A New Entry of Nucleophiles in Rhodium-Catalyzed Asymmetric 1,4-Addition Reactions: Addition of Organozinc Reagents for the Synthesis of 2-Aryl-4-Piperidones

Ryo Shintani, Norihito Tokunaga, Hidenori Doi, and Tamio Hayashi*

Department of Chemistry, Graduate School of Science, Kyoto University,
Sakyo, Kyoto 606-8502, Japan

Supporting Information

I. General

All air- and moisture-sensitive manipulations were carried out with standard Schlenk techniques under nitrogen or in a glove box under argon.

THF, 1,4-dioxane, and toluene were distilled over benzophenone ketyl under nitrogen.

4-piperidone monohydrate hydrochloride (TCI), phenylboronic acid (TCI), benzyl chloroformate (Wako Chemicals), Pd/C (Wako Chemicals; 10 wt%), *t*-BuLi (Kanto Chemicals; 1.48 M solution in pentane), allyl bromide (TCI), 2-cyclohexen-1-one (Wako Chemicals), and 5-methyl-3-hexen-2-one (TCI) were used as received. Pivaloyl chloride (TCI) was distilled under vacuum prior to use. Ph-9-BBN,¹ PhTi(*Oi*-Pr)₃,² Rh(acac)(C₂H₄)₂,³ [Rh(OMe)(cod)]₂,⁴ and [RhCl((*R*)-binap)]₂⁵ were synthesized following the literature procedure.

All other chemicals and solvents were purchased from Aldrich, Wako Chemicals, TCI, or Kanto Chemicals and used as received.

II. Synthesis of Substrates

The yields have not been optimized.

Benzyl 3,4-dihydro-4-oxo-1(2*H*)-pyridinecarboxylate (1) (CAS 185847-84-1)

¹ Kramer, G. W.; Brown, H. C. *J. Organomet. Chem.* **1974**, *73*, 1.

² Weidmann, B.; Widler, L.; Olivero, A. G.; Maycock, C. D.; Seebach, D. *Helv. Chim. Acta* **1981**, *64*, 357.

³ Cramer, R. *Inorg. Synth.* **1974**, *15*, 16.

⁴ Uson, R.; Oro, L. A.; Cabeza, J. A. *Inorg. Synth.* **1985**, *23*, 126.

⁵ Hayashi, T.; Takahashi, M.; Takaya, Y.; Ogasawara, M. *J. Am. Chem. Soc.* **2002**, *124*, 5052.

This was synthesized from 4-piperidone monohydrate hydrochloride and benzyl chloroformate, following the literature procedure for ethyl 3,4-dihydro-4-oxo-1(2*H*)-pyridinecarboxylate.⁶ White solid, 40% overall yield.

¹H NMR (CDCl₃): δ 7.85 (bs, 1H), 7.40-7.37 (m, 5H), 5.35 (bs, 1H), 5.27 (s, 2H), 4.05 (t, ³*J*_{HH} = 7.3 Hz, 2H), 2.56 (t, ³*J*_{HH} = 7.3 Hz, 2H). ¹³C NMR (CDCl₃): δ 193.2, 152.5, 143.3, 134.8, 128.74, 128.68, 128.4, 107.7, 69.0, 42.5, 35.6.

General Procedure for the Preparation of Arylzinc Chlorides

t-BuLi (13.5 mL, 20.0 mmol; 1.48 M solution in pentane) was added dropwisely to a solution of aryl bromide (10.0 mmol) in THF (5.0 mL) at -78 °C. The resulting mixture was stirred for 30 min at -78 °C, and then 15 min at room temperature. The aryllithium solution thus obtained was added to a suspension of ZnCl₂ (1.45 g, 10.6 mmol) in THF (2.5 mL) at 0 °C, with the aid of additional THF (5.0 mL). The reaction mixture was stirred for 15 min at room temperature, and was then concentrated under vacuum to remove pentane. THF (5.0 mL) was added to the resulting mixture to obtain a solution of arylzinc chloride in THF. The concentration was determined by acid-base titration with methyl orange (typically around 0.5 M).

III. 1,4-Addition Reactions

Procedure for Table 1, Entry 1. (CAS 335266-05-2)

A solution of **1** (57.8 mg, 0.25 mmol), PhB(OH)₂ (91.4 mg, 0.75 mmol), Rh(acac)(C₂H₄)₂ (1.9 mg, 7.3 μmol), and (*R*)-binap (5.1 mg, 8.2 μmol) in 1,4-dioxane (1.0 mL) and H₂O (0.1 mL) was stirred for 2 h at 100 °C. The reaction mixture was directly passed through a pad of silica gel with Et₂O and the solvent was removed under vacuum. The residue was purified by silica gel PTLC with Et₂O/hexane = 2/1 to afford the desired 1,4-adduct (*R*)-**2a** as a white solid (25.6 mg, 83 μmol; 33% yield).

The ee was determined on a Daicel Chiralcel OD-H column with hexane : isopropanol = 90 : 10, flow = 1.0 mL/min. Retention times: 20.9 min [(*S*)-enantiomer], 27.0 min [(*R*)-enantiomer]. 96% ee.

¹H NMR (CDCl₃): δ 7.36-7.31 (m, 7H), 7.29-7.24 (m, 3H), 5.84 (bs, 1H), 5.25 (d, ²*J*_{HH} = 12.3 Hz, 1H), 5.20 (d, ²*J*_{HH} = 12.3 Hz, 1H), 4.28 (bs, 1H), 3.19 (t, ³*J*_{HH} = 11.0 Hz, 1H), 2.99 (d, ²*J*_{HH} = 13.8 Hz, 1H), 2.86 (dd, ²*J*_{HH} = 15.5 Hz and ³*J*_{HH} = 7.0 Hz, 1H), 2.57-2.50 (m, 1H), 2.37 (d, ²*J*_{HH} = 15.8 Hz, 1H). ¹³C NMR (CDCl₃): δ 207.0, 155.3, 139.6, 136.2, 128.7, 128.5, 128.1, 127.9, 127.6, 126.6, 67.7, 54.5, 44.1, 40.4, 38.8.

⁶ Kozikowski, A. P.; Park, P.-u. *J. Org. Chem.* **1990**, *55*, 4668.

Procedure for Table 1, Entry 2.

A solution of **1** (46.4 mg, 0.20 mmol), PhB(OH)₂ (73.2 mg, 0.60 mmol), and [Rh(OH)((*R*)-binap)]₂ (4.5 mg, 6.0 μmol Rh) in 1,4-dioxane (0.7 mL) and H₂O (70 μL) was stirred for 5 h at 50 °C. The reaction mixture was directly passed through a pad of silica gel with Et₂O and the solvent was removed under vacuum. The residue was purified by silica gel PTLC with Et₂O/hexane = 2/1 to afford the desired 1,4-adduct (*R*)-**2a** as a white solid (48.6 mg, 0.157 mmol; 78% yield). 98% ee

Procedure for Table 1, Entry 3.

A solution of [Rh(OMe)(cod)]₂ (1.5 mg, 6.0 μmol Rh) and (*R*)-binap (4.1 mg, 6.6 μmol) in toluene (0.5 mL) was stirred for 2 min at 80 °C. **1** (46.3 mg, 0.20 mmol) and Ph-9-BBN (44 mg, 0.22 mmol) were successively added to this solution, and the mixture was stirred for 1 h at 80 °C. After quenching with MeOH (21 μL), the solvent was removed under vacuum, and then the residue was purified by silica gel PTLC with Et₂O/hexane = 2/1 to afford the desired 1,4-adduct (*R*)-**2a** as a white solid (20.5 mg, 66 μmol; 33% yield). 97% ee.

Procedure for Table 1, Entry 4.

A solution of **1** (46.3 mg, 0.20 mmol), PhTi(O*i*-Pr)₃ (97 mg, 0.32 mmol), and [Rh(OH)((*R*)-binap)]₂ (4.5 mg, 6.0 μmol Rh) in THF (0.5 mL) was stirred for 1 h at 20 °C. After quenching with MeOH (0.1 mL), the reaction mixture was passed through a pad of silica gel with Et₂O, and the solvent was then removed under vacuum (1,4-adduct **2a**/1,2-adduct ~ 3/1 by ¹H NMR). The residue was purified by silica gel PTLC with Et₂O/hexane = 2/1 to afford the desired 1,4-adduct (*R*)-**2a**, which was contaminated with the undesired 1,2-adduct (54.4 mg, 0.176 mmol; ~4/1 mixture, 87% yield combined). 1,4-adduct: >99.5% ee.

Procedure for Table 1, Entry 5.

PhZnCl (0.82 mL, 0.45 mmol; 0.55 M solution in THF) was added dropwisely to a stirring solution of **1** (69.4 mg, 0.30 mmol) and [RhCl((*R*)-binap)]₂ (6.8 mg, 9.0 μmol Rh) in THF (1.0 mL), and the mixture was stirred for 2 h at 20 °C. After quenching with H₂O (0.1 mL), the reaction mixture was passed through a pad of silica gel with Et₂O, and the solvent was then removed under vacuum. The residue was chromatographed on silica gel with Et₂O/hexane = 1/1 to afford the desired 1,4-adduct (*R*)-**2a** as a white solid (88.6 mg, 0.29 mmol; 95% yield). >99.5% ee. [α]_D²⁰ +74.3 (*c* 1.00, CHCl₃). The absolute configuration was assigned by analogy with equation 2.

General procedure for Table 2.

ArZnCl (0.30 mmol; THF solution) was added dropwisely to a stirring solution of **1** (46.3 mg, 0.20 mmol) and [RhCl((*R*)-binap)]₂ (4.6 mg, 6.0 μmol Rh) in THF (0.5 mL), and the mixture was stirred for 2 h at 20 °C. After quenching with H₂O (50 μL), the reaction mixture was passed through a pad of silica gel with Et₂O, and the solvent was then removed under vacuum. The residue was chromatographed on silica gel with Et₂O/hexane to afford the desired 1,4-adduct **2**.

Table 2, entry 2 ((*R*)-2b). The reaction was stirred for 4 h. Yellow solid. 97% yield. The ee was determined on a Daicel Chiralpak AD column with hexane : isopropanol = 90 : 10, flow = 1.0 mL/min. Retention times: 19.6 min [(*S*)-enantiomer], 24.1 min [(*R*)-enantiomer]. >99.5% ee. $[\alpha]_D^{20} +79.6$ (*c* 1.32, CHCl₃). The absolute configuration was assigned by analogy with equation 2.

¹H NMR (CDCl₃): δ 7.55 (t, ³*J*_{HH} = 7.1 Hz, 4H), 7.43 (t, ³*J*_{HH} = 7.4 Hz, 2H), 7.37-7.28 (m, 8H), 5.87 (bs, 1H), 5.27 (d, ²*J*_{HH} = 12.3 Hz, 1H), 5.21 (d, ²*J*_{HH} = 12.3 Hz, 1H), 4.31 (bs, 1H), 3.25 (t, ³*J*_{HH} = 11.3 Hz, 1H), 3.01 (d, ²*J*_{HH} = 15.1 Hz, 1H), 2.89 (dd, ²*J*_{HH} = 15.4 Hz and ³*J*_{HH} = 6.8 Hz, 1H), 2.58-2.52 (m, 1H), 2.39 (d, ³*J*_{HH} = 15.8 Hz, 1H). ¹³C NMR (CDCl₃): δ 207.2, 155.5, 140.7, 140.3, 138.6, 136.2, 128.8, 128.6, 128.2, 128.0, 127.48, 127.45, 127.1, 127.0, 67.8, 54.4, 44.2, 40.5, 39.0. Anal. Calcd for C₂₅H₂₃NO₃: C, 77.90; H, 6.01. Found: C, 77.64; H, 6.23.

Table 2, entry 3 ((*R*)-2c). The reaction was stirred for 12 h with 3.0 equiv of 4-MeOC₆H₄ZnCl in the presence of [RhCl((*R*)-binap)]₂ (6 mol% Rh). Colorless oil. 90% yield. The ee was determined on a Daicel Chiralcel OD-H column with hexane : isopropanol = 90 : 10, flow = 1.0 mL/min. Retention times: 30.6 min [(*S*)-enantiomer], 36.0 min [(*R*)-enantiomer]. 99% ee. $[\alpha]_D^{20} +71.1$ (*c* 1.51, CHCl₃). The absolute configuration was assigned by analogy with equation 2.

¹H NMR (CDCl₃): δ 7.39-7.32 (m, 5H), 7.16 (d, ³*J*_{HH} = 8.3 Hz, 2H), 6.85-6.83 (m, 2H), 5.82 (bs, 1H), 5.25 (d, ²*J*_{HH} = 12.2 Hz, 1H), 5.20 (d, ²*J*_{HH} = 12.2 Hz, 1H), 4.26 (bs, 1H), 3.79 (s, 3H), 3.13 (t, ³*J*_{HH} = 11.2 Hz, 1H), 2.95 (d, ²*J*_{HH} = 15.4 Hz, 1H), 2.84 (dd, ²*J*_{HH} = 15.5 Hz and ³*J*_{HH} = 7.0 Hz, 1H), 2.57-2.49 (m, 1H), 2.35 (d, ²*J*_{HH} = 15.5 Hz, 1H). ¹³C NMR (CDCl₃): δ 207.4, 159.0, 155.4, 136.3, 131.5, 129.6, 128.6, 128.2, 128.0, 114.1, 67.7, 55.2, 54.1, 44.3, 40.6, 38.7. Anal. Calcd for C₂₀H₂₁NO₄: C, 70.78; H, 6.24. Found: C, 70.56; H, 6.33.

Table 2, entry 4 ((*R*)-2d). (CAS 414910-20-6) The reaction was stirred for 7 h. Pale yellow oil. 91% yield. The ee was determined on a Daicel Chiralcel OD-H column with hexane : isopropanol = 90 : 10, flow = 1.0 mL/min. Retention times:

26.7 min [(*S*)-enantiomer], 36.3 min [(*R*)-enantiomer]. >99.5% ee. $[\alpha]_D^{20} +67.4$ (*c* 0.68, CHCl₃). The absolute configuration was assigned by analogy with equation 2.

¹H NMR (CDCl₃): δ 7.38-7.31 (m, 5H), 7.24-7.18 (m, 2H), 7.00 (t, *J* = 8.5 Hz, 2H), 5.82 (bs, 1H), 5.25 (d, ²*J*_{HH} = 12.2 Hz, 1H), 5.19 (d, ²*J*_{HH} = 12.2 Hz, 1H), 4.28 (bs, 1H), 3.16 (t, ³*J*_{HH} = 11.1 Hz, 1H), 2.94 (dd, ²*J*_{HH} = 15.4 Hz and ³*J*_{HH} = 1.9 Hz, 1H), 2.86 (dd, ²*J*_{HH} = 15.5 Hz and ³*J*_{HH} = 6.8 Hz, 1H), 2.57-2.50 (m, 1H), 2.37 (d, ²*J*_{HH} = 15.9 Hz, 1H). ¹³C NMR (CDCl₃): δ 207.0, 162.1 (d, ¹*J*_{CF} = 246.5 Hz), 155.3, 136.1, 135.5, 128.6, 128.5 (d, ³*J*_{CF} = 5.6 Hz), 128.3, 128.0, 115.7 (d, ²*J*_{CF} = 21.2 Hz), 67.8, 54.1, 44.2, 40.5, 38.9.

Table 2, entry 5 ((*R*)-2e). The reaction was stirred for 7 h with 3.0 equiv of 3,5-Me₂C₆H₃ZnCl in the presence of [RhCl((*R*)-binap)]₂ (6 mol% Rh). Yellow oil. 87% yield. The ee was determined on a Daicel Chiralcel OD-H column with hexane : isopropanol = 90 : 10, flow = 1.0 mL/min. Retention times: 16.1 min [(*S*)-enantiomer], 21.6 min [(*R*)-enantiomer]. 99% ee. $[\alpha]_D^{20} +74.7$ (*c* 1.13, CHCl₃). The absolute configuration was assigned by analogy with equation 2.

¹H NMR (CDCl₃): δ 7.36-7.32 (m, 5H), 6.90 (s, 1H), 6.82 (s, 2H), 5.75 (bs, 1H), 5.26 (d, ²*J*_{HH} = 12.3 Hz, 1H), 5.19 (d, ²*J*_{HH} = 12.2 Hz, 1H), 4.27 (bs, 1H), 3.21 (t, ³*J*_{HH} = 10.9 Hz, 1H), 2.96 (dd, ²*J*_{HH} = 15.5 Hz and ³*J*_{HH} = 2.0 Hz, 1H), 2.82 (dd, ²*J*_{HH} = 15.5 Hz and ³*J*_{HH} = 7.0 Hz, 1H), 2.55-2.48 (m, 1H), 2.37 (d, ²*J*_{HH} = 16.0 Hz, 1H), 2.27 (s, 6H). ¹³C NMR (CDCl₃): δ 207.3, 155.4, 139.6, 138.3, 136.3, 129.3, 128.5, 128.1, 127.9, 124.4, 67.6, 54.4, 44.2, 40.5, 38.9, 21.3. HRMS (ESI) calcd for C₂₁H₂₃NO₃Na (M+Na⁺) 360.1570, found 360.1570.

Table 2, entry 6 ((*R*)-2f). The reaction was stirred for 4 h with 3.0 equiv of 2-MeC₆H₄ZnCl in the presence of [RhCl((*R*)-binap)]₂ (6 mol% Rh). Yellow oil. 100% yield. The ee was determined on a Daicel Chiralcel OD-H column with hexane : isopropanol = 95 : 5, flow = 1 mL/min. Retention times: 26.0 min [(*R*)-enantiomer], 29.3 min [(*S*)-enantiomer]. 99% ee. $[\alpha]_D^{20} +75.9$ (*c* 0.47, CHCl₃). The absolute configuration was assigned by analogy equation 2.

¹H NMR (CDCl₃): δ 7.35-7.29 (m, 3H), 7.23-7.18 (m, 6H), 5.75 (bs, 1H), 5.18 (d, ²*J*_{HH} = 12.0 Hz, 1H), 5.14 (d, ³*J*_{HH} = 12.2 Hz, 1H), 4.28 (bs, 1H), 3.25 (bs, 1H), 2.86 (dd, ²*J*_{HH} = 15.6 Hz and ³*J*_{HH} = 4.4 Hz, 1H), 2.80 (dd, ²*J*_{HH} = 15.4 Hz and ³*J*_{HH} = 6.6 Hz, 1H), 2.58-2.46 (m, 1H), 2.46 (d, ²*J*_{HH} = 17.1 Hz, 1H), 2.26 (s, 3H). ¹³C NMR (CDCl₃): δ 207.8,

155.1, 138.6, 136.4, 136.1, 131.1, 128.5, 128.1, 127.9, 127.8, 126.2, 126.1, 67.7, 52.8, 44.7, 40.8, 38.9, 19.2. Anal. Calcd for C₂₀H₂₁NO₃: C, 74.28; H, 6.55. Found: C, 74.09; H, 6.56.

Procedure for Equation 2.

4-Fluoro-2-methylphenylzinc chloride (1.54 mL, 0.80 mmol; 0.52 M solution in THF) was added dropwisely to a stirring solution of **1** (46.3 mg, 0.20 mmol) and [RhCl((*R*)-binap)]₂ (12.2 mg, 16.0 μmol Rh) in THF (0.5 mL), and the mixture was stirred for 9 h at 20 °C. After quenching with H₂O (60 μL), the reaction mixture was passed through a pad of silica gel with Et₂O, and the solvent was then removed under vacuum. The residue was chromatographed on silica gel with Et₂O/hexane = 1/1 to afford the desired 1,4-adduct (CAS 414910-00-2) as a pale yellow oil (55.7 mg, 0.163 mmol; 82% yield).

The ee was determined on a Daicel Chiralcel OD-H column with hexane : isopropanol = 90 : 10, flow = 1.0 mL/min. Retention times: 20.5 min [(*R*)-enantiomer], 23.4 min [(*S*)-enantiomer]. 97% ee. [α]_D²⁰ +59.5 (*c* 0.61, CHCl₃).

¹H NMR (CDCl₃): δ 7.38-7.23 (m, 5H), 7.13-7.10 (m, 1H), 6.87-6.82 (m, 2H), 5.71 (bs, 1H), 5.19 (d, ²J_{HH} = 12.1 Hz, 1H), 5.14 (d, ²J_{HH} = 12.3 Hz, 1H), 4.28 (bs, 1H), 3.21 (bs, 1H), 2.84-2.76 (m, 2H), 2.57-2.50 (m, 1H), 2.46 (d, ²J_{HH} = 16.6 Hz, 1H), 2.25 (s, 3H). ¹³C NMR (CDCl₃): δ 207.6, 162.0 (d, ¹J_{CF} = 247.0 Hz), 155.1, 139.0, 136.0, 134.3, 128.5, 128.2, 128.0, 127.7, 117.9 (d, ²J_{CF} = 21.7 Hz), 112.7 (d, ²J_{CF} = 21.2 Hz), 67.8, 52.3, 44.8, 40.8, 38.9, 19.2.

The 1,4-adduct obtained above (32.9 mg, 96.4 μmol) was dissolved in MeOH (0.5 mL) and Pd/C (10%; 8.8 mg, 8.3 μmol Pd) was added to it. H₂ gas (~1 atm) was then purged and the mixture was stirred for 4 h at 20 °C. After releasing H₂, Pd/C was removed by filtration through celite with Et₂O. The resulting solution was washed with aqueous NaOH, dried over MgSO₄, filtered, and then concentrated under vacuum to afford compound (*R*)-**3** (CAS 414910-12-6 for (*R*)-enantiomer; 414909-99-2 for racemate) as an yellow oil (17.7 mg, 85.4 μmol; 89% yield). [α]_D²⁰ +77.4 (*c* 0.18, DMSO). The absolute configuration was determined by comparison of the optical rotation with the literature value.⁷

¹H NMR (CDCl₃): δ 7.57 (dd, ³J_{HH} = 8.4 Hz and ⁴J_{HF} = 5.8 Hz, 1H), 6.94-6.90 (m, 1H), 6.88 (dd, ³J_{HF} = 9.6 Hz and ⁴J_{HH} = 2.4 Hz, 1H), 4.17 (dd, ³J_{HH} = 11.5 Hz and ³J_{HH} =

⁷ Alvaro, G.; Di Fabio, R.; Tranquillini, M. E.; Spada, S. Application: WO 2003-EP1308 20030210.

3.2 Hz, 1H), 3.50-3.46 (m, 1H), 3.05 (td, $J_{\text{HH}} = 12.3$ Hz and $^3J_{\text{HH}} = 3.2$ Hz, 1H), 2.71 (td, $J_{\text{HH}} = 13.6$ Hz and $^3J_{\text{HH}} = 6.7$ Hz, 1H), 2.61-2.45 (m, 3H), 2.35 (s, 3H).

Procedure for Equation 3.

PhZnCl (0.55 mL, 0.30 mmol; 0.55 M solution in THF) was added dropwisely to a stirring solution of **1** (0.20 mmol) and $[\text{RhCl}((R)\text{-binap})]_2$ (4.6 mg, 6.0 μmol Rh) in THF (0.5 mL), and the mixture was stirred for 2 h at 20 °C. After cooling to 0 °C, an electrophile (0.4 mmol) was added dropwisely and the resulting solution was further stirred for 2 h at 20 °C. The mixture was then passed through a pad of silica gel with Et₂O and the solvent was removed under vacuum. The residue was purified by silica gel PTLC with Et₂O/hexane = 1/1 to afford the desired product.

Compound 5. Pale yellow oil. 83% yield. The ee was assumed to be >99.5% (2*R*,3*S*) based on the result in Table 1, entry 4. $[\alpha]_{\text{D}}^{20} +119.8$ (*c* 1.01, CHCl₃). The absolute configuration was assigned by analogy with equation 2.

¹H NMR (CDCl₃): δ 7.39-7.23 (m, 10H), 5.78-5.68 (m, 1H), 5.58 (bs, 1H), 5.24 (d, $^2J_{\text{HH}} = 12.2$ Hz, 1H), 5.21 (d, $^2J_{\text{HH}} = 12.3$ Hz, 1H), 5.10-5.02 (m, 2H), 4.32 (bs, 1H), 3.18 (ddd, $^2J_{\text{HH}} = 13.8$ Hz and $^3J_{\text{HH}} = 11.8$ Hz and 4.1 Hz, 1H), 3.05 (td, $^3J_{\text{HH}} = 7.0$ Hz and 2.6 Hz, 1H), 2.65-2.56 (m, 1H), 2.46-2.34 (m, 2H), 2.32 (d, $^2J_{\text{HH}} = 16.0$ Hz, 1H). ¹³C NMR (CDCl₃): δ 209.4, 155.8, 139.4, 136.2, 134.1, 128.7, 128.5, 128.2, 128.0, 127.8, 127.1, 118.2, 67.8, 58.1, 52.8, 38.9, 38.5, 34.9. Anal. Calcd for C₂₂H₂₃NO₃: C, 75.62; H, 6.63. Found: C, 75.44; H, 6.59.

Compound 6. Colorless oil. 97% yield. The ee was assumed to be >99.5% (*R*) based on the result in Table 1, entry 4. $[\alpha]_{\text{D}}^{20} +114.8$ (*c* 0.96, CHCl₃). The absolute configuration was assigned by analogy with equation 2.

¹H NMR (CDCl₃, 45 °C): δ 7.44 (bs, 1H), 7.37-7.28 (m, 9H), 5.85 (bs 1H), 5.55 (bs, 1H), 5.22 (d, $^2J_{\text{HH}} = 12.3$ Hz, 1H), 5.15 (d, $^2J_{\text{HH}} = 12.3$ Hz, 1H), 4.21 (bs, 1H), 3.12 (ddd, $^2J_{\text{HH}} = 13.6$ Hz and $^3J_{\text{HH}} = 12.0$ Hz and 4.1 Hz, 1H), 2.61-2.52 (m, 1H), 2.08 (d, $^2J_{\text{HH}} = 13.3$ Hz, 1H), 1.28 (s, 9H). ¹³C NMR (CDCl₃): δ 176.9, 154.9, 147.8, 140.0, 136.5, 128.51, 128.48, 128.46, 128.03, 127.97, 127.8, 113.7, 67.5, 67.4, 54.0, 38.9, 36.9, 27.1. Anal. Calcd for C₂₄H₂₇NO₄: C, 73.26; H, 6.92. Found: C, 73.37; H, 7.19.

Procedure for Equations 4 and 5.

PhZnCl (0.55 mL, 0.30 mmol; 0.55 M solution in THF) was added dropwisely to a stirring solution of α,β -enone (0.20 mmol) and $[\text{RhCl}((R)\text{-binap})]_2$ (4.6 mg, 6.0 μmol Rh) in THF (0.5 mL), and the mixture was stirred for 1 h at 20 °C. After quenching with H_2O (0.1 mL), the reaction mixture was passed through a pad of silica gel with Et_2O , and the solvent was then removed under vacuum. The residue was purified by silica gel PTLC with $\text{EtOAc}/\text{hexane} = 1/3$ to afford the desired 1,4-adduct.

Equation 4 ((*R*)-7). (CAS 34993-51-6) Colorless oil. 98% yield. The ee was determined on a Daicel Chiralcel OD-H column with hexane : isopropanol = 98 : 2, flow = 0.5 mL/min. Retention times: 24.0 min [(*S*)-enantiomer], 25.6 min [(*R*)-enantiomer]. 99% ee.

Equation 5 ((*R*)-8). (CAS 162239-77-2) Colorless oil. 99% yield. The ee was determined on a Daicel Chiralcel OD-H column with hexane : isopropanol = 98 : 2, flow = 0.5 mL/min. Retention times: 19.2 min [(*R*)-enantiomer], 21.9 min [(*S*)-enantiomer]. 94% ee.