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DIRECT ASYMMETRIC α -ALLYLATION OF KETONES WITH ALLYLIC ALCOHOLS VIA Pd/ENAMINE COOPERATIVE FUNCTION

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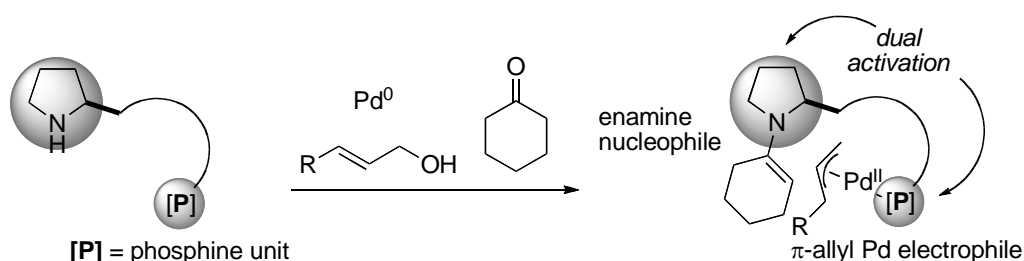
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This paper is dedicated to Professor Eiichi Negishi on the occasion of his 77th birthday.

Abstract – Direct asymmetric α -allylation of ketones with allylic alcohols is described. The combination of palladium with a new phosphine ligand bearing a chiral proline moiety promoted the reaction to afford the corresponding α -allylated ketones in moderate yield and enantioselectivity.

The palladium-catalyzed asymmetric Tsuji-Trost allylation is a highly attractive and powerful tool in organic synthesis.¹ Typically, preactivation of allylic alcohols as allylic acetates and carbonates is required for the efficient formation of π -allyl electrophiles, and a stoichiometric amount of byproducts are co-produced. In this regard, the direct use of allylic alcohols as substrates would be highly attractive because the extra step required for the preparation of activated allylic alcohols is avoided, and the byproduct is water.^{2,3} Recent advances in transition-metal catalyzed asymmetric Tsuji-Trost allylations allow for the direct use of allylic alcohols as allylic electrophiles.⁴ The variety of compatible nucleophiles, however, is limited to heteroatom nucleophiles,⁵ metal enolates,⁶ and indoles,^{7,8} some of which require the combined use of a stoichiometric amount of Brønsted acid or Lewis acid to promote the reaction, and simple carbonyl compounds have not been implemented in this class of reaction. Therefore, the development of asymmetric allylations with allylic alcohols using simple carbonyl compounds is highly desirable. Very recently, the direct catalytic asymmetric α -allylation of aldehydes with allylic alcohols was reported by List and coworkers.⁹ For an analogous process using less reactive

simple ketones as nucleophiles,¹⁰⁻¹² there is only one example in a racemic system in which a combination of amine organocatalysis and Pd catalysis is used, and the process has not been rendered asymmetric.²¹ In that system, the enamine nucleophile generated in situ from the amine and ketone undergoes nucleophilic attack on an in situ-generated π -allyl Pd complex.¹³ Inspired by this work, we hypothesized that by covalently tethering a Pd complex and a chiral proline unit, dual activation of allylic alcohol and ketone would act in close proximity to efficiently promote the reaction in an asymmetric environment (Scheme 1). Herein we report the first example of a direct asymmetric α -allylation of simple ketones with simple allylic alcohols using a tethered complex that harnesses the cooperative function of π -allyl Pd activation and enamine activation.



Scheme 1. Strategy for Direct Asymmetric α -Allylation of Ketones with Allylic Alcohols

To realize the dual activation of allylic alcohol and ketone as delineated in Scheme 1, we designed a chiral ligand **1a** bearing a proline and 2-(diphenylphosphino)benzylamine, which are covalently tethered by an amide linkage.¹⁴ Upon complexation with Pd⁰, the π -allyl Pd electrophile would be formed from allylic alcohols close to the enamine nucleophile generated in situ from the pyrrolidino group in **1a** and the ketone substrate (Figure 1). As an analogous ligand, **1b** and **1c** bearing fluoro-substituted proline units were also synthesized, and **1a–c** were evaluated in an α -allylation of cyclohexanone (**3a**) with 3-phenyl-2-propen-1-ol (**2a**) (Table 1).

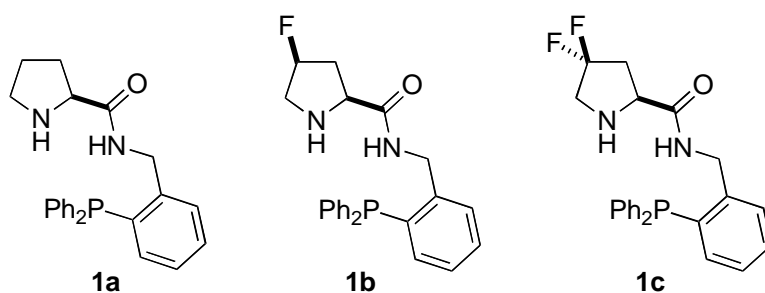
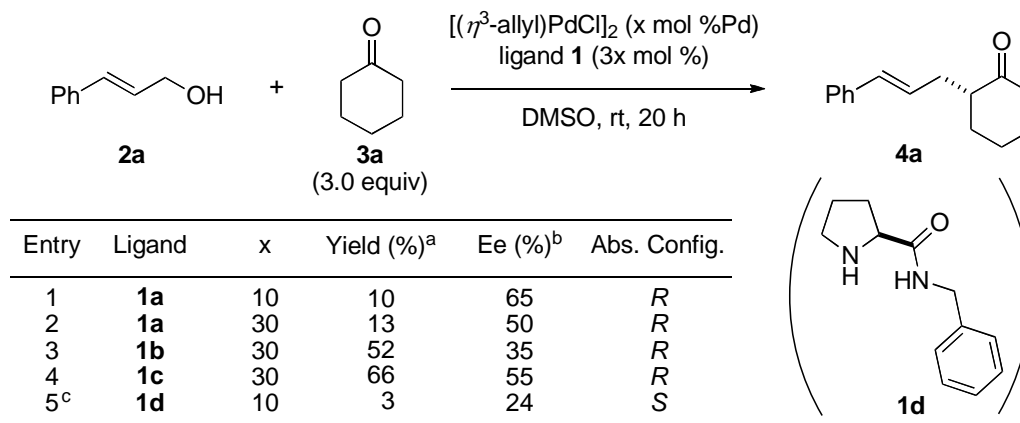


Figure 1. Phosphine ligands **1a–c** bearing chiral proline ring through amide bond.

The reactions were conducted in the presence of $[(\eta^3\text{-allyl})\text{PdCl}]_2$ and ligand **1** in a 1:3 ratio in DMSO at room temperature.¹⁵ As expected, the reaction with ligand **1a** proceeded to afford the desired product **4a** with moderate enantioselectivity, although the yield was only 10% (Table 1, Entry 1). Changing the ratio of Pd/**1a** to 1:1 or 1:2 led to a significantly lower conversion. The yield increased slightly with a higher loading of Pd and ligand **1a** (Entry 2). Ligand **1b**, bearing a 4-fluoro-substituted proline unit, exhibited a higher reaction efficiency and afforded **4a** in better yield, albeit with lower enantioselectivity (Entry 3). The best result was obtained with the reaction using ligand **1c** bearing a 4,4-difluoro-substituted proline unit, which afforded the highest yield and modest enantioselectivity (Entry 4). To examine the cooperative function of π -allyl Pd activation and enamine activation in close proximity, the following control experiment was performed. The reaction with **1d**, a ligand analogous to **1a** lacking a phosphine moiety, and PPh_3 hardly proceeded, and resulted in lower enantioselectivity (Entry 5), suggesting that linkage of the phosphine unit and the chiral proline unit allows for dual activation of the allylic alcohol and ketone in proximity. Decreasing the amount of Pd salt and ligand **1** led to a remarkable loss of conversion.

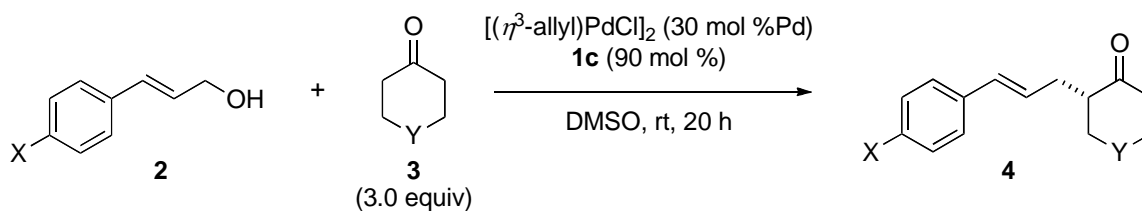
Table 1. Evaluation of Ligands **1** for Direct Asymmetric α -Allylation of **3a** with **2a**.



Entry	Ligand	x	Yield (%) ^a	Ee (%) ^b	Abs. Config.
1	1a	10	10	65	<i>R</i>
2	1a	30	13	50	<i>R</i>
3	1b	30	52	35	<i>R</i>
4	1c	30	66	55	<i>R</i>
5 ^c	1d	10	3	24	<i>S</i>

^aIsolated yield. ^bDetermined by HPLC analysis using a DAICEL CHIRALCEL OD-H. ^cwith 20 mol % PPh_3 .

The scope of the present asymmetric α -allylation using the $[(\eta^3\text{-allyl})\text{PdCl}]_2$ /**1c** system is summarized in Table 2. In addition to **2a**, the present system was applicable to substituted cinnamyl alcohols **2b–e**. Although similar enantioselectivity was observed irrespective of the electronic nature of substituents, an electron-donating substituent led to decreased reaction efficiency. The reaction of oxygen-containing heterocyclic ketone **3b** produced the corresponding product **4f**, albeit with low yield and enantioselectivity (Table 2, Entry 6).

Table 2. Scope of Direct Asymmetric α -Allylation of Ketones **3** with Allylic Alcohols **2** with Ligand **1c**.

Entry	X	2	Y	3	4	Yield (%) ^a	Ee (%) ^b
1	H	2a	C	3a	4a	66	55
2	CF ₃	2b	C	3a	4b	55	54
3	F	2c	C	3a	4c	39	56
4	OMe	2d	C	3a	4d	39	60
5	NMe ₂	2e	C	3a	4e	14	52
6	H	2a	O	3b	4f	25	36

^aIsolated yield. ^bDetermined by HPLC analysis. See experimental section for details.

The proposed mechanism for the present reaction is shown in Scheme 2. Initially, enamine intermediate **A** is produced by reaction of the pyrrolidino group in ligand **1** with a ketone. Complexation of **A** and $[(\eta^3\text{-allyl})\text{PdCl}]_2$ through a phosphine moiety forms π -allyl Pd^{II} complex **B'**, and a subsequent intramolecular nucleophilic attack of enamine to π -allyl Pd^{II} generates iminium cation **C'**, in which Pd^{II} is reduced to Pd⁰. Hydrolysis of **C'** leads to intermediate **D**, and the release of α -allyl ketone **4**¹⁶ and HCl. There is another possible pathway from **C'** to **E**, in which a ligand exchange of **C'** with **A** occurs and forms **E**, releasing iminium cation **G**. Pd⁰ complex **D** is responsible for the following catalytic cycle. Coordination of allylic alcohol to **E** forms Pd⁰ olefin complex **F** and oxidative addition occurs with the aid of HCl to generate π -allyl Pd^{II} complex **B**. Subsequent intramolecular nucleophilic attack of enamine on π -allyl Pd^{II} and hydrolysis of iminium cation **C** to release product **4** proceed in a manner similar to that of the initial cycle. We assume that the substituent on the proline unit slightly changes the conformation of the ring, which affects the reactivity and enantioselectivity in this intramolecular attack of enamine, and the most favorable conformation is attained with ligand **1c**. Although the Pd/**1** = 1:1 complex is shown in Scheme 2 for clarity, spectroscopic analysis of the Pd/**1** mixture was unsuccessful and therefore the structure of Pd/**1** is not clear. Based on the fact that 3 equivalents of ligand **1** to Pd are required for efficient conversion, an active Pd complex can be the Pd/**1** complex in a ratio of 1:2 or 1:3. We assume that another reason for the requirement of excessive amounts of ligand **1** to Pd (3 equiv to Pd, 0.9 equiv to allylic alcohol) is the reluctant hydrolysis of iminium cations (**C**, **C'**, **G**, and **G'**). If the hydrolysis does not proceed easily, ligand **1** is arrested as an inactive form.

In summary, we demonstrated the allylation of simple ketones at the α -position with simple allylic alcohols under a new system consisting of Pd and phosphine ligand bearing a chiral proline unit. Linkage of a phosphine ligand and a chiral proline unit were essential for enantioinduction. There is still

reported in the scale relative to H_3PO_4 (δ 0.0 ppm in D_2O) as an external reference. NMR data are reported as follows: chemical shifts, multiplicity (s: singlet, d: doublet, dd: doublet of doublets, t: triplet, q: quartet, m; multiplet, br: broad signal), coupling constant (Hz), and integration. Optical rotation was measured using a 2 mL cell with a 1.0 dm path length on a JASCO polarimeter P-1030. High-resolution mass spectra (ESI TOF (+)) were measured on ThermoFisher Scientific LTQ Orbitrap XL. HPLC analysis was conducted on a JASCO HPLC system equipped with Daicel chiral-stationary-phase columns (0.46 cm ϕ x 25 cm). The absolute configuration of **4a** was determined by comparing the sign of optical rotation with the literature data reported by Koga *et al.*¹⁷ The absolute configuration of other products was assigned by analogy.

Materials. Unless otherwise noted, materials were purchased from commercial suppliers and were used without purification. THF and CH_2Cl_2 were purified by passing through a solvent purification system (Glass Contour). Dry DMSO and CHCl_3 were purchased from Kanto Chemical Co. Ltd. and used as received. $[(\eta^3\text{-allyl})\text{PdCl}]_2$ was purchased from Aldrich and used as received. Chiral proline derivatives used for synthesis of ligands **1** were purchased from Aldrich and WATANABE CHEMICAL Ind. Ltd. Allylic alcohol **2a** was purchased from Kanto Chemical Co. Ltd. **2b** was prepared by following the literature procedure.¹⁸ Column chromatography was performed with Silica gel Merck 60 (230–400 mesh ASTM).

Preparation of Allylic Alcohols 2c–e. These compounds were synthesized by the following procedure.

(E)-3-(4-Methoxyphenyl)prop-2-en-1-ol (2d). To a 300 mL pear-shaped flask equipped with a magnetic stirring bar, 4-methoxycinnamaldehyde (5.68 g, 35.0 mmol) and MeOH (140 mL) were added at room temperature. The resulting solution was cooled to 0 °C and then NaBH_4 (1.59 g, 42.0 mmol) was added to the solution. After stirring for 30 min at 0 °C, sat. NaHCO_3 aq. (200 mL) and CH_2Cl_2 (200 mL) were sequentially added to the reaction mixture. After stirring for 5 min at room temperature, the organic layer and aqueous layer were separated. Aqueous layer was extracted with CH_2Cl_2 (3 x 100 mL) and combined organic layer was dried over Na_2SO_4 . After filtration, the filtrate was concentrated. The resulting residue was purified by silica gel column chromatography system (combiflash[®]: *n*-hexane/EtOAc as eluent) to afford **2d** (5.55 g, 97%) as a white solid; ^1H NMR (CDCl_3) δ 7.32 (d, J = 8.7 Hz, 2H), 6.85 (d, J = 8.7 Hz, 2H), 6.55 (d, J = 16.0 Hz, 1H), 6.23 (dt, J = 6.0, 16.0 Hz, 1H), 4.29 (d, J = 6.0 Hz, 2H), 3.80 (s, 3H), 1.75 (brs, 1H); ^{13}C NMR (CDCl_3) δ 159.2, 130.8, 129.4, 127.6, 126.2, 113.9, 63.8, 55.2.

(E)-3-(4-Fluorophenyl)prop-2-en-1-ol (2c): white solid; ^1H NMR (CDCl_3) δ 7.33–7.30 (m, 2H), 7.01–6.97 (m, 2H), 6.55 (d, J = 16.0 Hz, 1H), 6.26 (dt, J = 5.7, 16.0 Hz, 1H), 4.29 (d, J = 5.7 Hz, 2H), 2.32 (brs, 1H); ^{13}C NMR (CDCl_3) δ 162.3 (d, $J_{\text{C-F}}$ = 245.0 Hz), 132.8 (d, $J_{\text{C-F}}$ = 3.8 Hz), 129.8, 128.2 (d, $J_{\text{C-F}}$ = 1.9 Hz), 127.9 (d, $J_{\text{C-F}}$ = 7.6 Hz), 115.4 (d, $J_{\text{C-F}}$ = 21.9 Hz), 63.4; ^{19}F NMR (CDCl_3) δ -114.1.

(E)-3-(4-(N,N-Dimethylamino)phenyl)prop-2-en-1-ol (2e): yellow solid; ^1H NMR (CDCl_3) δ 7.26 (d, $J = 9.0$ Hz, 2H), 6.66 (d, $J = 9.0$ Hz, 2H), 6.55 (d, $J = 15.8$ Hz, 1H), 6.15 (dt, $J = 6.0, 15.8$ Hz, 1H), 4.23 (d, $J = 6.0$ Hz, 2H), 3.27 (brs, 1H), 2.92 (s, 6H); ^{13}C NMR (CDCl_3) δ 149.7, 131.0, 127.2, 125.1, 124.0, 112.3, 63.5, 40.2.

NMR data of **2c**,¹⁹ **2d**,²⁰ and **2e**²⁰ are identical to literature data.

Preparation of Phosphine Ligands 1a–c. These compounds were synthesized over 4 steps starting from commercially available 2-(diphenylphosphino)benzoic acid.

2-(Diphenylphosphino)benzamide (S1). To a 100 mL pear-shaped flask equipped with a magnetic stirring bar, 2-(diphenylphosphino)benzoic acid (2.90 g, 10.0 mmol), and CHCl_3 (40 mL) were added at room temperature. To the resulting suspension, $(\text{NH}_4)\text{HCO}_3$ (3.64 g, 46.0 mmol) and *N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinone (3.46 g, 14.0 mmol) were added sequentially. After stirring for 28 h at room temperature, the reaction mixture was diluted with CH_2Cl_2 (350 mL). The mixture was washed with 1N HCl aq. (3 x 100 mL), 1N NaOH aq. (2 x 100 mL), and brine (100 mL), and then dried over Na_2SO_4 . After filtration, the filtrate was concentrated. The resulting residue was purified by silica gel column chromatography (eluent: *n*-hexane/EtOAc = 1/1 to 1/2) to afford **S1** (1.91 g, 62%) as a white solid; ^1H NMR (CDCl_3) δ 7.55–7.52 (m, 1H), 7.27–7.16 (m, 12H), 6.91–6.88 (m, 1H), 6.07 (brs, 2H); ^{13}C NMR (CDCl_3) δ 170.8, 139.8 (d, $J_{\text{C-P}} = 24.8$ Hz), 137.1 (d, $J_{\text{C-P}} = 10.5$ Hz), 136.6 (d, $J_{\text{C-P}} = 21.9$ Hz), 134.2, 133.9, 133.7, 130.4, 128.6 (d, $J_{\text{C-P}} = 9.5$ Hz), 128.5 (d, $J_{\text{C-P}} = 7.6$ Hz), 127.9 (d, $J_{\text{C-P}} = 3.8$ Hz); ^{31}P NMR (CDCl_3) δ -8.6.

NMR data are identical to literature data.²¹

(2-(Diphenylphosphino)phenyl)methylamine (S2). To a 300 mL pear-shaped flask equipped with a magnetic stirring bar, **S1** (1.59 g, 5.21 mmol), and THF (100 mL) were added at room temperature. The resulting solution was cooled to 0 °C and then LiAlH_4 (593 mg, 15.6 mmol) was added to the solution. After stirring for 12 h at room temperature, the reaction mixture was cooled to 0 °C, and then H_2O (15 mL), 8% NaOH aq. (30 mL), H_2O (30 mL) were added sequentially. The resulting mixture was extracted with CH_2Cl_2 (2 x 100 mL) and dried over Na_2SO_4 . After filtration, the filtrate was concentrated. The resulting residue was purified by silica gel column chromatography (eluent: *n*-hexane/EtOAc = 1/2 to EtOAc only) to afford **S2** (1.15 g, 76%) as a white solid; ^1H NMR (CDCl_3) δ 7.46–7.43 (m, 1H), 7.37–7.25 (m, 11H), 7.16 (ddd, $J = 1.2, 7.6, 8.7$ Hz, 1H), 6.91–6.88 (m, 1H), 4.03 (d, $J = 1.6$ Hz, 2H), 1.49 (brs, 2H); ^{13}C NMR (CDCl_3) δ 147.3 (d, $J_{\text{C-P}} = 22.9$ Hz), 136.3 (d, $J_{\text{C-P}} = 9.5$ Hz), 135.0 (d, $J_{\text{C-P}} = 13.4$ Hz), 133.8 (d, $J_{\text{C-P}} = 19.1$ Hz), 133.4, 129.2, 128.7, 128.5 (d, $J_{\text{C-P}} = 19.1$ Hz), 127.9 (d, $J_{\text{C-P}} = 4.8$ Hz), 127.0, 45.1 (d, $J_{\text{C-P}} = 21.9$ Hz); ^{31}P NMR (CDCl_3) δ -15.3.

NMR data are identical to literature data.²²

tert-Butyl (S)-2-((2-(diphenylphosphino)phenyl)methylcarbamoyl)pyrrolidine-1-carboxylate (S3).

To a 50 mL pear-shaped flask equipped with a magnetic stirring bar, *N*-(*tert*-butoxycarbonyl)-L-proline (513 mg, 2.38 mmol), *N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinone (607 mg, 2.45 mmol), and CH₂Cl₂ (6.0 mL) were added at room temperature. The resulting solution was cooled to 0 °C, and then **S2** (715 mg, 2.45 mmol) in CH₂Cl₂ (6.0 mL) was added. After stirring for 12 h at room temperature, the reaction mixture was washed with 1N HCl aq. (3 x 50 mL), sat. NaHCO₃ aq. (2 x 50 mL), H₂O (50 mL), and brine (2 x 50 mL), and then dried over Na₂SO₄. After filtration, the filtrate was concentrated. The resulting residue was purified by silica gel column chromatography (eluent: *n*-hexane/EtOAc = 2/1) to afford **S3** (929 mg, 80%) as a white solid.

(S)-N-(2-(Diphenylphosphino)phenyl)methylpyrrolidine-2-carboxamide (1a). To a 100 mL pear-shaped flask equipped with a magnetic stirring bar, **S3** (1.03 g, 2.12 mmol) and CH₂Cl₂ (2.5 mL) were added at room temperature. The resulting solution was cooled to 0 °C, and then 4N HCl/CPME (2.12 mL, 8.48 mmol) was added. After stirring for 14 h at room temperature, sat. NaHCO₃ aq. (60 mL) was added to the reaction mixture. After stirring for additional 20 min, the resulting mixture was extracted with CH₂Cl₂ (3 x 60 mL). The combined organic layer was dried over Na₂SO₄. After filtration, the filtrate was concentrated. The resulting residue was purified by silica gel column chromatography (eluent: CHCl₃ only to CHCl₃/MeOH = 20/1) to afford **1a** (750 mg, 92%) as a colorless viscous oil; IR (neat) 3326, 3054, 2970, 2871, 1661, 1513, 1478, 1434, 1092, 747, 697, 665 cm⁻¹; ¹H NMR (CDCl₃) δ 7.80 (brs, 1H), 7.42 (dd, *J* = 4.4, 6.8 Hz, 1H), 7.35–7.32 (m, 7H), 7.29–7.23 (m, 4H), 7.19 (dd, *J* = 7.6, 7.6 Hz, 1H), 6.91 (dd, *J* = 4.4, 7.6 Hz, 1H), 4.73 (dd, *J* = 6.2, 14.7 Hz, 1H), 4.60 (dd, *J* = 5.7, 14.7 Hz, 1H), 3.54 (dd, *J* = 5.2, 8.9 Hz, 1H), 2.85 (ddd, *J* = 6.6, 6.9, 10.1 Hz, 1H), 2.71 (ddd, *J* = 6.2, 6.2, 10.1 Hz, 1H), 2.10–2.01 (m, 1H), 1.87–1.79 (m, 2H), 1.64–1.57 (m, 2H); ¹³C NMR (CDCl₃) δ 174.7, 142.8 (d, *J*_{C-P} = 24.8 Hz), 136.2 (d, *J*_{C-P} = 9.5 Hz), 135.5 (d, *J*_{C-P} = 14.3 Hz), 133.8 (d, *J*_{C-P} = 7.6 Hz), 133.6 (d, *J*_{C-P} = 6.7 Hz), 129.2, 129.0 (d, *J*_{C-P} = 5.7 Hz), 128.7 (d, *J*_{C-P} = 4.8 Hz), 128.5 (d, *J*_{C-P} = 1.9 Hz), 128.4 (d, *J*_{C-P} = 2.9 Hz), 127.5, 60.3, 46.9, 41.6 (d, *J*_{C-P} = 22.9 Hz), 30.5, 25.9; ³¹P NMR (CDCl₃) δ -15.4; HRMS (ESI) calcd. for C₂₄H₂₆N₂OP *m/z* 389.1777 [M+H]⁺, found 389.1780; [α]_D²¹ -18.0 (*c* 2.0, CHCl₃).

1b and **1c** were synthesized by the above procedure using commercially available *N*-(*tert*-butoxycarbonyl)-*cis*-4-fluoro-L-proline and *N*-(*tert*-butoxycarbonyl)-4,4-difluoro-L-proline,²³ respectively, instead of *N*-(*tert*-butoxycarbonyl)-L-proline.

N-(2-(Diphenylphosphino)phenyl)methyl-(4S)-fluoropyrrolidine-(2S)-carboxamide (1b): colorless viscous oil; IR (neat) 3336, 3005, 1660, 1520, 1478, 1434, 1271, 1217, 1112, 956, 747, 698, 666 cm⁻¹; ¹H NMR (CDCl₃) δ 7.75 (brs, 1H), 7.44–7.41 (m, 1H), 7.33–7.20 (m, 11H), 7.15 (dd, *J* = 7.6, 7.6 Hz, 1H), 6.88 (dd, *J* = 4.6, 7.6 Hz, 1H), 5.07 (ddd, *J* = 3.7, 3.9, 53.2 Hz, 1H), 4.72 (dd, *J* = 6.2, 14.9 Hz, 1H), 4.58 (dd, *J* = 6.0, 14.9 Hz, 1H), 3.59 (dd, *J* = 3.0, 10.3 Hz, 1H), 3.15 (dd, *J* = 12.1, 21.5 Hz, 1H),

3.01 (ddd, $J = 3.7, 12.1, 35.7$ Hz, 1H), 2.41–2.32 (m, 1H), 2.26–2.09 (m, 1H), 1.85 (brs, 1H); ^{13}C NMR (CDCl_3) δ 173.6, 142.6 (d, $J_{\text{C-P}} = 24.8$ Hz), 136.2 (d, $J_{\text{C-P}} = 9.5$ Hz), 136.1 (d, $J_{\text{C-P}} = 9.5$ Hz), 135.2 (d, $J_{\text{C-P}} = 14.3$ Hz), 133.9, 133.7 (d, $J_{\text{C-P}} = 9.5$ Hz), 133.5 (d, $J_{\text{C-P}} = 10.5$ Hz), 129.1, 128.6 (d, $J_{\text{C-P}} = 2.9$ Hz), 128.5 (d, $J_{\text{C-P}} = 1.9$ Hz), 128.4 (d, $J_{\text{C-P}} = 2.9$ Hz), 127.4, 93.4 (d, $J_{\text{C-F}} = 175.4$ Hz), 58.9, 53.0 (d, $J_{\text{C-F}} = 21.9$ Hz), 41.6 (d, $J_{\text{C-P}} = 23.8$ Hz), 37.3 (d, $J_{\text{C-F}} = 21.9$ Hz); ^{19}F NMR (CDCl_3) δ -173.4–173.9 (m); ^{31}P NMR (CDCl_3) δ -15.3; HRMS (ESI) calcd. for $\text{C}_{24}\text{H}_{25}\text{FN}_2\text{OP}$ m/z 407.1683 $[\text{M}+\text{H}]^+$, found 407.1685; $[\alpha]_{\text{D}}^{21}$ -13.5 (c 1.0, CHCl_3).

(S)-N-(2-(Diphenylphosphino)phenyl)methyl-4,4-difluoropyrrolidine-2-carboxamide (1c):

colorless viscous oil; IR (neat) 3330, 3055, 3004, 1667, 1519, 1478, 1434, 1358, 1249, 1157, 1093, 746, 698 cm^{-1} ; ^1H NMR (CDCl_3) δ 7.59 (brs, 1H), 7.45 (dd, $J = 4.6, 7.3$ Hz, 1H), 7.38–7.36 (m, 7H), 7.30–7.22 (m, 5H), 6.95 (ddd, $J = 0.9, 4.6, 7.6$ Hz, 1H), 4.77 (dd, $J = 6.4, 14.4$ Hz, 1H), 4.64 (dd, $J = 5.5, 14.4$ Hz, 1H), 3.66 (dd, $J = 7.1, 9.2$ Hz, 1H), 3.14–3.06 (m, 1H) 2.92–2.82 (m, 1H), 2.59–2.48 (m, 1H), 2.37–2.24 (m, 1H), 1.90 (brs, 1H); ^{13}C NMR (CDCl_3) δ 171.7, 142.3 (d, $J_{\text{C-P}} = 25.7$ Hz), 136.3 (d, $J_{\text{C-P}} = 1.9$ Hz), 136.2 (d, $J_{\text{C-P}} = 1.9$ Hz), 135.7 (d, $J_{\text{C-P}} = 14.3$ Hz), 134.0, 133.9 (d, $J_{\text{C-P}} = 7.6$ Hz), 133.7 (d, $J_{\text{C-P}} = 6.7$ Hz), 130.1 (dd, $J_{\text{C-F}} = 246.0, 251.7$ Hz), 129.6 (d, $J_{\text{C-P}} = 4.8$ Hz), 129.4, 128.8 (d, $J_{\text{C-P}} = 3.8$ Hz), 128.6 (d, $J_{\text{C-P}} = 2.9$ Hz), 128.5 (d, $J_{\text{C-P}} = 3.8$ Hz) 127.9, 58.5–58.4 (m), 52.9 (dd, $J_{\text{C-F}} = 28.6, 28.6$ Hz), 42.2 (d, $J_{\text{C-P}} = 21.0$ Hz), 38.1 (dd, $J_{\text{C-F}} = 24.8, 25.8$ Hz); ^{19}F NMR (CDCl_3) δ -99.1–99.9 (m), -104.9–105.6 (m); ^{31}P NMR (CDCl_3) δ -15.6; HRMS (ESI) calcd. for $\text{C}_{24}\text{H}_{24}\text{F}_2\text{N}_2\text{OP}$ m/z 425.1589 $[\text{M}+\text{H}]^+$, found 425.1590; $[\alpha]_{\text{D}}^{21}$ -8.3 (c 1.0, CHCl_3).

(S)-N-Benzylpyrrolidine-2-carboxamide (1d). This compound was synthesized by the same procedure as for **S3** and **1a** starting from commercially available *N*-(*tert*-butoxycarbonyl)-L-proline and benzylamine; colorless viscous oil; IR (neat) 3316, 3062, 3030, 2966, 2871, 1655, 1522, 1454, 1360, 1249, 1104, 733, 699 cm^{-1} ; ^1H NMR (CDCl_3) δ 7.93 (brs, 1H), 7.25–7.21 (m, 2H), 7.18–7.15 (m, 3H), 4.33 (d, $J = 6.0$ Hz, 2H), 3.68 (dd, $J = 5.3, 9.2$ Hz, 1H), 2.89 (ddd, $J = 6.6, 6.9, 10.3$ Hz, 1H), 2.77 (ddd, $J = 6.2, 6.4, 10.3$ Hz, 1H), 2.12 (brs, 1H), 2.10–2.01 (m, 1H), 1.89–1.81 (m, 1H), 1.66–1.55 (m, 2H); ^{13}C NMR (CDCl_3) δ 175.0, 138.5, 128.4, 127.3, 127.0, 60.4, 47.0, 42.6, 30.6, 26.0; HRMS (ESI) calcd. for $\text{C}_{12}\text{H}_{17}\text{N}_2\text{O}$ m/z 205.1335 $[\text{M}+\text{H}]^+$, found 205.1337; $[\alpha]_{\text{D}}^{21}$ -45.7 (c 1.0, CHCl_3).

NMR data are identical to literature data.²⁴

Typical Procedure for the Direct Asymmetric α -Allylation of Ketones **3 with Allylic Alcohols **2**.**

(R)-2-((E)-3-Phenylprop-2-en-1-yl)cyclohexanone (4a). To a flame dried test tube equipped with a stirring bar and 3-way glass stopcock, $[(\eta^3\text{-allyl})\text{PdCl}]_2$ (8.2 mg, 0.023 mmol), 3-phenyl-prop-2-en-1-ol (**2a**, 20 mg, 0.15 mmol) in DMSO (0.60 mL), cyclohexanone (44 mg, 0.45 mmol), and DMSO solution of ligand **1c** (1.35 mL, 0.135 mmol, 0.10 M) were added sequentially at room temperature. After stirring

for 20 h at room temperature, EtOAc (5 mL) and H₂O (5 mL) were added to the reaction mixture. After separation of organic layer and aqueous layer, aqueous layer was extracted with EtOAc (3 x 5 mL). The combined organic layer was filtered through a short pad of silica gel with EtOAc as eluent, and the filtrate was concentrated. The resulting residue was purified by silica gel column chromatography (eluent: *n*-hexane/EtOAc = 40/1 to 20/1) to afford **4a** (21.1 mg, 66%) as a colorless oil; ¹H NMR (CDCl₃) δ 7.37–7.27 (m, 4H), 7.19 (t, *J* = 7.1 Hz, 1H), 6.40 (d, *J* = 15.8 Hz, 1H), 6.20 (ddd, *J* = 6.6, 8.0, 15.8 Hz, 1H), 2.71–2.64 (m, 1H), 2.47–2.39 (m, 2H), 2.36–2.29 (m, 1H), 2.22–2.12 (m, 2H), 2.09–2.04 (m, 1H), 1.90–1.85 (m, 1H), 1.74–1.61 (m, 2H), 1.46–1.36 (m, 1H); ¹³C NMR (CDCl₃) δ 212.5, 137.5, 131.6, 128.4, 128.3, 127.0, 126.0, 50.7, 42.1, 33.5, 33.0, 27.9, 25.0; [α]_D²¹ 16.3 (*c* 1.1, CHCl₃, 55% ee); HPLC [DAICEL CHIRALCEL OD-H, detection at 254 nm, 9:1 *n*-hexane/ⁱPrOH, flow rate = 1.0 mL/min, *t*_R = 5.7 min (minor), 6.5 min (major)].

NMR data are identical to literature data.²ⁱ

(R)-2-((E)-3-(4-Trifluoromethylphenyl)prop-2-en-1-yl)cyclohexanone (4b): colorless oil; IR (neat) 2936, 2863, 1711, 1614, 1449, 1414, 1326, 1164, 1122, 1067, 1016, 971, 858 cm⁻¹; ¹H NMR (CDCl₃) δ 7.52 (d, *J* = 8.2 Hz, 2H), 7.40 (d, *J* = 8.2 Hz, 2H), 6.41 (d, *J* = 16.0 Hz, 1H), 6.35–6.27 (m, 1H), 2.71–2.65 (m, 1H), 2.48–2.40 (m, 2H), 2.36–2.28 (m, 1H), 2.21–2.13 (m, 2H), 2.10–2.02 (m, 1H), 1.90–1.83 (m, 1H), 1.75–1.61 (m, 2H), 1.46–1.36 (m, 1H); ¹³C NMR (CDCl₃) δ 212.2, 140.9, 131.3, 130.3, 128.7 (q, *J*_{C-F} = 32.4 Hz), 126.1, 125.3 (q, *J*_{C-F} = 3.8 Hz), 124.2 (q, *J*_{C-F} = 269.8 Hz), 50.5, 42.1, 33.7, 33.0, 27.9, 25.0; ¹⁹F NMR (CDCl₃) δ -62.2; HRMS (ESI) calcd. for C₁₆H₁₈F₃O *m/z* 283.1304 [M+H]⁺, found 283.1304; [α]_D²¹ 11.8 (*c* 1.1, CHCl₃, 54% ee); HPLC [DAICEL CHIRALCEL OJ-3, detection at 254 nm, 99:1 *n*-hexane/ⁱPrOH, flow rate = 1.0 mL/min, *t*_R = 14.6 min (minor), 15.6 min (major)].

(R)-2-((E)-3-(4-Fluorophenyl)prop-2-en-1-yl)cyclohexanone (4c): colorless oil; IR (neat) 3036, 2935, 2861, 1709, 1601, 1508, 1448, 1430, 1227, 1158, 1129, 970, 852, 823 cm⁻¹; ¹H NMR (CDCl₃) δ 7.60–7.56 (m, 2H), 7.26 (dd, *J* = 8.7, 8.9 Hz, 2H), 6.64 (d, *J* = 15.8 Hz, 1H), 6.40 (ddd, *J* = 6.6, 7.8, 15.8 Hz, 1H), 2.98–2.91 (m, 1H), 2.75–2.67 (m, 2H), 2.65–2.58 (m, 1H), 2.49–2.34 (m, 3H), 2.18–2.15 (m, 1H), 2.03–1.91 (m, 2H), 1.75–1.65 (m, 1H); ¹³C NMR (CDCl₃) δ 212.5, 161.9 (d, *J*_{C-F} = 244.1 Hz), 133.7 (d, *J*_{C-F} = 3.8 Hz), 130.4, 128.1 (d, *J*_{C-F} = 1.9 Hz), 127.4 (d, *J*_{C-F} = 7.6 Hz), 115.3 (d, *J*_{C-F} = 21.0 Hz), 50.7, 42.1, 33.6, 33.0, 27.9, 25.0; ¹⁹F NMR (CDCl₃) δ -115.3; HRMS (ESI) calcd. for C₁₅H₁₈FO *m/z* 233.1336 [M+H]⁺, found 233.1337; [α]_D²¹ 15.5 (*c* 0.7, CHCl₃, 56% ee); HPLC [DAICEL CHIRALPAK AY-3, detection at 254 nm, 9:1 *n*-hexane/ⁱPrOH, flow rate = 1.0 mL/min, *t*_R = 8.0 min (minor), 9.5 min (major)].

(R)-2-((E)-3-(4-Methoxyphenyl)prop-2-en-1-yl)cyclohexanone (4d): colorless oil; IR (neat) 3583, 2934, 2860, 1708, 1607, 1510, 1464, 1446, 1290, 1248, 1175, 1128, 1035, 969 cm⁻¹; ¹H NMR (CDCl₃) δ 7.26 (d, *J* = 8.7 Hz, 2H), 6.83 (d, *J* = 8.7 Hz, 2H), 6.33 (d, *J* = 15.8 Hz, 1H), 6.05 (ddd, *J* = 6.6, 8.0, 15.8

Hz, 1H), 3.79 (s, 3H), 2.68–2.61 (m, 1H), 2.44–2.28 (m, 3H), 2.20–2.03 (m, 3H), 1.89–1.85 (m, 1H), 1.74–1.60 (m, 2H), 1.46–1.35 (m, 1H); ^{13}C NMR (CDCl_3) δ 212.7, 158.7, 130.9, 130.3, 127.0, 126.1, 113.9, 55.3, 50.8, 42.1, 33.5, 33.0, 27.9, 25.0; HRMS (ESI) calcd. for $\text{C}_{16}\text{H}_{20}\text{NaO}_2$ m/z 267.1356 $[\text{M}+\text{Na}]^+$, found 267.1356; $[\alpha]_{\text{D}}^{21}$ 18.5 (c 0.7, CHCl_3 , 60% ee); HPLC [DAICEL CHIRALCEL OD-H, detection at 254 nm, 9:1 *n*-hexane/ i PrOH, flow rate = 1.0 mL/min, t_{R} = 6.6 min (minor), 7.1 min (major)].

(R)-2-((E)-3-(4-(N,N-Dimethylamino)phenyl)prop-2-en-1-yl)cyclohexanone (4e): yellow oil; IR (neat) 2932, 2859, 2801, 1708, 1610, 1521, 1445, 1352, 1223, 1188, 1165, 1127, 966, 814 cm^{-1} ; ^1H NMR (CDCl_3) δ 7.23 (d, J = 8.9 Hz, 2H), 6.67 (d, J = 8.9 Hz, 2H), 6.30 (d, J = 15.6 Hz, 1H), 5.98 (ddd, J = 6.6, 8.0, 15.6 Hz, 1H), 2.94 (s, 6H), 2.68–2.61 (m, 1H), 2.44–2.28 (m, 3H), 2.21–2.00 (m, 3H), 1.88–1.85 (m, 1H), 1.74–1.59 (m, 2H), 1.46–1.35 (m, 1H); ^{13}C NMR (CDCl_3) δ 212.8, 149.7, 131.3, 126.8, 126.2, 123.9, 112.5, 51.0, 42.1, 40.6, 33.4, 33.0, 27.9, 25.0; HRMS (ESI) calcd. for $\text{C}_{17}\text{H}_{24}\text{NO}$ m/z 258.1852 $[\text{M}+\text{H}]^+$, found 258.1855; $[\alpha]_{\text{D}}^{21}$ 24.0 (c 0.1, CHCl_3 , 52% ee); HPLC [DAICEL CHIRALPAK AY-H, detection at 254 nm, 9:1 *n*-hexane/ i PrOH, flow rate = 1.0 mL/min, t_{R} = 19.1 min (minor), 21.7 min (major)].

(R)-3-((E)-3-Phenylprop-2-en-1-yl)-4H-pyran-4-one (4f): colorless oil; ^1H NMR (CDCl_3) δ 7.33–7.27 (m, 4H), 7.22–7.18 (m, 1H), 6.41 (d, J = 15.6 Hz, 1H), 6.15 (ddd, J = 6.2, 8.0, 15.6 Hz, 1H), 4.22–4.16 (m, 2H), 3.76 (ddd, J = 3.4, 10.8, 14.4 Hz, 1H), 3.47 (dd, J = 9.2, 11.4 Hz, 1H), 2.72–2.58 (m, 3H), 2.44 (dt, J = 3.4, 14.4 Hz, 1H), 2.24–2.16 (m, 1H); ^{13}C NMR (CDCl_3) δ 207.6, 137.1, 132.2, 128.5, 127.2, 126.6, 126.0, 72.2, 68.6, 51.2, 42.4, 29.3; $[\alpha]_{\text{D}}^{21}$ 15.0 (c 0.4, CHCl_3 , 36% ee); HPLC [DAICEL CHIRALCEL OD-H, detection at 254 nm, 9:1 *n*-hexane/ i PrOH, flow rate = 1.0 mL/min, t_{R} = 11.0 min (minor), 13.2 min (major)].

NMR data are identical to literature data.²ⁱ

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