Title

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Journal

The Journal of Antibiotics, 72(6)

ISSN

0021-8820

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Publication Date

2019-06-01

DOI

10.1038/s41429-019-0181-0

Peer reviewed

HHS Public Access

Author manuscript

J Antibiot (Tokyo). Author manuscript; available in PMC 2020 June 01.

Published in final edited form as:

J Antibiot (Tokyo). 2019 June ; 72(6): 389–396. doi:10.1038/s41429-019-0181-0.

Chiral aminophosphines derived from hydroxyproline and their application in allene–imine [4 + 2] annulation

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Abstract

A robust synthetic route from L-hydroxyproline (L-Hyp) to phosphines has established an expandable library of six chiral aminophosphines, which were then applied to the phosphine-catalyzed [4 + 2] allene–imine annulation. The enantioinduction in the annulations—induced by a purely steric effect—were moderate (up to 57% ee). A switch of the reaction site from the γ- to the β′-carbon atom of the allenoate was observed during the annulations performed using sterically demanding chiral phosphines.

Introduction

Piperidines are among the nitrogen heterocycles most frequently used in pharmaceuticals [1]. Apart from their appearance in pharmaceutically interesting substances [2], tetrahydropyridines, and piperidines are present as common structural motifs in many bioactive natural products [3–5]. Because of the interesting biological effects exerted by tetrahydropyridine- and piperidine-containing compounds, many methods have been developed to access these valuable structures [2, 6]. In 2003, we disclosed that functionalized tetrahydropyridines could be synthesized through a PBu_3-catalyzed [4 + 2] reaction of allenoates and imines [7, 8]. Subsequently, Fu [9], Zhao [10], Guo [11], and Sasai [12] realized asymmetric versions of the [4 + 2] reaction using various chiral phosphines. In the last 50 years, major efforts have been exerted in the development of chiral phosphine ligands [13–15]. The chirality of a phosphine may reside on the phosphorus center, in the carbon backbone, or in the phosphine's molecular framework [16]. As part of our efforts in phosphine organocatalysis, we have developed a class of structurally unique *P*-chiral [2.2.1] bicyclic phosphines [17, 18]. Recently, we applied one such bridged bicyclic *P*-chiral phosphine, exo-(*p*-anisyl)-Hyp-Phos, in the asymmetric allene–imine [4 + 2]

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Dedicated to Professor Samuel J. Danishefsky and his great scientific contributions to total syntheses of highly complex and biologically important natural products.

Conflict of interest The authors declare that they have no conflict of interest.

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Supplementary information The online version of this article (https://doi.org/10.1038/s41429-019-0181-0) contains supplementary material, which is available to authorized users.

annulation to afford valuable chiral piperidines in good yields and with excellent enantioselectivities [19]. Herein, we report a class of new chiral phosphines derived from L-hydroxyproline (L-Hyp) and their application in the allene–imine [4 + 2] annulation.

The abundance and ready availability of chiral α-amino acids have made them desirable sources of chirality. Indeed, many bifunctional chiral aminophosphines have been derived from α-amino acids [14]. In previous studies, the presence of a free NH group, responsible for hydrogen bonding, has been the major focus when designing chiral aminophosphines for asymmetric phosphine organocatalysis (Scheme 1a) [14]. Progress in the field of enamine and iminium catalysis has revealed that steric interaction is another useful mode of asymmetric induction [20–23]. Nevertheless, steric interaction has not previously been considered a promising platform for the design of α-amino acid-derived aminophosphines. L-Hyp, an abundant non-proteinogenic amino acid having a proline skeleton and an additional OH group for further steric tuning, has been chosen as the platform for our catalyst design (Scheme 1a). In addition to introducing sterically tunable protecting groups at the pyrroline nitrogen atom and the 4-OH group, a hydrogen-bonding site could also be installed—for example, as a urea or thiourea motif—at the pyrroline nitrogen atom. We envisioned that the aminophosphines **2a–f** could be obtained from L-Hyp by installing a diphenylphosphino group through the displacement of the mesylate in **1** and subsequent functional group manipulations (Scheme 1b). The synthesis of the mesylate **1** also appeared to be straightforward. Starting from commercially available L-Hyp, various alcohol and amine protecting groups could be installed prior to substitution of the mesylate by a diphenylphosphino group.

Results and discussion

The synthesis of compound **2a** is illustrated in Scheme 2. First, the Boc-protection of L-Hyp proceeded to provide *N*-Boc-L-Hyp **3**. Benzylation of the free OH group followed by borane-mediated reduction of the carboxyl group resulted in the primary alcohol **5**. Only one column chromatographic purification through SiO_2 was necessary to prepare 16.3 g of **5** in 70% yield in the three-step process. Mesylation of **5** led to the key intermediate **1** for phosphine synthesis. The mesylate **1** was converted into the phosphine **2a** in high yield after slow addition of an excess of potassium diphenylphosphide at low temperature.

Having prepared the aminophosphine **2a**, the acid-liable *N*-Boc protecting group was readily replaced with several acyl groups to afford the chiral aminophosphines **2b–f** of varying steric bias (Scheme 3). After Boc-deprotection, an excess of triethylamine was added to neutralize TFA and promote the acylation with the acyl chloride. Using this one-pot procedure, the four aminophosphines **2b–e** were prepared in high yields. When phenyl isocyanate was used instead of an acyl chloride, the phosphine **2f**, presenting a hydrogen-bonding site, was obtained in 77% yield.

The six chiral phosphines with varied *N*-substituents were then applied to our [4 + 2] annulation [7]. We first examined the [4 + 2] annulation of the activated allenoate **8** and the imine **7** mediated by the phosphine **2a** in CH_2Cl_2 (Table 1, entry 1). An inseparable mixture of the tetrahydropyridine **9** and the tetrahydropyridine **10** was obtained in 68% yield, with

the ee of **9** being 30%. When the solvent was switched to benzene, the ee of **9** increased to 42%, but **10** was now the major product (entry 2). We then tested the other phosphines for the annulation in CH_2Cl_2 (entries 3–6). When using the catalyst **2b** for the annulation in CH_2Cl_2, the ee of **9** increased to 42% compared with that of **2a** in the same solvent (cf. entries 3 and 1). Under otherwise identical conditions, the ratio of **10** had also increased. The phosphine **2d**, featuring a bulkier acyl substituent on the nitrogen atom, produced the tetrahydropyridine **9** with a higher ee of 53% (entry 5). Interestingly, in the reaction catalyzed by the phosphine **2e** presenting an adamantylcarbonyl group, the selectivity of the product was completely reversed—now favoring the tetrahydropyridine **10**, which was isolated in 80% yield and contaminated with only a trace of **9** (entry 6). The NH group in the phosphine **2f** seemed to have little effect on the enantioselectivity, but the formation of **10** was largely inhibited (entry 7). From these preliminary results, it appeared that the enantioselectivity increased upon increasing the bulk of the N-acyl substituent, presumably through a mechanism involving steric control.

It was also interesting that more sterically demanding phosphines could facilitate the formation of **10** over **9**. The reversed regioselectivity can be explained by two possible pathways of the imine–allene [4 + 2] reaction (Scheme 4) [7, 19, 24]. At the onset of the [4 + 2] reaction, addition of the phosphine **2** to the allene **8** generates intermediate **A**, which is in resonance with structure **B**, which, in turn, is in equilibrium with intermediate **B′**. In path **I**, γ-addition of intermediate **B** to the imine **7** affords intermediate **C**, followed by the formation of **9**. In path II, β′-addition of intermediate **B′** to the imine **7** generates intermediate **C′**, followed by the formation of **10**. When a bulkier phosphine was used in the reaction, the γ-position of intermediate **B** was more encumbered, relative to its β′-position. In this case, path II, which afforded the product **10**, became the favored pathway.

The same catalysts were then employed in the allene–imine [4 + 2] annulation of the less activated α-methylallenoate **11** (Table 2). Because the reaction was slower with this allene **11**, the catalyst loading was increased to 30 mol% and 4-Å MS were added to minimize hydrolysis of the imine **7**. Although the conversion of the imine **7** and the yield of **12** were not good, we observed a similar trend in the induction of enantioselectivity as that in Table 1. Increasing the bulk of the N-acyl substituent in the phosphine **2** afforded greater enantioselectivity for the formation of the tetrahydropyridine **12**. When using the catalyst **2d**, an ee of 41% was induced (entry 4). The bulky phosphines again facilitated the formation of the β′-addition product, in this case **13** (cf. entries 4 vs. 1 and 2). These preliminary findings, obtained from nonoptimized reaction conditions, were consistent with the model of steric control.

Conclusion

Taking advantage of the ready availability of naturally occurring chiral α-amino acids, we have chosen L-Hyp, a nonproteinogenic—but abundantly available—amino acid, for the design of several chiral phosphines. With the goal of exploiting steric interactions for enantioinduction, we have developed a synthetic route toward a number of L-Hyp–derived chiral phosphines. The preliminary application of these phosphines in the allene–imine [4 + 2] annulation has proven moderately successful in terms of enantioselectivities. When

using bulky phosphines, an interesting switch of the reaction site occurred: from the γ-to the β′-carbon atom of the allenoate. The clear trend in the enantioinduction hints at the potential of developing chiral phosphines that operate with steric tuning as the sole source of enantioselectivity control in the [4 + 2] annulation.

Experimental

4-Benzyloxy-2-methanesulfonyloxymethylpyrrolidine-1-carboxylic acid tert-butyl ester(1)

Boc_2O (18.3 g, 83.9 mmol) was added slowly to a solution of L-Hyp (10.0 g, 76.3 mmol) in 1,4-dioxane (80 mL) and 1 N aqueous NaOH (80 mL) at 0 °C. The reaction mixture was stirred for 8 h at room temperature, then concentrated under reduced pressure, acidified to pH 1 using 2 N aqueous HCl, and extracted with EtOAc. The extract was washed with brine, dried (Na_2SO_4), and concentrated to provide the Boc-protected L-Hyp **3** [25] as a clear viscous oil. This crude product was used in the next step without further purification.

The Boc-protected L-Hyp **3** was dissolved in THF (100 mL) and then cannulated into a slurry of NaH (60% in mineral oil, 11.2 g, 155 mmol) in THF (200 mL) at 0 °C. Benzyl bromide (15.0 g, 87.7 mmol) was added dropwise to the reaction mixture. The flask was warmed to room temperature and then the mixture was heated under reflux for 6h. The reaction mixture was cooled to room temperature and poured over ice. The organic solvent was evaporated under reduced pressure and the aqueous solution was washed with EtOAc. The aqueous phase was acidified with 2N HCl until the pH was 2, and then it was extracted with EtOAc. The organic phase was concentrated under reduced pressure to yield **4** as a brownish yellow oil. This brownish yellow oil was dissolved in dry THF (300 mL) and cooled to 0 °C. BH_3·DMS (5.7 mL, 58 mmol) was added dropwise to the reaction mixture, which was then kept stirring at 0 °C for an additional 1 h. The flask was removed from the ice bath, and the mixture stirred overnight at room temperature. The reaction mixture was poured over ice and sequentially extracted with EtOAc, washed with saturated aqueous $NaHCO_3$, washed with brine, and dried (Na_2SO_4). The solution was concentrated under reduced pressure and purified through flash column chromatography (FCC; gradient EtOAc/hexanes, from 30 to 50%) to yield **5** [26] as a slightly yellow oil (16.3 g, 70% over three steps).

The slightly yellow oil from the previous step (16.1 g, 52.3 mmol) was dissolved in dry CH_2Cl_2 (160 mL) and cooled to 0 °C. Et_3N (7.8 mL, 56.0 mmol) was added and then MsCl (6.3 g, 54.9 mmol) was added slowly. After the reaction had reached completion (checked using TLC), the solvent was evaporated under reduced pressure. The residue was dissolved in EtOAc and washed sequentially with water, saturated aqueous $NaHCO_3$, and brine, then dried (Na_2SO_4). The product was isolated through FCC (EtOAc/hexanes, 30%) to provide **1** [26] (20.0 g, 99%) as a slightly yellow viscous oil.

(2S,4R)-tert-butyl 4-(benzyloxy)-2-((diphenylphosphino)methyl)pyrrolidine-1-carboxylate (2a)

Compound **1** (771 mg, 2 mmol) was placed in a flame-dried round-bottom flask containing a stirrer bar. Dry THF (20 mL) was added via syringe under argon. The flask was cooled to

−45 °C (MeCN/dry ice bath) and then 0.5 N Ph_2PK solution in THF (6 mL, 3 mmol) was added over 2 h via syringe pump. When the addition was complete, the mixture was stirred at the same temperature for an additional 7 h. The flask was warmed to room temperature and then H_2O (1–1.5 mL) was added until the reaction color disappeared. CH_2Cl_2 (20 mL) was added and then the organic phase was collected. The aqueous phase was extracted twice with CH_2Cl_2. The combined organic phases were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified through FCC (EtOAc/hexanes, from 1:10 to 1:5) to afford **2a** (846 mg, 89%) as a clear viscous oil. $[\alpha]_D^{26}$ −47.4 (*c* 0.35, acetone); ^1H NMR(500 MHz, $CDCl_3$) δ 7.61 (br s, 1H), 7.54 (br s, 1H), 7.46 (app t, *J* = 6.6 Hz, 2H), 7.38−7.30 (m, 11H), 4.49 (br s, 2H),4.27−4.10 (m, 2H), 3.90−3.43 (m, 2H), 3.04−2.88 (m, 1H),2.33−2.12 (m, 3H), 1.49 (s, 9H); ^{13}C NMR (125 MHz,$CDCl_3$) δ 154.4, 137.8, 132.7 (d, *J* = 19.2Hz), 132.3 (d, *J* = 19.5 Hz), 128.6, 128.3 (d, *J* = 7.1 Hz), 128.2, 127.4, 127.3, 79.4, 70.6, 54.1 (d, *J* = 18.9 Hz), 53.2, 38.6, 35.0 (d, *J* = 10.8 Hz), 33.5 (br s), 28.3; ^{31}P NMR (202 MHz,$CDCl_3$) δ −22.9; IR (film) ν_{max} 2975, 2930, 2362, 2338, 1690, 1393, 1171, 739, 697 cm^{-1}; HRMS-DART: calcd for $C_{29}H_{35}NO_3P$ ($[M+H]^+$) *m/z* 476.2349; found 476.2345.

General procedure for preparing 2b–e

The phosphine **2a** (0.20 g, 0.42 mmol) was dissolved in CH_2Cl_2 (1.5 mL) in a flame-dried round-bottom flask containing a stirrer bar. TFA (0.5 mL) was added dropwise to the solution at 0 °C and then the mixture was stirred at room temperature for 1 h. CH_2Cl_2 (3 mL) was added and then the mixture was cooled to 0 °C. NEt_3 (1.2 mL) was added dropwise, and then an acyl chloride (1.2 eq) was added slowly. The mixture was stirred at room temperature overnight and then washed with H_2O. The organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified through FCC.

((2S,4R)-4-(Benzyloxy)-2-((diphenylphosphino) methyl)pyrrolidin-1-yl)(3,5-bis(trifluoromethyl) phenyl)methanone (2b)

Obtained as a white solid (70%) $[\alpha]_D^{24}$ −58.77 (*c* 0.65, acetone); ^1H NMR (500 MHz, $CDCl_3$) δ 7.87 (s, 1H), 7.60 (s, 2H), 7.57−7.53 (m, 4H), 7.38−7.16 (m, 11H), 4.78−4.70 (m, 1H), 4.46 (d, *J* = 11.9Hz, 1 H), 4.30 (d, *J* = 11.9 Hz, 1H), 4.14 (br s, 1H), 3.53 (dd, *J* = 11.3, 3.3 Hz, 1H), 3.32 (d, *J* = 11.3 Hz, 1H), 2.84−2.76 (m, 2H), 2.48 (dd, *J* = 13.2, 7.9 Hz, 1H), 2.34 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.1, 138.4, 137.6, 137.5, 137.49, 132.8 (d, *J* = 21.3 Hz), 132.4 (d, *J* = 18.6 Hz), 131.5 (q, *J* = 33.7 Hz), 129.1, 128.63, 128.56 (d, *J* = 7.5 Hz), 128.54 (d, *J* = 6.8 Hz), 128.4, 127.7, 127.6 (br s), 127.4, 123.6 (sp, *J* = 3.6 Hz), 122.8 (q, *J* = 273.7 Hz), 77.1, 70.8, 55.6, 55.0 (d, *J* = 16.9 Hz), 36.9 (d, *J* = 10.6 Hz), 32.3 (d, *J* = 12.9 Hz); ^{31}P NMR (202 MHz, $CDCl_3$) δ −26.4; IR (film) ν_{max} 3057, 2926, 2867, 1642, 1363, 1280, 1137, 906, 740, 697 cm^{-1}; HRMS-DART: calcd for $C_{33}H_{29}F_6NO_2P$ ($[M+H]^+$) *m/z* 616.1830; found 616.1830.

1-((2S,4R)-4-(benzyloxy)-2-((diphenylphosphino) methyl)pyrrolidin-1-yl)-2,2-dimethylpropan-1-one (2c)

Obtained as a white solid (78%). $[\alpha]_D^{26}$ −4.0 (*c* 0.75, acetone); ^1H NMR (500 MHz, $CDCl_3$) δ 7.60 (t, *J* = 7.5 Hz, 2H), 7.44−7.41 (m, 2H), 7.37 (app t, *J* = 7.0 Hz, 2H), 7.34−7.26 (m, 9H),

4.52−4.43 (m, 3H) (apparent overlapping peaks), 4.17 (app s, 1H), 3.90 (d, J = 11.4 Hz, 1H), 3.56 (dd, J = 11.4, 4.4 Hz, 1 H), 2.91 (d, J = 13.9 Hz, 1H),2.24−2.19 (m, 2 H), 2.16−2.10 (m, 1H), 1.17 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.7, 137.8, 132.8 (d, J = 18.8 Hz), 132.7 (d, J = 19.4 Hz), 128.6, 128.5 (d, J = 7.0 Hz), 128.35 (d, J = 7.0 Hz), 128.32, 127.6, 127.3, 77.4, 70.6, 55.7 (d, J = 17.5 Hz), 53.1, 38.8, 35.5 (d, J = 9.3 Hz), 32.8 (d, J = 13.7 Hz), 27.5; ^{31}P NMR (202 MHz, $CDCl_3$) δ −23.5; IR (film) ν_{max} 2969, 2930, 1620, 1407, 1093, 1074, 738, 697 cm^{-1}; HRMS-DART: calcd for $C_{29}H_{35}NO_2P$ ([M+H]$^+$) m/z 460.2400; found 460.2397.

1-((2S,4R)-4-(benzyloxy)-2-((diphenylphosphino) methyl)pyrrolidin-1-yl)-2,2-diphenylethanone (2d)

Obtained as a pale-yellow solid (73%). $[\alpha]_D^{27}$ −50.14 (c 0.17, acetone); ^{1}H NMR (500 MHz, $CDCl_3$) δ (in aliphatic region, major rotamer) 5.00 (s, 1H), 4.52−4.50 (m, 1H) (overlapping peaks), 4.25 (d, J = 12.2 Hz, 1H), 4.17 (d, J = 11.9 Hz, 1H), 4.13−4.10 (m, 1H), 3.66 (d, J = 10.2 Hz, 1H), 3.49 (dd, J = 11.0, 4.7 Hz, 1H), 3.26 (dt, J = 13.5, 4.5 Hz, 1H), 2.24−2.14 (m, 2H), 2.05−2.00 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (major rotamer) 170.3, 139.4, 138.9, 137.7, 133.0 (d, J = 19.3 Hz), 132.7 (d, J = 19.3 Hz), 129.1, 128.9, 128.8, 128.6, 128.59, 128.56, 128.43, 128.41, 128.35, 128.32, 127.6, 127.5, 126.9 (d, J = 8.0 Hz), 76.5 (d, J = 1.8 Hz), 70.7, 57.0, 54.9 (d, J = 19.2 Hz), 51.9, 36.9 (d, J = 9.8 Hz), 32.7 (d, J = 12.5 Hz); ^{31}P NMR (202 MHz, $CDCl_3$) δ −22.5 (major rotamer), −23.2 (minor rotamer); IR (film) ν_{max} 3060, 3028, 1645, 1411, 1192, 738, 697 cm^{-1}; HRMS-DART: calcd for $C_{38}H_{37}NO_2P$ ([M+H]$^+$) m/z 570.2556; found 570.2554.

(1S,3R)-adamantan-1-yl((2S,4R)-4-(benzyloxy)-2-((diphenylphosphino)methyl)pyrrolidin-1-yl) methanone (2e)

Obtained as a colorless sticky compound (98%). $[\alpha]_D^{27}$ + 2.7 (c 1.20, acetone); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (t, J = 7.3 Hz, 2H), 7.44−7.41 (m, 2H), 7.39−7.28 (m, 11H), 4.54−4.50 (m, 2H) (overlapping peaks), 4.44 (d, J = 12 Hz, 1H), 4.19 (br s, 1H), 3.99 (d, J = 11.2 Hz, 1H), 3.62 (dd, J = 11.3, 4.4 Hz, 1H), 2.88 (d, J = 13.3 Hz, 1H), 2.19 (dd, J = 13.4, 9.5 Hz, 2H), 2.12 (br s, 1H), 1.99 (s, 3H), 1.87 (s, 6H), 1.71−1.65 (app q, J = 12.4 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.1, 137.9, 132.8 (d, J = 18.8 Hz), 132.7 (d, J = 19.6 Hz), 128.53, 128.48, 128.34, 128.30, 127.6, 127.5, 77.6, 70.8, 55.9 (d, J = 16.3 Hz), 53.1, 41.6, 38.0, 36.5, 35.2 (d, J = 8.2 Hz), 32.9 (d, J = 12.0 Hz), 28.3; ^{31}P NMR (202 MHz, $CDCl_3$) δ −21.8; IR (film) ν_{max} 3053, 2905, 2850, 2235, 1610, 1391, 1073, 909, 734, 697 cm^{-1}; HRMS-DART: calcd for $C_{35}H_{41}F_6NO_2P$ ([M + H]$^+$) m/z 538.2869; found 538.2872.

(2S,4R)-4-(benzyloxy)-2-((diphenylphosphanyl) methyl)-N-phenylpyrrolidine-1-carboxamide (2f)

The phosphine **2a** (76.0 mg, 0.158 mmol) was dissolved in CH_2Cl_2 (0.5 mL) in a flame-dried round-bottom flask containing with a stirred bar. TFA (0.17 mL) was added dropwise to the solution at 0 °C and then the mixture was stirred at room temperature for 1 h. CH_2Cl_2 (1 mL) was added and then the mixture was cooled to 0 °C. NEt_3 (0.4 mL) was added dropwise and then the reaction was quenched through the addition of H_2O (2 mL). The aqueous phase was exacted with CH_2Cl_2. The combined organic phases were washed with

brine, dried (Na_2SO_4), and concentrated. The residue was dissolved in CH_2Cl_2 (1 mL). Phenyl isocyanate (21.0 mg, 0.176 mmol) was added and then the mixture was stirred overnight. The solution was concentrated and the residue purified through FCC (hexanes/EtOAc, 5:1) to give **2f** as a white semisolid. $[\alpha]_D^{28}$ −39.8 (*c* 1.00, acetone); ^{1}H NMR (500 MHz, d_6-acetone) δ 8.12 (s, 1H), 7.66−6.87 (m, 20H), 4.47 (s, 2H), 4.37−4.21 (m, 2H), 3.68 (d, *J* = 4.1 Hz, 2H), 3.05 (dt, *J* = 13.5, 3.4 Hz, 1H), 2.28−2.20 (m, 1H), 2.18−2.06 (m, 1H). ^{13}C NMR (100 MHz, d_6-acetone) δ 154.4, 140.5, 139.6 (d, *J* = 12.9 Hz), 138.7, 138.2 (d, *J* = 13.0 Hz), 132.8 (d, *J* = 19.6 Hz), 132.6 (d, *J* = 20.0 Hz), 128.7, 128.6 (d, *J* = 2.5 Hz), 128.5, 128.4 (d, *J* = 7.0 Hz), 128.3, 128.25 (d, *J* = 8.1 Hz), 127.4, 121.9 (d, *J* = 16.7 Hz), 119.5, 118.5, 77.0 (d, *J* = 1.7 Hz), 70.4, 54.70 (d, *J* = 20.4 Hz), 51.9, 37.3 (d, *J* = 8.4 Hz), 33.7 (d, *J* = 13.9 Hz). ^{31}P NMR (121 MHz, d_6-acetone) δ −23.12. IR (film) ν_{max} 3324, 3054, 2926, 2426, 1700, 1633, 1443, 1385, 1246, 750, 695 cm^{-1}; HRMS-DART: calcd for $C_{31}H_{32}N_2O_2P$ ($[M+H]^+$) *m/z* 495.2196;found 485.2219.

General experimental procedure for the allene–imine [4 + 2] annulation (with the allene 8)

The allenoate (0.12 mmol) was added in one portion to a solution of *N*-tosylimine (0.1 mmol) and the aminophosphine catalyst (0.02 mmol) in the solvent (2 mL). The flask was capped with a Teflon cap under a N_2 flow. The mixture was stirred at room temperature for 2 days. The resulting solution was concentrated and the residue purified through FCC on silica gel (eluent: 20–30% EtOAc in hexane) to give the product.

Diethyl (2S,3S)-2-phenyl-1-tosyl-1,2,3,6-tetrahydropyridine-3,4-dicarboxylate (10)

Obtained as a white solid (80%). 57% ee—determined using an SFC instrument, a Daicel ChiralPak IC-3 column, and 20% MeCN; t_R (minor) = 3.74 min; t_R (major) = 4.81 min; $[\alpha]_D^{25}$ −38.0 (c 1.10, acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 8.3 Hz, 2H), 7.28−7.16 (m, 7H), 6.94 (dd, *J* = 3.7, 2.7 Hz, 1H), 5.93 (s, 1H), 4.24−4.12 (m, 4H), 4.11−3.97 (m, 2H), 3.69 (dt, *J* = 19.9, 2.4 Hz, 1H), 2.38 (s, 3H), 1.26 (t, *J* = 7.4 Hz, 3H), 1.22 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 165.2, 143.5, 137.8, 136.9, 135.2, 129.4, 128.6, 127.8, 127.4, 126.8, 126.4, 61.6, 61.1, 56.1, 44.9, 41.7, 21.4, 14.08, 13.97; IR (film) ν_{max} 2981, 1717, 1344, 1260, 1160, 1096 cm^{-1}. HRMS-DART: calcd for $C_{24}H_{28}NSO_6$ ($[M + H]^+$) *m/z* 458.1632; found 458.1628.

General experimental procedure for the allene–imine [4+2] annulation (with the allene 11)

The allenoate (0.2 mmol) was added in one portion to a mixture of *N*-tosylimine (0.1 mmol), the aminophosphine catalyst (0.03 mmol), and 4-Å MS (10 mg) in CH_2Cl_2 (2 mL). The flask was capped with a Teflon cap under a N_2 flow. The mixture was stirred at room temperature for 3 days. The resulting solution was concentrated and mesitylene was added as an internal standard to determine the yield and conversion. This mixture was dissolved in THF and then 1 N HCl was added to hydrolyze the imine. The aqueous phase was exacted with CH_2Cl_2. The combine extracts were washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified through PTLC (hexane/EtOAc, 5:1) to give the product for ee determination.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

Financial support for this study was provided by the NIH (R01GM071779). We thank Dr. Saeed Khan (UCLA) for the crystallographic analyses. C.X. thanks Prof. Neil K. Garg and Sarah Anthony (UCLA) for sharing their SFC instrument.

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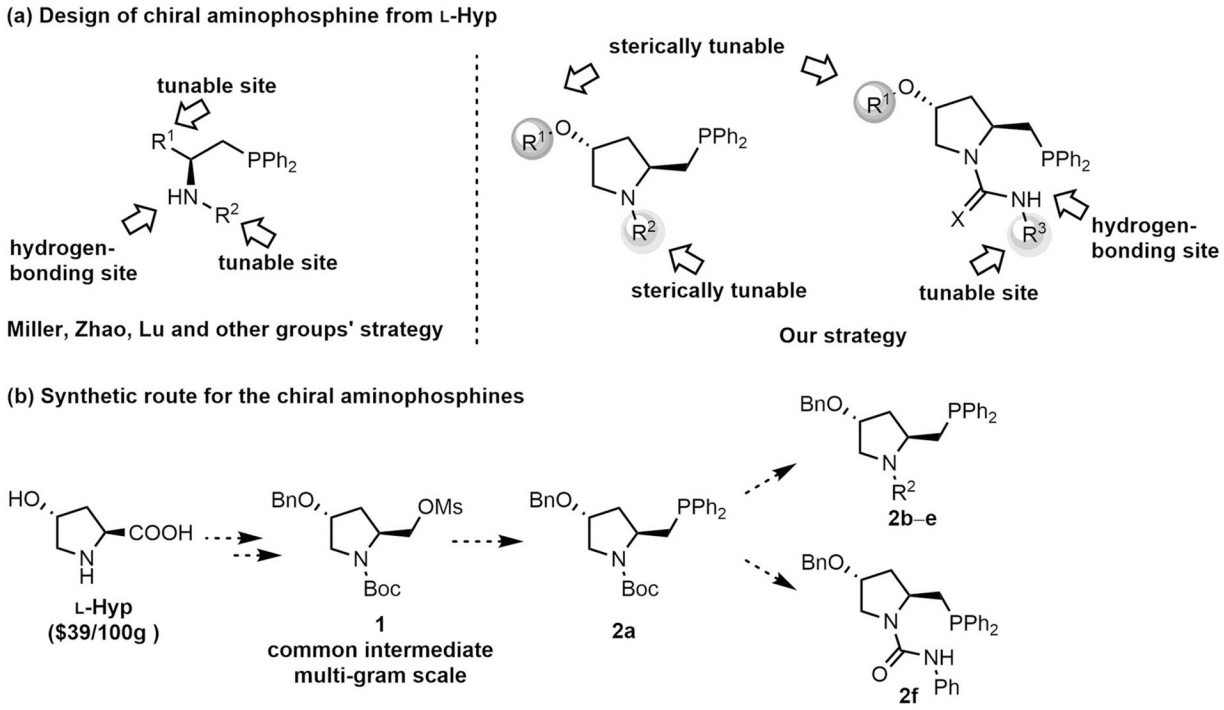
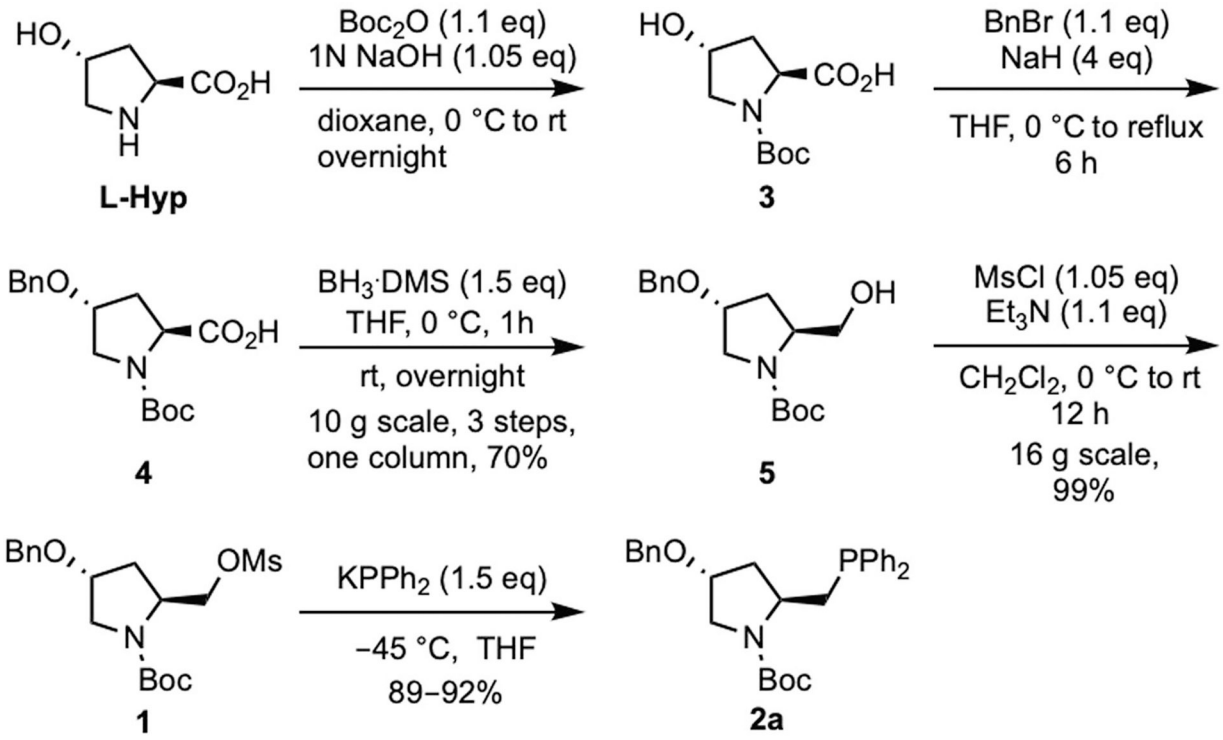
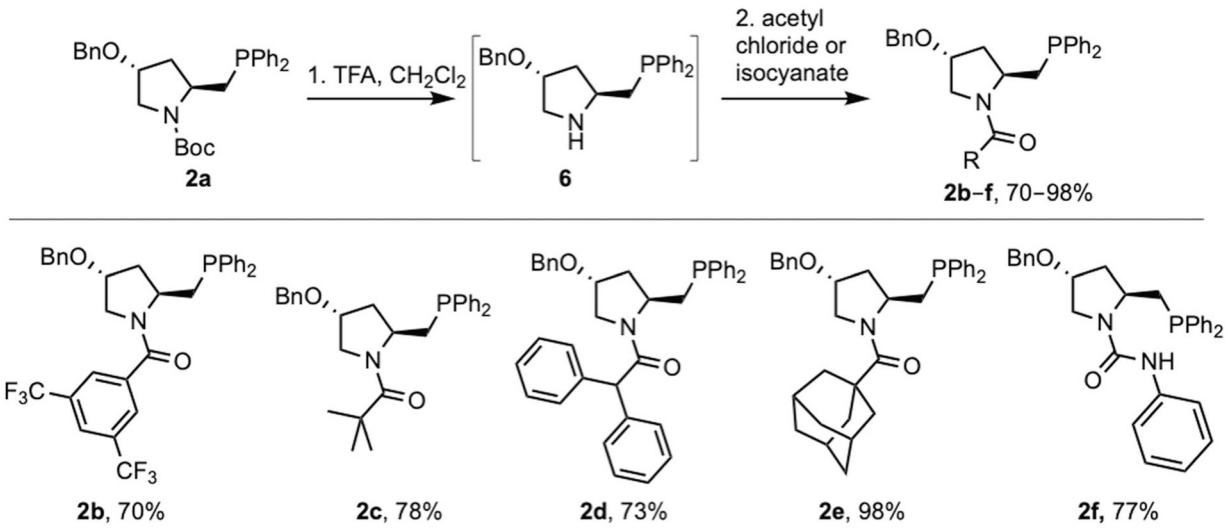


Scheme 1.

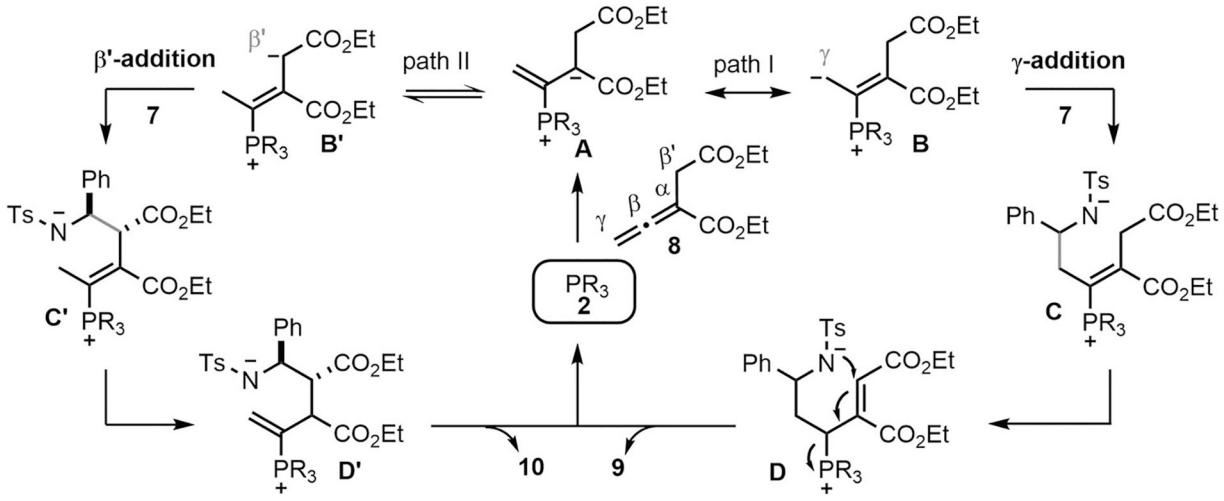
Synthetic design of chiral aminophosphines **2** from L-Hyp



Scheme 2.
Preparation of the phosphine **2a**



Scheme 3.
Preparation of the phosphines **2b–f**

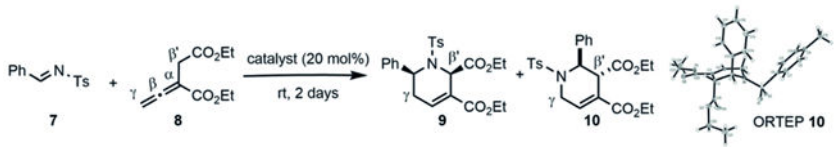


Scheme 4.

Possible reaction pathways for the allene–imine [4 + 2] annulation

Table 1

Phosphines 2–catalyzed [4 + 2] annulation of the allenoate 8[a]



Entry	Catalyst	Solvent	Conv (%)[b]	Dr[c] (*cis-9/trans*-9)	Ratio[c] (9/10)	Yield (%)[d] (9 + 10)	ee (%)[e] (9)
1	**2a**	CH_2C1_2	>99	5.9:1	3.0:1	68	30
2	**2a**	benzene	97	9.1:1	1:3.1	35	42
3	**2b**	CH_2C1_2	>99	5.5:1	1:2.3	44	42
4	**2c**	CH_2C1_2	>99	6.2:1	1:4.4	66	45
5	**2d**	CH_2C1_2	>99	7.7:1	1:12.5	70	53
6	**2e**	CH_2C1_2	>99	–	1:63.0	80	57[f]
7	**2f**	CH_2C1_2	49	6.7:1	15:1	39	27

[a]Reaction conditions: **7** (1 equiv, 0.1 mmol), **8** (1.2 equiv), the phosphine **2** (20 mol%), and the solvent (2 mL)

[b]Conversion determined using mesitylene as an internal standard

[c]Determined from the ^{1}H NMR spectrum of the crude mixture

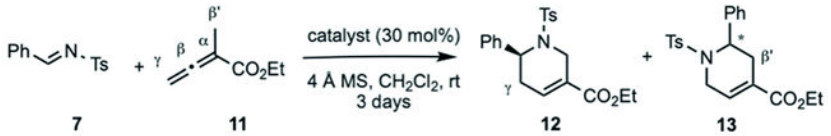
[d]Isolated yield

[e]The ee value of **9** was determined through chiral HPLC analysis; its absolute configuration was determined through comparison with the data of the known compound in ref.[9]

[f]The ee of compound **10**; the absolute configuration was not determined

Table 2

Phosphines 2–catalyzed [4 + 2] annulation of the α-methylallenoate 11[a]



7 11 12 13

Entry	Catalyst	Conv (%)[b]	Ratio[c,d] (12:13)	Yield (%)[e] (12)	ee (%)[f] (12)
1	**2a**	56	10:1	23	20
2	**2b**	74	>50:l	9	29
3	**2c**	77	7.1:1	10	28
4	**2d**	70	1.9:1	11	41
5	**2e**	80	14.1:1	26	23
6	**2f**	47	>50:l	6	14

[a]Reaction conditions: **7** (1 equiv, 0.1 mmol), **11** (2 equiv), the phosphine **2** (30 mol%), 4-Å MS (10 mg), and CH_2Cl_2 (2 mL)

[b]Conversion was determined using mesitylene as an internal standard

[c]Determined from the ^{1}H NMR spectrum of the crude mixture

[d]**12** and **13** were obtained as a mixture; no pure **13** was isolated, but its structure was inferred according to our mechanistic proposal in Scheme 4

[e]NMR yield (internal standard: mesitylene)

[f]Determined through chiral HPLC analysis; the absolution configuration was determined through comparison with the data of the known compound in ref. [19].