(*S*)-H_8BINOL as a white powder in 70% yield (440 mg). The NMR spectra match those reported.[8a] (b) Paraformaldehyde (5.0 mmol, 150 mg, 5 equiv) was added to a two-neck round-bottom flask fitted with condenser under nitrogen. The flask was then charged with dioxane (10 mL, degassed), and the mixture was cooled to 0 °C. Morpholine (5.0 mmol, 431 mL, 5 equiv) was added dropwise into the mixture over 20 min. After the addition was completed, the ice bath was removed and the mixture was warmed to room temperature for 2 h. It was then heated at 65 °C for 18 h. After the solution was cooled to room temperature, *O*-Me-(*S*)-H_8BINOL (1.0 mmol, 308 mg, 1 equiv) dissolved in dioxane (5 mL) was added, and the resulting solution was reheated to 95 °C for 20 h. Upon completion of the reaction, the mixture was diluted with ethyl acetate (15 mL) and washed with saturated $NaHCO_3$ (3 × 15 mL) and H_2O (3 × 15 mL). The organic layer was then dried over anhydrous Na_2SO_4 and concentrated by rotary evaporation. The crude mixture was purified by flash column chromatography on silica gel eluted with hexanes/ethyl acetate (20/1 to 10/1) to give pure (*S*)-**4** as a white powder in 65% yield (265 mg). mp 80−82 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.31 (s, 1H), 7.12 (d, 1H, J = 8.4 Hz), 6.87 (d, 1H, J = 8.4 Hz), 6.81 (s, 1H), 3.83 (d, 1H, J = 13.8 Hz), 3.76 (m, 7H), 3.70 (d, 1H, J = 13.8 Hz), 2.83 (m, 4H), 2.62 (s, 4H), 2.38 (m, 2H), 2.20 (m, 2H), 1.76 (m, 8H). ^{13}C {^{1}H} NMR (150 MHz, $CDCl_3$) δ 154.8, 152.0, 136.5, 136.2, 129.6, 129.0, 128.6, 127.5, 125.7, 124.3, 117.7, 109.2, 66.7, 61.9, 56.1, 53.0, 29.5, 29.3, 27.2, 27.1, 23.4, 23.35, 23.32, 23.2. HRMS [ESI(TOF)] for $C_{26}H_{34}NO_3$ [M + H$^+$]: *m*/*z*: calcd for: 408.2539; found: 408.2536.

*Synthesis and Characterization of (S)-**5**.* (a) To a solution of (*S*)-H_8BINOL (1.7 mmol, 500 mg, 1 equiv) in 10 mL of THF was added nBuLi (2.0 mmol, 2.5 M in hexanes, 0.8 mL, 1.2 equiv) at 0 °C under nitrogen. The reaction was stirred for 20 min. Then TBSCl (2.0 mmol, 306 mg, 1.2 equiv) in 5 mL of THF was added, and the resulting solution was warmed to room temperature. After 20 h, the reaction was quenched with saturated NH_4Cl solution (10 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The organic layer was then dried over anhydrous Na_2SO_4 and concentrated by rotary evaporation. The crude mixture was purified by flash column chromatography on silica gel eluted with hexanes/CH_2Cl_2 (8/1 to 5/1) to give *O*-TBS-(*S*)-H_8BINOL as a white powder in 74% yield (512 mg). The NMR spectra match those reported.[8b] (b) Paraformaldehyde (6.25 mmol, 188 mg, 5 equiv) was added to a two-neck round-bottom flask fitted with condenser under nitrogen. The flask was then charged with dioxane (10 mL, degassed), and the mixture was cooled to 0 °C. Morpholine (6.25 mmol, 548 mL, 5 equiv) was added dropwise into the mixture over 20 min. After the addition was completed, the ice bath was removed and the mixture was warmed to room temperature for 2 h. It was then heated at 65 °C for 18 h. After the solution was cooled to room temperature, *O*-TBS-(*S*)-H_8BINOL (1.25 mmol, 512 mg, 1 equiv) dissolved in dioxane (5 mL) was added, and the resulting solution was reheated to 95 °C for 20 h. Upon completion of the reaction, the mixture was diluted with ethyl acetate (15 mL) and washed with saturated $NaHCO_3$ (3 × 15 mL) and H_2O (3 × 15 mL). The organic layer was then dried over anhydrous Na_2SO_4 and concentrated by rotary evaporation. The crude mixture was purified by flash column chromatography on silica gel with hexanes/ethyl acetate (25/1 to 15/1) to give pure (*S*)-**5** as a white powder in 59% yield (374 mg). mp 70−73 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.21 (s, 1H), 6.97 (d, 1H, J = 8.4 Hz), 6.71 (m, 2H), 3.79 (d, 1H, J = 13.2 Hz), 3.70 (s, 4H), 3.54 (d, 1H, J = 13.8 Hz), 2.78 (m, 2H), 2.71 (m, 2H), 2.60 (m, 4H),

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2.48 (m, 2H), 2.16 (m, 2H), 1.70 (m, 8H), 0.70 (s, 9H), 0.16 (s, 3H), −0.01 (s, 3H). ^{13}C {^1H} NMR (150 MHz, $CDCl_3$) δ 152.1, 150.1, 137.0, 136.4, 129.6, 128.8, 128.08, 128.06, 127.5, 124.7, 117.6, 116.0, 66.7, 61.9, 52.9, 29.5, 29.4, 27.3, 27.0, 25.3, 23.4, 23.33, 23.30, 23.2, 17.7, −4.1, −4.8. HRMS [ESI(TOF)] for $C_{31}H_{46}NO_3Si$ [M + H$^+$]: *m/z*: calcd for: 508.3247; found: 508.3253.

*Synthesis and Characterization of (S)-**11***. Paraformaldehyde (23.8 mmol, 714.3 mg, 4 equiv) was added to a two-neck round-bottom flask fitted with condenser under nitrogen. The flask was then charged with dioxane (20 mL, degassed), and the mixture was cooled to 0 °C. 1-(Diphenylmethyl)piperazine (23.8 mmol, 6.0 g, 4 equiv) was added dropwise into the mixture over 20 min. After the addition was completed, the ice bath was removed, and the mixture was warmed to room temperature for 2 h. It was then heated at 65 °C for 18 h. After the solution was cooled to room temperature, (*S*)-H_8BINOL (6.0 mmol, 1.76 g, 1 equiv) dissolved in dioxane (10 mL) was added, and the resulting solution was reheated to 65 °C for 18 h. Upon completion of the reaction, the mixture was diluted with ethyl acetate (20 mL) and washed with saturated $NaHCO_3$ (3 × 20 mL) and H_2O (3 × 20 mL). The organic layer was then dried over anhydrous Na_2SO_4 and concentrated by rotary evaporation. The crude solid was washed with EtOH to give pure (*S*)-**11** as a white powder in 90% yield (4.44 g). mp 182−185 °C. ^1H NMR (600 MHz, $CDCl_3$) δ 10.46 (s, 2H), 7.42 (m, 8H), 7.28 (m, 8H), 7.20 (m, 4H), 6.74 (s, 2H), 4.27 (m, 2H), 3.87 (d, 2H, *J* = 13.8 Hz), 3.58 (d, 2H, *J* = 13.8 Hz), 2.76−2.33 (m, 22H), 2.17 (m, 2H), 1.72 (m, 8H). ^{13}C {^1H} NMR (150 MHz, $CDCl_3$) δ 152.4, 142.6, 142.5, 135.6, 128.6, 128.5, 128.4, 127.9, 127.3, 127.1, 127.0, 124.0, 118.2, 76.0, 61.6, 52.8, 51.5, 29.3, 27.0, 23.4, 23.3, $[\alpha]^{24}_D$ = +16.5 (c = 1.10, $CHCl_3$). HRMS [ESI(TOF)] for $C_{56}H_{63}N_4O_2$ [M + H$^+$]: *m/z*: calcd for: 823.4951; found: 823.4950.

Compounds (*S*)-**8**, (*S*)-**9**, and (*S*)-**10** were prepared in the same way as for (*S*)-**11** by using the corresponding commercially available 1-substituted piperazine as the starting material.

*Characterization of (S)-**8***. Prepared from (*S*)-H_8BINOL (3.4 mmol), white solid, 1.36 g, 77% yield. mp 180−182 °C. ^1H NMR (600 MHz, $CDCl_3$) δ 6.69 (s, 2H), 3.77 (d, 2H, *J* = 13.2 Hz), 3.58 (d, 2H, *J* = 13.8 Hz), 2.70 (m, 4H), 2.59−2.43 (m, 16H), 2.36 (m, 2H), 2.25 (s, 6H), 2.15 (m, 2H), 1.69 (m, 8H). ^{13}C {^1H} NMR (150 MHz, $CDCl_3$) δ 152.2, 135.7, 128.5, 127.3, 124.0, 118.2, 61.4, 54.7, 52.4, 45.8, 29.2, 27.0, 23.3, 23.2. HRMS [ESI(TOF)] for $C_{32}H_{47}N_4O_2$ [M + H$^+$]: *m/z*: calcd for: 519.3699; found: 519.3701.

*Characterization of (S)-**9***. Prepared from (*S*)-H_8BINOL (2.2 mmol), white solid, 1.13 g, 80% yield. mp 240−243 °C. ^1H NMR (600 MHz, $CDCl_3$) δ 10.45 (s, 2H), 7.25 (m, 4H), 6.89 (m, 6H), 6.76 (s, 2H), 3.87 (d, 2H, *J* = 13.8 Hz), 3.66 (d, 2H, *J* = 13.8 Hz), 3.19 (s, 8H), 2.74 (m, 12H), 2.38 (m, 2H), 2.19 (m, 2H), 1.72 (m, 8H). ^{13}C {^1H} NMR (150 MHz, $CDCl_3$) δ 152.2, 151.0, 135.9, 129.1, 128.6, 127.5, 124.0, 120.0, 118.1, 116.4, 61.5, 52.5, 49.1, 29.2, 27.0, 23.3, 23.2. HRMS [ESI(TOF)] for $C_{42}H_{51}N_4O_2$ [M + H$^+$]: *m/z*: calcd for: 643.4012; found: 643.4015.

*Characterization of (S)-**10***. Prepared from (*S*)-H_8BINOL (3.4 mmol), white solid, 1.94 g, 85% yield. mp 193−195 °C. ^1H NMR (600 MHz, $CDCl_3$) δ 10.67 (s, 2H), 7.30 (m, 10H), 6.73 (s, 2H), 3.83 (d, 2H, *J* = 13.8 Hz), 3.59 (d, 2H, *J* = 13.8 Hz), 3.48 (s, 4H), 2.74−2.16 (m, 28H), 1.72 (m, 8H). ^{13}C {^1H} NMR (150 MHz, $CDCl_3$) δ 152.3, 138.0, 135.6, 129.0, 128.4, 128.2, 127.2, 127.1, 124.0, 118.2, 62.8, 61.5, 52.7, 52.5, 29.2, 27.0, 23.3, 23.2. HRMS [ESI(TOF)] for $C_{44}H_{55}N_4O_2$ [M + H$^+$]: *m/z*: calcd for: 671.4325; found: 671.4324.

*General Procedure for the Alkyne Addition to N-(Diphenylphosphinoyl)imines Catalyzed by (S)-**11***. Under nitrogen, (*S*)-**11** (30 mol %, 24.8 mg) and imidazole (30 mol %, 2 mg) were added into a vial and dissolved in toluene (0.3 mL). An alkyne (4 equiv or 7.2 equiv) and Et_2Zn (4 equiv or 6 equiv) were then added, and the mixture was stirred at room temperature for 5 h. Then $Ti(O^iPr)_4$ (1 equiv) was added and the stirring continued at room temperature for 3 h. A *N*-(diphenylphosphinoyl)imine (0.1 mmol, 1 equiv) was added, and the mixture was cooled to 0 °C and stirred for 48 h. The reaction was quenched with the addition of water (2 mL) and extracted with ethyl acetate (3 × 4 mL). The organic layer was dried with anhydrous Na_2SO_4, filtered, and then concentrated by rotary evaporation. The crude mixture was purified by flash column chromatography on silica gel with hexanes/ethyl acetate (1/1) to give the propargyl phosphonamide products in 40−80% yield and 52−85% ee.

We have also conducted a larger scale reaction of **2** (1.15 mmol) with 1-hexyne which gave the product **12** in 45% yield and 85% ee.

Characterization of the Propargyl Phosphonamides Prepared from the Asymmetric Alkyne Addition to N-(Diphenylphosphinoyl)-imines. Compounds **12**,[6] **15**,[6] **16**,[5a] **19**,[5a] **21**,[6] **22**,[6] **23**,[5a] **26**,[6] and **27**[6] are known compounds, and their NMR spectra match those reported (see SI).

*(S)-P,P-Diphenyl-N-(1-(p-tolyl)hept-2-yn-1-yl)phosphinic Amide, **13***. White solid, 27.2 mg, 68% yield. mp 138−140 °C. 80% ee determined by HPLC analysis: CHIRALPAK AD-H column, 90:10 hexanes:^{i}PrOH, flow rate = 1.0 mL/min, λ = 225 nm, retention time: t_{minor} = 16.6 min, t_{major} = 20.0 min. $[\alpha]^{25}_D$ = −13.7 (*c* = 0.96, $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$) δ 8.02 (m, 2H), 7.82 (m, 2H), 7.52 (m, 1H), 7.47 (m, 5H), 7.38 (m, 2H), 7.12 (d, 2H, *J* = 7.8 Hz), 5.09 (t, 1H, *J* = 9.6 Hz), 3.37 (t, 1H, *J* = 9 Hz), 2.31 (s, 3H), 2.19 (t, 2H, *J* = 7.2 Hz), 1.47 (m, 2H), 1.40 (m, 2H), 0.91 (t, 3H, *J* = 7.2 Hz). ^{13}C {^1H} NMR (150 MHz, $CDCl_3$) δ 138.2 (d, *J* = 4.7 Hz), 137.4, 132.7 (d, *J* = 9.8 Hz), 131.9, 131.8, 129.1, 128.4 (d, *J* = 12.6 Hz), 127.1, 86.0, 79.8 (d, *J* = 6 Hz), 46.6, 30.7, 22.0, 21.1, 18.5, 13.6. ^{31}P {^1H} NMR (243 MHz, $CDCl_3$) δ 23.1. HRMS [ESI(TOF)] for $C_{26}H_{29}NOP$ [M + H$^+$]: *m/z*: calcd for: 402.1987; found: 402.1985.

*(S)-N-(1-(4-Bromophenyl)hept-2-yn-1-yl)-P,P-diphenylphosphinic Amide, **14***. White solid, 28.5 mg, 61% yield. mp 140−143 °C. 81% ee determined by HPLC analysis: CHIRALPAK AD-H column, 90:10 hexanes:^{i}PrOH, flow rate = 1.0 mL/min, λ = 225 nm, retention time: t_{minor} = 14.9 min, t_{major} = 20.2 min. $[\alpha]^{23}_D$ = −10.9 (*c* = 1.18, $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$) δ 8.01 (m, 2H), 7.79 (m, 2H), 7.53 (m, 1H), 7.48 (m, 5H), 7.43 (m, 2H), 7.38 (m, 2H), 5.08 (t, 1H, *J* = 9 Hz), 3.44 (t, 1H, *J* = 7.8 Hz), 2.21 (m, 2H), 1.48 (m, 2H), 1.40 (m, 2H), 0.91 (t, 3H, *J* = 7.2 Hz). ^{13}C {^1H} NMR (150 MHz, $CDCl_3$) δ 140.1 (d, *J* = 3.8 Hz), 132.6 (d, *J* = 9.9 Hz), 132.0 (d, *J* = 10.5 Hz), 131.7 (d, *J* = 9.8 Hz), 131.5, 129.1, 128.4 (d, *J* = 12.9 Hz), 121.7, 86.6, 79.1 (d, *J* = 6.9 Hz), 46.4, 30.6, 22.0, 18.4, 13.6. ^{31}P {^1H} NMR (243 MHz, $CDCl_3$) δ 23.5. HRMS [ESI(TOF)] for $C_{25}H_{26}NOPBr$ [M + H$^+$]: *m/z*: calcd for: 466.0935; found: 466.0932.

*(S)-P,P-diphenyl-N-(1-phenylnon-2-yn-1-yl)phosphinic Amide, **17***. White solid, 27.0 mg, 65% yield. mp 110−112 °C. 77% ee determined by HPLC analysis: CHIRALPAK AD-H column, 90:10 hexanes:^{i}PrOH, flow rate = 1.0 mL/min, λ = 225 nm, retention time: t_{minor} = 10.4 min, t_{major} = 11.5 min. $[\alpha]^{24}_D$ = −13.4 (*c* = 0.95, $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$) δ 8.03 (m, 2H), 7.82 (m, 2H), 7.60 (d, 2H, *J* = 8.4 Hz), 7.52 (m, 1H), 7.46 (m, 3H), 7.37 (m, 2H), 7.32 (t, 2H, *J* = 7.2 Hz), 7.25 (m, 1H), 5.13 (t, 1H, *J* = 9.6 Hz), 3.41 (t, 1H, *J* = 9 Hz), 2.20 (m, 2H), 1.49 (m, 2H), 1.38 (m, 2H), 1.29 (m, 4H), 0.88 (t, 3H, *J* = 7.2 Hz). ^{13}C {^1H} NMR (150 MHz, $CDCl_3$) δ 141.0 (d, *J* = 4.7 Hz), 132.7 (d, *J* = 9.9 Hz), 131.9 (d, *J* = 7.4 Hz), 131.8 (d, *J* = 9.6 Hz), 128.5, 128.4 (d, *J* = 12.8 Hz), 127.7, 127.2, 86.3, 79.7 (d, *J* = 6.2 Hz), 46.8, 31.3, 28.6, 28.5, 22.5, 18.8, 14.0. ^{31}P {^1H} NMR (243 MHz, $CDCl_3$) δ 23.2. HRMS [ESI(TOF)] for $C_{27}H_{31}NOP$ [M + H$^+$]: *m/z*: calcd for: 416.2143; found: 416.2141.

*(S)-N-(6-Chloro-1-phenylhex-2-yn-1-yl)-P,P-diphenylphosphinic Amide, **18***. White solid, 18.7 mg, 46% yield. mp 107−109 °C. 77% ee determined by HPLC analysis: CHIRALPAK AD-H column, 90:10 hexanes:^{i}PrOH, flow rate = 1.0 mL/min, λ = 225 nm, retention time: t_{minor} = 21.6 min, t_{major} = 25.2 min. $[\alpha]^{24}_D$ = −11.5 (*c* = 0.61, $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$) δ 8.00 (m, 2H), 7.82 (m, 2H), 7.56 (d, 2H, *J* = 7.8 Hz), 7.52 (m, 1H), 7.47 (m, 3H), 7.39 (m, 2H), 7.33 (t, 2H, *J* = 7.8 Hz), 7.26 (t, 1H, *J* = 7.2 Hz), 5.14 (t, 1H, *J* = 9.6 Hz), 3.61 (t, 2H, *J* = 6.6 Hz), 3.42 (t, 1H, *J* = 8.4 Hz), 2.39 (m, 2H), 1.92 (m, 2H). ^{13}C {^1H} NMR (150 MHz, $CDCl_3$) δ 140.7 (d, *J* = 4.8 Hz), 132.5 (d, *J* = 9.8 Hz), 132.0 (d, *J* = 6.9 Hz), 131.8 (d, *J* = 9.8 Hz), 128.6, 128.4 (d, *J* = 12.6 Hz), 127.9, 127.1, 84.1, 80.8 (d, *J* = 5.6 Hz), 46.7, 43.7, 31.2, 16.2. ^{31}P {^1H} NMR (243 MHz, $CDCl_3$) δ 23.2. HRMS [ESI(TOF)] for $C_{24}H_{24}NOPCl$ [M + H$^+$]: *m/z*: calcd for: 408.1284; found: 408.1280.

*(S)-N-(3-(Cyclohex-1-en-1-yl)-1-phenylprop-2-yn-1-yl)-P,P-diphenylphosphinic Amide, **20***. White solid, 29.2 mg, 71% yield. mp 154−156 °C. 78% ee determined by HPLC analysis: CHIRALCEL OD-H column, 93:7 hexanes:^{i}PrOH, flow rate = 1.0 mL/min, λ = 225 nm,

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retention time: t_{minor} = 10.7 min, t_{major} = 8.3 min. $[\alpha]^{24}_{D}$ = −26.7 (c = 1.21, $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$) δ 8.04 (m, 2H), 7.81 (m, 2H), 7.61 (d, 2H, J = 7.2 Hz), 7.52 (m, 1H), 7.46 (m, 3H), 7.37 (m, 2H), 7.32 (d, 2H, J = 7.8 Hz), 7.25 (m, 1H), 6.09 (s, 1H), 5.26 (t, 1H, J = 9.6 Hz), 3.46 (t, 1H, J = 9 Hz), 2.09 (d, 4H, J = 6 Hz), 1.62 (m, 4H). ^{13}C {^1H} NMR (150 MHz, $CDCl_3$) δ 140.7 (d, J = 4.4 Hz), 135.1, 132.8 (d, J = 9.8 Hz), 131.9 (d, J = 7.8 Hz), 131.8 (d, J = 9.8 Hz), 128.5, 128.4 (d, J = 12.8 Hz), 127.8, 127.3, 120.2, 87.4, 86.0 (d, J = 6.3 Hz), 47.1, 29.1, 25.6, 22.2, 21.5. ^{31}P {^1H} NMR (243 MHz, $CDCl_3$) δ 23.3. HRMS [ESI(TOF)] for $C_{27}H_{27}NOP$ [M + H^+]: m/z: calcd for: 412.1830; found: 412.1829.

(S)-P,P-Diphenyl-N-(1-phenyl-3-(p-tolyl)prop-2-yn-1-yl)-phosphinic Amide, 24. White solid, mp 172−174 °C, 32.0 mg, 76% yield. 80% ee determined by HPLC analysis: CHIRALPAK AD-H column, 93:7 hexanes:^{i}PrOH, flow rate = 1.0 mL/min, λ = 254 nm, retention time: t_{minor} = 28.6 min, t_{major} = 32.7 min. $[\alpha]^{23}_{D}$ = −46.8 (c = 1.10, $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$) δ 8.08 (m, 2H), 7.84 (m, 2H), 7.68 (d, 2H, J = 7.8 Hz), 7.52 (m, 1H), 7.46 (m, 3H), 7.40−7.34 (m, 4H), 7.29 (m, 3H), 7.11 (d, 2H, J = 7.8 Hz), 5.38 (t, 1H, J = 9.6 Hz), 3.53 (t, 1H, J = 8.4 Hz), 2.35 (s, 3H). ^{13}C {^1H} NMR (150 MHz, $CDCl_3$) δ 140.4 (d, J = 4.2 Hz), 138.5, 132.8 (d, J = 9.9 Hz), 132.0 (d, J = 8.9 Hz), 131.8 (d, J = 9.8 Hz), 131.5, 129.0, 128.6, 128.5 (d, J = 12.9 Hz), 127.9, 127.3, 119.6, 88.1 (d, J = 6 Hz), 85.7, 47.2, 21.5. ^{31}P {^1H} NMR (243 MHz, $CDCl_3$) δ 23.4. HRMS [ESI(TOF)] for $C_{28}H_{25}NOP$ [M + H^+]: m/z: calcd for: 422.1674; found: 422.1660.

(S)-N-(3-(3-Methoxyphenyl)-1-phenylprop-2-yn-1-yl)-P,P-diphenylphosphinic Amide, 25. Colorless oil, 32.8 mg, 75% yield. 74% ee determined by HPLC analysis: CHIRALPAK AD-H column, 90:10 hexanes:^{i}PrOH, flow rate = 1.0 mL/min, λ = 254 nm, retention time: t_{minor} = 22.2 min, t_{major} = 26.3 min. $[\alpha]^{23}_{D}$ = −38.9 (c = 0.65, $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$) δ 8.07 (m, 2H), 7.84 (m, 2H), 7.67 (d, 2H, J = 7.8 Hz), 7.51 (m, 1H), 7.47 (m, 3H), 7.39−7.35 (m, 4H), 7.29 (t, 1H, J = 7.8 Hz), 7.21 (t, 1H, J = 7.8 Hz), 7.00 (d, 1H, J = 7.2 Hz), 6.92 (s, 1H), 6.87 (d, 1H, J = 8.4 Hz), 5.39 (t, 1H, J = 9.6 Hz), 3.79 (s, 3H), 3.54 (t, 1H, J = 9 Hz). ^{13}C {^1H} NMR (150 MHz, $CDCl_3$) δ 159.2, 140.3 (d, J = 4.4 Hz), 132.8 (d, J = 9.9 Hz), 132.0 (d, J = 6.9 Hz), 131.8 (d, J = 9.8 Hz), 129.3, 128.7, 128.5 (d, J = 12.8 Hz), 128.0, 127.3, 124.2, 123.7, 116.6, 114.9, 88.6 (d, J = 6.2 Hz), 85.4, 55.3, 47.1. ^{31}P {^1H} NMR (243 MHz, $CDCl_3$) δ 23.4. HRMS [ESI(TOF)] for $C_{28}H_{25}NO_2P$ [M + H^+]: m/z: calcd for: 438.1623; found: 438.1631.

(S)-N-(3-(4-Bromophenyl)-1-phenylprop-2-yn-1-yl)-P,P-diphenylphosphinic Amide, 28. White solid, mp 175−178 °C, 19.5 mg, 40% yield. 52% ee determined by HPLC analysis: CHIRALPAK AD-H column, 90:10 hexanes:^{i}PrOH, flow rate = 1.0 mL/min, λ = 254 nm, retention time: t_{minor} = 26.2 min, t_{major} = 29.0 min. $[\alpha]^{25}_{D}$ = −12.2 (c = 0.48, $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$) δ 8.04 (m, 2H), 7.84 (m, 2H), 7.64 (d, 2H, J = 7.2 Hz), 7.52 (m, 1H), 7.46−7.35 (m, 9H), 7.29 (m, 1H), 7.22 (d, 2H, J = 7.8 Hz), 5.38 (t, 1H, J = 9 Hz), 3.56 (t, 1H, J = 8.4 Hz). ^{13}C NMR (150 MHz, $CDCl_3$) δ 140.1 (d, J = 4.4 Hz), 133.1, 132.7 (d, J = 9.6 Hz), 132.0, 131.8 (d, J = 9.5 Hz), 131.5, 128.7, 128.5 (d, J = 12.5 Hz), 128.1, 127.2, 122.6, 121.6, 90.0 (d, J = 5.0 Hz), 84.5, 47.1. ^{31}P {^1H} NMR (243 MHz, $CDCl_3$) δ 23.4. HRMS [ESI(TOF)] for $C_{27}H_{22}NOPBr$ [M + H^+]: m/z: calcd for: 486.0622; found: 486.0636.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01599.

NMR spectra and HPLC plots of the propargylic amine products (PDF)

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Notes

The authors declare no competing financial interest.

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