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A New Chiral P,N-Ligand Derived from 1-Phenylphospholane-2-carboxylic Acid (Phenyl-P-proline) for Palladium-Catalyzed Asymmetric Allylic Substitution Reactions

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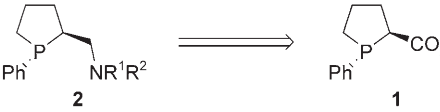
Abstract: New types of P,N-ligands, *cis*- and *trans*-**3**, containing a tetrahydroisoquinoline skeleton as an N-donor were synthesized from (1*R*,2*S*)-1-phenylphospholane-2-carboxylic acid (phenyl-P-proline, **1**). The *cis* isomer, *cis*-**3**, was found to act as an excellent ligand in palladium-catalyzed asymmetric allylic substitution reactions. The reactions of 1,3-diphenyl-2-propenyl acetate (**5**) with several nucleophiles in the presence of $[Pd(\pi\text{-allyl})Cl]_2$, *cis*-**3** (Pd:ligand = 1:2), and a base afforded the desired products in high yields with high enantioselectivity. It was suggested that these ligands did not serve as P,N-bidentate ligands but as P-monodentate ligands in these reactions.

Keywords: allylic substitution; asymmetric catalysis; palladium; P,N-ligands

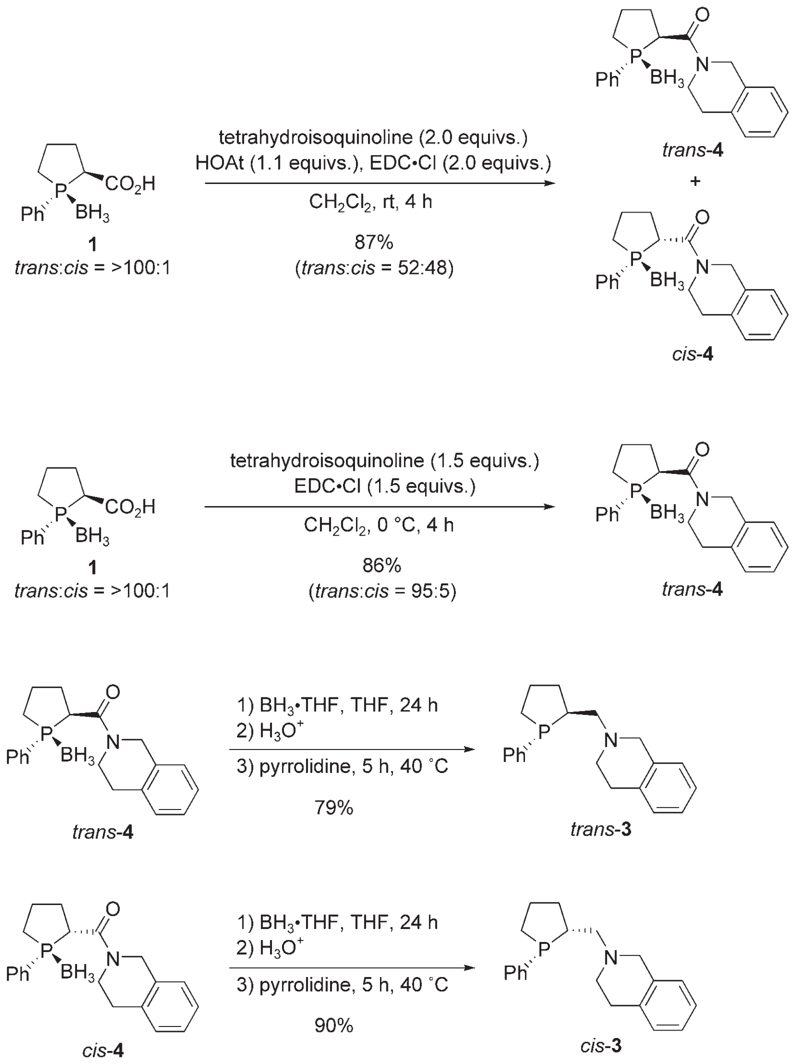
The design and synthesis of chiral phosphine ligands have played a significant role in the development of transition metal-catalyzed asymmetric reactions.[1] Among them, P-stereogenic tertiary phosphines provide one of the most important and promising ligands.[2] On the other hand, chiral bidentate ligands with two different donor atoms (so-called 'hybrid ligands') also give effective asymmetric environments, and the catalytic ability of metal complexes with these ligands has been well documented.[3] One advantage of this type of chiral ligand lies in the difference in *trans* influence between two donor atoms.[4] Furthermore, coordination ability of the donor atoms may affect reactivity and stereoselectivity in asymmetric catalysis.[5] Recently, we have designed a new type of P-stereogenic phosphine, (1*R*,2*S*)-1-phenylphospholane-2-carboxylic acid (phenyl-P-proline, **1**), and established an efficient synthetic route to it.[6] The P-stereogenic phosphine constructed an asymmetric environment near the palladium center, and consequently, exhibited good enantioselectivity in a palladium-catalyzed asymmetric allylic substitution reaction. To obtain higher enantioselectivity, a new class of P,N hybrid ligand **2** has been designed (Scheme 1). Herein, we report the synthesis of **2** and its use in palladium-catalyzed allylic substitution reactions.



Scheme 1. Design of a new type of P,N-ligand **2**.

New types of hybrid P,N-ligands **3** containing a tetrahydroisoquinoline skeleton as an N-donor were synthesized from **1** *via* intermediate amides **4** as shown in Scheme 2. The synthesis of the intermediate **4** was achieved by amidation of **1** with 1,2,3,4-tetrahydroisoquinoline in the presence of 1-hydroxy-7-azabenzotriazole (HOAt),[7] and a mixture of isomers, *trans*-**4** and *cis*-**4**, was obtained in high yield with a ratio of 52:48, respectively. These isomers could be easily separated by column chromatography on silica gel. When the reaction was conducted in the absence of HOAt at 0 °C, *trans*-**4** was obtained selectively in good yield (*trans*-**4**:*cis*-**4** = 95:5). Borane reduction of the amide group of **4** followed by deboronation[8] of the phosphorus by treatment with pyrrolidine afforded *trans*-**3** and *cis*-**3** in good yields, respectively.

The P,N hybrid ligands thus prepared were first evaluated in the palladium-catalyzed asymmetric allylic substitution of allyl acetate. $[Pd(\pi\text{-allyl})Cl]_2$ (2 mol % Pd) and BSA (150 mol %)–NaOAc (5 mol %) were used as a palladium source and a base, respectively. It was surprising to find that no desired product was obtained when 2 mol % of *trans*-**3** (Pd:ligand = 1:1) was used (Table 1, entry 4). The desired product was obtained in low yield with 45% ee when 2.5 mol % of *trans*-**3**



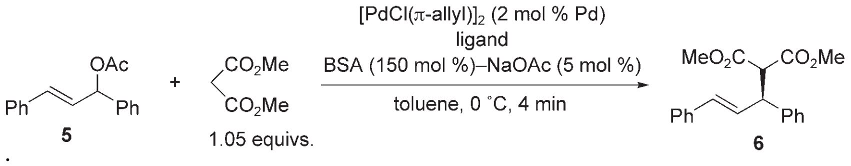
Scheme 2. Preparation of P,N-ligands **3**.

(Pd : ligand = 1 : 1.25) was used (Table 1, entry 5). The same tendency was observed, albeit with higher ee, when *cis*-**3** was used as a ligand (entry 14). To clarify these interesting observations the reaction was carefully investigated by changing the molar ratios of Pd to the ligand and the reaction time. It was revealed that no desired product was obtained when the molar ratio of the ligand to Pd was less than 1. On the other hand, when the molar ratio was more than 1, the desired product was obtained (entries 5–9, 14–18). Interestingly, the enantioselectivities obtained in these cases were independent of the molar ratios of the ligand to Pd and the reaction time. These results strongly indicate that *trans*-**3** and *cis*-**3** did not serve as P,N-bidentate ligands but as P-monodentate ligands.

The following experiments were performed to probe the composition of the catalyst mixtures at various ligand-to-metal ratios. When Pd was mixed with *cis*-**3** in toluene-d_8 at $-60\,^{\circ}C$ in a ratio of 1 : 1, a ^{31}P NMR spectrum with two major peaks at 27.0 ppm and 27.8 ppm was obtained. These peaks may correspond to those of the complexes of Pd:*cis*-**3** = 1 : 1, in which *cis*-**3** coordinates to the palladium in P,N-bidentate and P-monodentate fashions. Furthermore, when another 0.5 equivalent of the ligand was added to the mixture, a new peak at 28.2 ppm appeared. This is the only peak observed in the ^{31}P NMR spectrum of a 1 : 2 mixture of Pd and *cis*-**3** in toluene-d_8 at $-60\,^{\circ}C$. In the case of *trans*-**3**, the same tendency was observed. These results indicate that the real catalyst species is the complex of Pd:*trans*-**3** or *cis*-**3** = 1 : 2, in which *trans*-**3** or *cis*-**3** does not serve as a P,N-bidentate ligand but as a P-monodentate ligand.[5a]

Next, to optimize the reaction conditions, the effect of solvents, BSA activators, temperature, and palladium sources were examined. While no significant effect of solvents was observed (Table 2, entries 1–5), the highest ee was obtained when toluene was used as the solvent (entry 5). As for BSA activators LiOAc, NaOAc, KOAc, and CsF gave high yields and enantioselectivities

Table 1. Allylic substitution reactions using catalyst mixtures of various ligand-to-metal ratios.



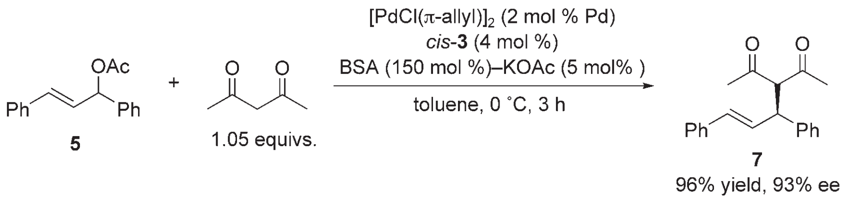
Entry	Ligand	Pd : ligand	Yield [%]	ee [%]
1	*trans*-**3**	1 : 0.5	0 (0)[a]	– (–)[a]
2	*trans*-**3**	1 : 0.75	0 (0)[a]	– (–)[a]
3	*trans*-**3**	1 : 0.9	0 (0)[a]	– (–)[a]
4	*trans*-**3**	1 : 1	0 (0)[a]	– (–)[a]
5	*trans*-**3**	1 : 1.25	1	45
6	*trans*-**3**	1 : 1.5	4 (93)[a]	45 (45)[a]
7	*trans*-**3**	1 : 2	16 (96)[a]	45 (45)[a]
8	*trans*-**3**	1 : 2.5	48 (95)[a]	45 (45)[a]
9	*trans*-**3**	1 : 3	59	46
10	*cis*-**3**	1 : 0.5	0 (0)[b]	– (–)[b]
11	*cis*-**3**	1 : 0.75	0 (0)[b]	– (–)[b]
12	*cis*-**3**	1 : 0.9	0 (0)[b]	– (–)[b]
13	*cis*-**3**	1 : 1	0 (0)[b]	– (–)[b]
14	*cis*-**3**	1 : 1.25	3 (50)[b]	93 (94)[b]
15	*cis*-**3**	1 : 1.5	12 (93)[b]	94 (94)[b]
16	*cis*-**3**	1 : 2	42 (97)[b]	94 (94)[b]
17	*cis*-**3**	1 : 2.5	42 (99)[b]	94 (94)[b]
18	*cis*-**3**	1 : 3	32	94

[a] The reaction time was 4 h.
[b] The reaction time was 6 h.

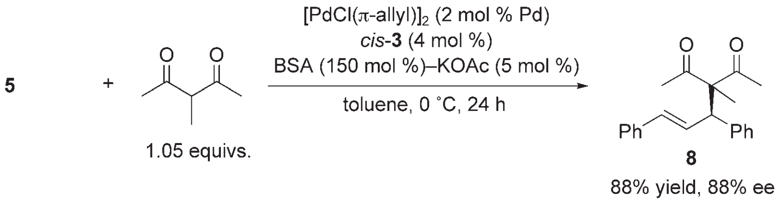
(entries 5–10). In particular, the reaction was accelerated when KOAc was used as a BSA activator (entries 7 and 8).[9] While the enantioselectivity was slightly improved at lower temperature (entry 8), the yield was significantly decreased when $Pd_2(dba)_3 \cdot CHCl_3$ was used as a palladium source instead of [Pd(π-allyl)Cl]$_2$ (entry 11).

Finally, other nucleophiles were tested [Eqs. (1)–(3)]. 1,3-Diketones and benzylamine reacted with **5** under the standard reaction conditions to afford the desired products in high yields with high enantiomeric excesses.

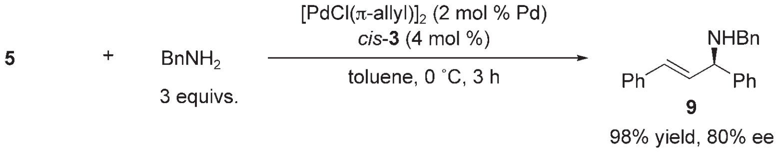
In conclusion, new types of P,N-ligands, *cis*-**3** and *trans*-**3**, derived from phenyl-P-proline were synthesized, and li-



(1)

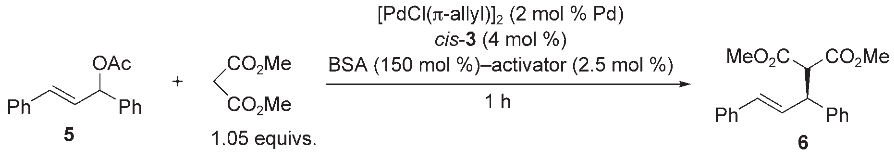


(2)



(3)

Table 2. Optimization of the reaction conditions.



Entry	Solvent	Temp. [°C]	Activator	Yield [%]	ee [%]
1	CH_2Cl_2	0	NaOAc	93	87
2	CH_3CN	0	NaOAc	98	89
3	DMF	0	NaOAc	98	89
4	THF	0	NaOAc	86	90
5	toluene	0	NaOAc	80	94
6	toluene	0	LiOAc	80	90
7	toluene	0	KOAc	98	94
8	toluene	–20	KOAc	99	96
9	toluene	0	CsF	98	94
10	toluene	–20	CsF	90	96
11[a]	toluene	–20	KOAc	19	95

[a] $Pd_2(dba)_3 \cdot CHCl_3$ was used as a palladium source.

gand *cis*-**3** achieved high enantioselectivity in Pd-catalyzed allylic substitution reactions. It is suggested that the ligands do not serve as P,N-bidentate ligands but as P-monodentate ligands in these reactions. Further investigations to utilize P,N-ligands derived from phenyl-P-proline in asymmetric catalysis are in progress.

Experimental Section

Synthesis of *trans*- and *cis*-4

To a mixture of **1**[6] (1.554 g, 7.0 mmol) and HOAt (1.063 g, 7.7 mmol) in CH_2Cl_2 (16 mL), 1,2,3,4-tetrahydroisoquinoline (1.6 mL, 14.0 mmol) was added. After stirring for 10 min at 0 °C, EDC · HCl (2.684 g, 14.0 mmol) was added to the mixture. The reaction mixture was then warmed to room temperature and stirred for 4 h. The reaction was quenched by adding a 1.0 N aqueous solution of HCl, and the aqueous solution was extracted with CH_2Cl_2. The organic layer was dried with Na_2SO_4 and the solvents were evaporated to dryness. The crude product was purified by column chromatography on silica gel (eluent: hexane/AcOEt, 2:1) affording *trans*-**4** in 45% yield and *cis*-**4** in 42% yield, respectively.

***trans*-4:** colorless viscous oil; $[\alpha]_D^{28}$: –52.5° (*c* 1.0, EtOH); ^1H NMR (600 MHz, $CDCl_3$): δ=0.71 (brq, 3H, *J*=149.8 Hz), 2.11–6.39 (m, 13H), 7.03–7.86 (m, 9H); ^{13}C NMR (150 MHz, $CDCl_3$): δ=25.76 (d, *J*=4.3 Hz), 28.22 (d, *J*=7.2 Hz), 28.45, 28.50, 29.43, 31.67 (d, *J*=4.3 Hz), 31.73 (d, *J*=4.3 Hz), 40.31, 43.35, 43.54, 44.19, 44.36, 44.87, 47.79, 125.70, 125.97, 126.41, 126.54, 126.68, 126.72, 127.91, 128.82, 129.22, 129.29, 130.68 (d, *J*=17.2 Hz), 130.96 (d, *J*=17.2 Hz), 131.67, 131.73, 131.81, 131.87, 131.93, 133.28, 133.96, 135.15, 167.57, 168.06; ^{31}P NMR (243 MHz, $CDCl_3$): δ=39.44, 41.55; IR (KBr): ν=2929, 2375, 1645, 1437 cm^{-1}; ESI-MS: *m*/*z*=360 [M+Na]; anal. calcd. for $C_{20}H_{25}BNOP$: C 71.24, H 7.47, N 4.15, found: C 70.98, H 7.49, N 4.07.

***cis*-4:** white solid; mp 113.9–114.0 °C; $[\alpha]_D^{27}$: –150.5° (*c* 1.0, EtOH); ^1H NMR (600 MHz, $CDCl_3$): δ=1.00 (brq, 3H, *J*=111 Hz), 1.73–4.78 (m, 13H), 6.86–7.76 (m, 9H); ^{13}C NMR (150 MHz, $CDCl_3$): δ=26.56, 26.73, 27.12, 27.38, 27.66, 27.68, 29.16, 31.28, 31.54, 39.85, 43.26, 43.34, 43.48, 43.65, 44.39, 47.04, 125.41 (d, *J*=44.5 Hz), 126.23 (d, *J*=44.5 Hz), 126.19, 126.30, 126.45, 128.00, 128.10 (d, *J*=10.1 Hz), 128.32 (d, *J*=10.1 Hz), 128.57, 131.53, 131.89, 132.08, 132.68, 132.81, 132.87, 132.92, 133.96, 134.32, 167.15 (d, *J*=4.3 Hz), 167.69 (d, *J*=4.3 Hz); ^{31}P NMR (243 MHz, $CDCl_3$): δ=37.37 (d, *J*=72.4 Hz), 37.67 (d, *J*=72.4 Hz); IR (KBr): ν=2927, 2368, 2333, 1646, 1434 cm^{-1}; ESI-MS *m*/*z*=360 [M+Na]; anal. calcd. for $C_{20}H_{25}BNOP$: C 71.24, H 7.47, N 4.15; found: C 70.98, H 7.52, N 4.00.

Synthesis of the P,N-Type Ligand 3

To a solution of *cis*-**4** (2.004 g, 5.9 mmol) in THF (12 mL), $BH_3 \cdot THF$ in THF (1.8 M, 33 mL, 59.4 mmol) was added. The reaction mixture was then stirred for 24 h at 40 °C. The mixture was quenched with a 1.0 N aqueous solution of HCl at 0 °C, neutralized with a 1.0 N aqueous solution of NaOH, and then the aqueous solution was extracted with CH_2Cl_2. The organic layer was dried with Na_2SO_4 and the solvents were evaporated to dryness. The crude intermediate was dissolved in Et_2O, and filtered through silica gel to remove an insoluble by-product. A degassed pyrrolidine (30 mL) solution of the intermediate was stirred for 5 h at 40 °C under argon. Pyrrolidine was evaporated and the residue was treated with a 1.0 N aqueous solution of HCl (pH=3), then neutralized by a 1.0 N aqueous solution of NaOH. The product was extracted with CH_2Cl_2. The organic layer was dried with Na_2SO_4 and the solvents were evaporated to dryness. The crude product was purified by column chromatography on silica gel (eluent: hexane/AcOEt 2:1) affording *cis*-**3**.

***cis*-3:** yield: 90%; white solid; mp 64.1–64.2 °C; $[\alpha]_D^{29}$: –113.6° (*c* 0.60, EtOH); ^1H NMR (600 MHz, $CDCl_3$): δ=

1.36–1.41 (m, 1H), 1.72–1.76 (m, 1H), 1.96–2.38 (m, 7H), 2.55–2.66 (m, 2H), 2.88 (m, 2H), 3.43 (d, 1H, J = 14.4 Hz), 3.61 (d, 1H, J=14.4 Hz), 6.98–7.31 (m, 7H), 7.51 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=23.03 (d, J=11.4 Hz), 26.37 (d, J=2.9 Hz), 28.82, 31.85 (d, J=4.3 Hz), 40.36 (d, J=12.4 Hz), 50.67, 55.83, 58.30, 125.58, 126.05, 126.56, 127.72 (d, J=6.7 Hz), 128.44, 128.57, 133.84, 134.02, 134.34, 136.00; ^{31}P NMR (162 MHz, $CDCl_3$): δ=9.82; IR (KBr): ν=3064, 2935, 2861, 2786, 2753, 1425, 1375, 744 cm^{-1}; ESI-MS (HR): m/z= 310.1706 [M+H]; calcd. for $C_{20}H_{25}NP$: 310.1719.

***trans*-3:** yield: 79%; colorless oil; $[\alpha]_D^{20}$: −52.3° (c 1.0, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.46–1.56 (m, 1H), 1.73–1.85 (m, 1H), 1.87–2.11 (m, 4H), 2.52–2.61 (m, 1H), 2.67–2.89 (m, 6H), 3.62 (d, 1H, J=15.1 Hz), 3.74 (d, 1H, J=15.1 Hz), 6.97–7.14 (m, 4H), 7.22–7.30 (m, 3H), 7.44–7.48 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ=26.03 (d, J=11.4 Hz), 27.88 (d, J=2.9 Hz), 28.91, 33.35, 42.99 (d, J=10.49 Hz), 50.83, 56.32, 62.68 (d, J=36.2 Hz), 126.02, 126.56, 127.50, 128.28 (d, J=5.9 Hz), 128.59, 130.73, 130.89, 134.44, 141.84 (d, J=21.9 Hz) ppm; ^{31}P NMR (243 MHz, $CDCl_3$): δ=4.18; IR (neat): ν=3068, 2929, 2795, 1585, 1497, 1430, 1372, 1193, 740 cm^{-1}; ESI-MS (HR): m/z=310.1718 [M+H]; calcd. for $C_{20}H_{25}NP$: 310.1719.

General Procedure for Palladium-Catalyzed Allylic Substitution of 5 using *cis*-3

To a mixture of 1,3-diphenyl-2-propenyl acetate (126 mg, 0.5 mmol), $[Pd(\pi\text{-allyl})Cl]_2$ (1.8 mg, 0.005 mmol), *cis*-**3** (6.2 mg, 0.02 mmol), and NaOAc (2.1 mg, 0.025 mmol) in toluene (1 mL), dimethyl malonate (60 μL, 0.525 mmol) was added. The mixture was stirred for 5 min at room temperature, cooled to 0°C, and stirred for 10 min. BSA (185 mL, 0.75 mmol) was added and the mixture was then stirred for 1 h at 0°C. H_2O and CH_2Cl_2 were added to the reaction mixture. After extracting with CH_2Cl_2, the organic layer was dried with Na_2SO_4 and the solvents were evaporated to dryness. The crude product was purified by PTLC on silica gel (eluent: hexane/AcOEt, 6:1) affording (S)-(E)-1,3-diphenyl-2-methoxycarbonyl-4-penpenoate (**6**); yield: 98% with 94% ee. The enantiomeric excess (ee) of **6** was determined by chiral HPLC (column, chiralpak AD; eluent, 2-propanol/hexane, 1:19; flow rate, 1.0 mL/min; detection, 254-nm light). The absolute configuration of the product was determined by comparison of its chiral HPLC behavior with that described in the literature.[10]

***(S)-(E)-3-Acetyl-4,6-diphenyl-5-hexen-2-one* (7):** yield: 96%; 93% ee (S); $[\alpha]_D^{23}$: +5.9° (c 1.3, EtOH). The enantiomeric excess was determined by chiral HPLC analysis (column, chiralcel OJ; eluent, 2-propanol/hexane, 1:9; flow rate, 1.0 mL/min; detection, 254-nm light). The absolute configuration of **7** was determined by the optical rotation according to the literature.[3c]

***(R)-(E)-3-Acetyl-3-methyl-4,6-diphenyl-5-hexen-2-one* (8):** yield: 88%; 88% ee (R); $[\alpha]_D^{23}$: +25.0° (c 1.8, EtOH). The enantiomeric excess was determined by chiral HPLC analysis (column, chiralcel OJ; eluent, 2-propanol/hexane, 1:9; flow rate, 1.0 mL/min; detection, 254-nm light). The absolute configuration of **8** was determined by the optical rotation according to the literature.[11]

(*R*)-(*E*)-1-Benzylamino-1,3-diphenyl-2-propene (9)

To a mixture of **5** (126 mg, 0.5 mmol), $[Pd(\pi\text{-allyl})Cl]_2$ (1.8 mg, 0.005 mmol), *cis*-**3** (6.2 mg, 0.02 mmol) in toluene (1 mL), benzylamine (0.164 mL, 1.5 mmol) was added at 0°C. After being stirred for 3 h at 0°C, H_2O and CH_2Cl_2 were added to the reaction mixture. After extracting with CH_2Cl_2, the organic layer was dried with Na_2SO_4 and the solvents were evaporated to dryness. The crude product was purified by PTLC on silica gel (eluent: hexane/AcOEt, 6:1) affording (R)-(E)-1-benzylamino-1,3-diphenyl-2-propene (**9**); yield: 98%; 80% ee; $[\alpha]_D^{23}$: −21.3° (c 1.5, $CHCl_3$). The enantiomeric excess of **9** was determined by chiral HPLC (column, chiralcel OJ; eluent, 2-propanol/hexane, 1:19; flow rate, 1.0 mL/min; detection, 254-nm light). The absolute configuration of **9** was determined by the optical rotation according to the literature.[12]

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