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Asymmetric construction of chiral C–N axes through rhodium-catalyzed 1,4-addition

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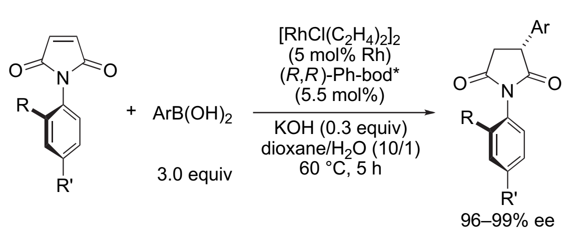
Abstract—Catalytic asymmetric construction of chiral C–N axes has been developed through a rhodium-catalyzed asymmetric 1,4-addition reaction. Both central chirality and axial chirality have been controlled at the same time using Rh/(*R*,*R*)-Ph-bod* catalyst with high enantio- and diastereoselectivity. This method has also been applied to the preparation of a planar-chiral ferrocene derivative. The resulting chiral C–N axis can be used as a good template to control the stereochemistry in the subsequent transformations such as alkylation and Diels–Alder reactions.

1. Introduction

Since Curran reported the first example of C–N axially chiral anilides as stable atropisomers,[1] the synthesis and the application of enantio-enriched C–N axially chiral compounds have been extensively investigated in the past decade.[1–3] However, the preparation of these compounds usually begins with enantio-enriched substrates or involves optical resolution of racemates using chiral HPLC.[2] The first catalytic asymmetric synthesis of these compounds was achieved by Taguchi[3a] and Curran[3b] through a palladium-catalyzed N-allylation reaction with moderate ee (30–53%). More effective methods have begun to appear very recently. Thus, high enantioselectivity (up to 98% ee) has been reported in a palladium-catalyzed asymmetric N-arylation of anilides by Taguchi,[3c,3d] in a rhodium-catalyzed asymmetric [2+2+2] cycloaddition of 1,6-diynes with alkynamides by Tanaka,[3e] and in a cinchona-alkaloid-catalyzed Friedel–Crafts amination of 2-naphthols by Bella and Jørgensen.[3f] Here we report the development of a highly enantio- and diastereoselective construction of axially chiral *N*-arylsuccinimides by way of a rhodium-catalyzed asymmetric 1,4-addition reaction (Eq. 1).[4]



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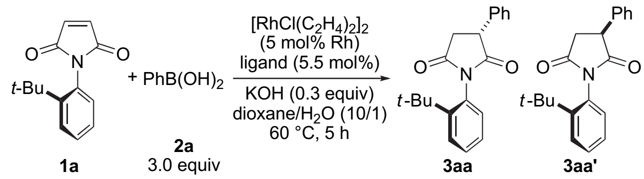
2. Results and discussion

The reaction of 1-(2-*tert*-butylphenyl)maleimide (**1a**) with phenylboronic acid (**2a**) in the presence of 5 mol % Rh/(*R*)-binap catalyst[5,6] gave the 1,4-adduct as a mixture of two diastereomers, **3aa** and **3aa′**, in a ratio of 65/35 with 83 and 75% ee, respectively (Table 1, entry 1). Somewhat better stereoselectivity was observed by employing (*R*)-phosphoramidite,[7] but it was still unsatisfactory (entry 2; 73/27 with 83 and 85% ee). In contrast, the use of chiral diene ligands[8–10] significantly improved the selectivity toward the formation of **3aa** (**3aa**/**3aa′**=96/4), and the enantioselectivity of **3aa** was as high as 92% ee with (*R*,*R*)-Bn-bod*[8,9] (entry 3). The highest ee of **3aa** was achieved by the use of (*R*,*R*)-Ph-bod*[8] as the ligand (entry 4; 99% ee).

The scope of this reaction is illustrated in Table 2 under the optimized conditions with Rh/(*R*,*R*)-Ph-bod*. Thus, a variety of arylboronic acids can be coupled with **1a** to give the corresponding axially chiral succinimides **3** with high diastereoselectivity and excellent enantioselectivity (entries 1–7; dr=93/7–98/2, 96–99% ee). Other maleimides such as **1b** and **1c** are also suitable for this system to give the products with similar efficiency (entries 8 and 9; dr=91/9–97/3, 99% ee).

The absolute configuration of **3ae** (Table 2, entry 5) was determined to be (*R*) for the carbon central chirality and (*S*) for the C–N axial chirality by X-ray crystallographic analysis (Fig. 1).[11] In addition, by reducing the two carbonyl groups of **3aa** and **3aa′** given in Table 1, entry 1 to the corresponding pyrrolidine **4**, and comparing their values of optical rotation, we determined the absolute configuration of **3aa′** obtained by the reaction with Rh/(*R*)-binap to be ($3S,S_a$) (Eqs. 2 and 3).

Table 1. Rhodium-catalyzed asymmetric 1,4-addition of phenylboronic acid to maleimide **1a**: ligand effect



Entry	Ligand	dr[a]	Yield[b] (%)	ee of **3aa**[c] (%)	ee of **3aa′**[c] (%)
1[d]	(*R*)-binap	65/35	100	83	75
2[e]	(*S*)-Phosphoramidite	73/27	93	83	85
3	(*R*,*R*)-Bn-bod*	96/4	99	92	−67
4	(*R*,*R*)-Ph-bod*	96/4	99	99	−37

[a] Ratio of **3aa/3aa′** (determined by ^{1}H NMR of the crude material).
[b] Combined yield of **3aa** and **3aa′**.
[c] Determined by HPLC on a Chiralcel OD-H column with hexane/2-propanol=80/20.
[d] The reaction was conducted at 50 °C.
[e] Ligand of 11 mol % was used.

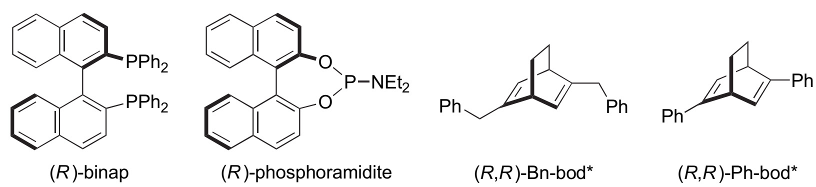
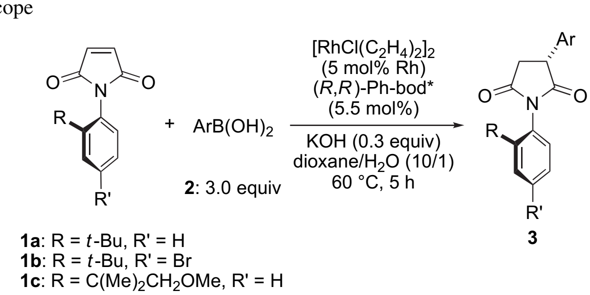


Table 2. Rhodium-catalyzed asymmetric construction of C–N axes: scope



Entry	Maleimide	Ar	Product	dr[a]	Yield[b] (%)	ee[c] (%)
1	**1a**	Ph (**2a**)	**3aa**	96/4	96	99
2	**1a**	4-MeOC$_6$H$_4$ (**2b**)	**3ab**	98/2	95	97
3	**1a**	4-FC$_6$H$_4$ (**2c**)	**3ac**	96/4	92	99
4	**1a**	4-BrC$_6$H$_4$ (**2d**)	**3ad**	93/7	88	98
5	**1a**	3-ClC$_6$H$_4$ (**2e**)	**3ae**	93/7	88	96
6	**1a**	2-Naphthyl (**2f**)	**3af**	96/4	93[d]	97
7	**1a**	2-MeC$_6$H$_4$ (**2g**)	**3ag**	98/2	97	98
8	**1b**	Ph (**2a**)	**3ba**	91/9	81	99
9	**1c**	Ph (**2a**)	**3ca**	97/3	96	99

[a] Determined by ^{1}H NMR of the crude material.
[b] Isolated yield of the major diastereomer.
[c] ee of the major diastereomer (determined by HPLC).
[d] Mixture (97/3) of diastereomers.

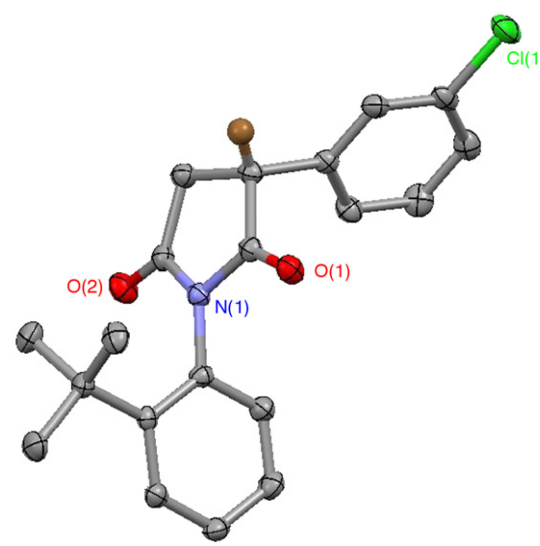
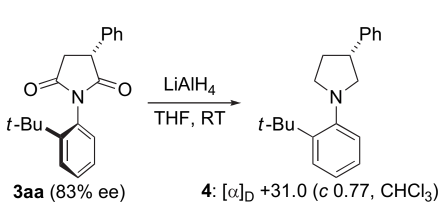
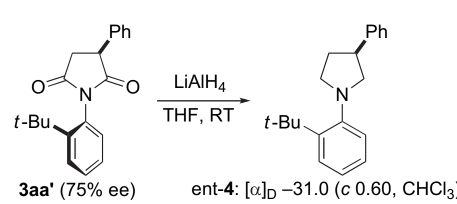


Figure 1. X-ray structure of (3*R*,*S*$_a$)-**3ae** with thermal ellipsoids drawn at the 50% probability level.

The stereochemical outcome observed in the reaction with Rh/(*R*,*R*)-Ph-bod* catalyst can be explained as follows (Fig. 2). To avoid the unfavorable steric interaction between the imide moiety of maleimide and the phenyl group on the olefin of (*R*,*R*)-Ph-bod*, intermediate **A** is preferred to **B**,



(2)



(3)

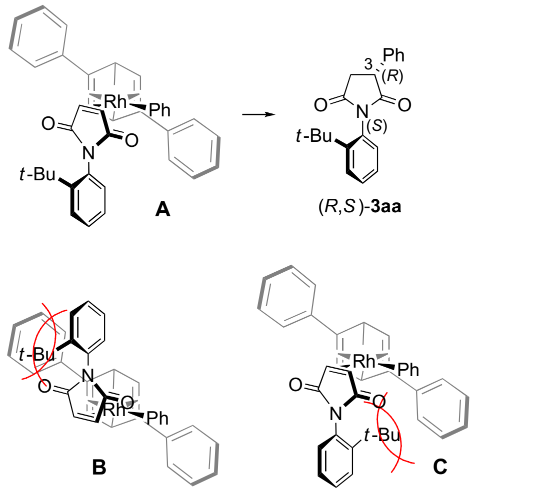
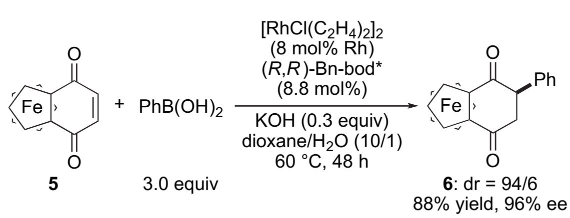


Figure 2. Proposed stereochemical pathway for the reaction of **1a** with phenylboronic acid catalyzed by Rh/(*R*,*R*)-Ph-bod*.

giving product **3aa** with (*R*)-configuration at 3-position. For the control of axial chirality, due to the steric hindrance of the *tert*-butyl group on maleimide, the coordination of **1a** is more favorable in **A** than in **C**, leading to the formation of C–N axis in (*S*)-configuration.

This mode of facial discrimination by a Rh/chiral diene catalyst can also be applied to the reaction of ferrocobenzoquinone **5** with phenylboronic acid (Eq. 4). Thus, phenylation occurs at the opposite side of iron of the ferrocene, effectively creating a carbon central chirality in (*R*)-configuration and a ferrocene planar chirality in (R_p)-configuration at the same time (Fig. 3).[12,13]



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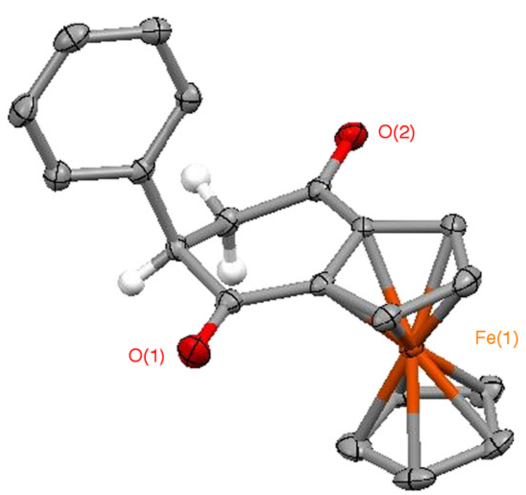
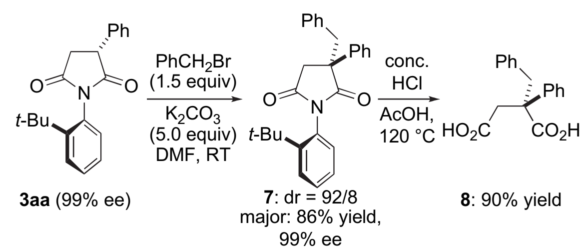
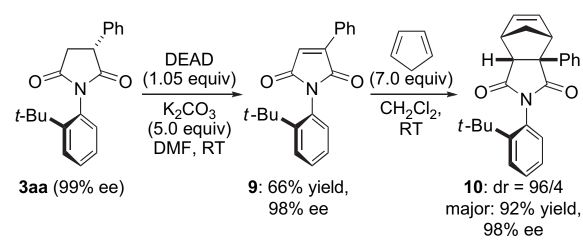


Figure 3. X-ray structure of (*R*,R_p)-**6** with thermal ellipsoids drawn at the 50% probability level.

The stereochemical information of the chiral C–N axis can be used as a good template to control the stereochemistry of subsequent transformations. For example, benzylation at 3-position of **3aa** selectively occurs in such a way that the electrophile approaches an enolate of **3aa** from the opposite face to the *tert*-butyl group, furnishing alkylated product **7** with high diastereoselectivity (92/8) without any decrease of ee (Eq. 5). The 2-*tert*-butylphenyl group can be removed by hydrolysis of **7** under acidic conditions to give the corresponding diacid **8** bearing a quaternary carbon stereocenter in high yield. In addition, succinimide **3aa** can be oxidized by DEAD/K_2CO_3 to maleimide **9**, whose chirality is due only to the C–N axis, with retaining the stereochemical integrity (Eq. 6). The Diels–Alder reaction of maleimide **9** with cyclopentadiene smoothly proceeds with the same mode of stereoinduction by the C–N axis, giving cycloadduct **10** in high diastereomeric ratio (96/4).[14] The relative configurations of compounds **7** and **10** were confirmed by X-ray crystallographic analysis as illustrated in Figures 4 and 5, respectively.[15]



(5)



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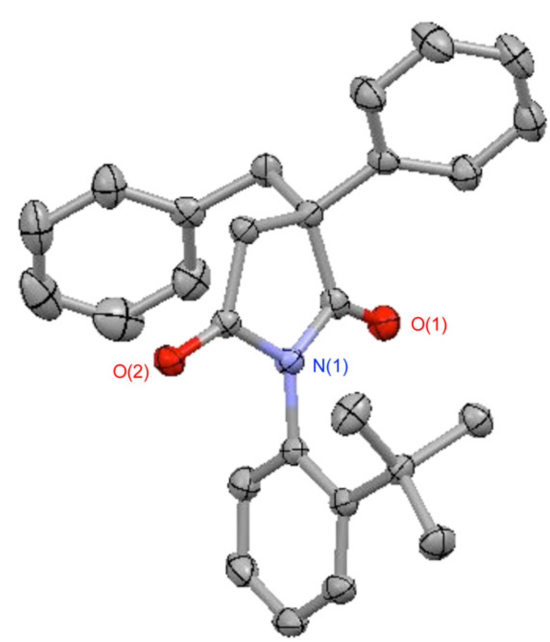

Figure 4. X-ray structure of (±)-**7** with thermal ellipsoids drawn at the 50% probability level.

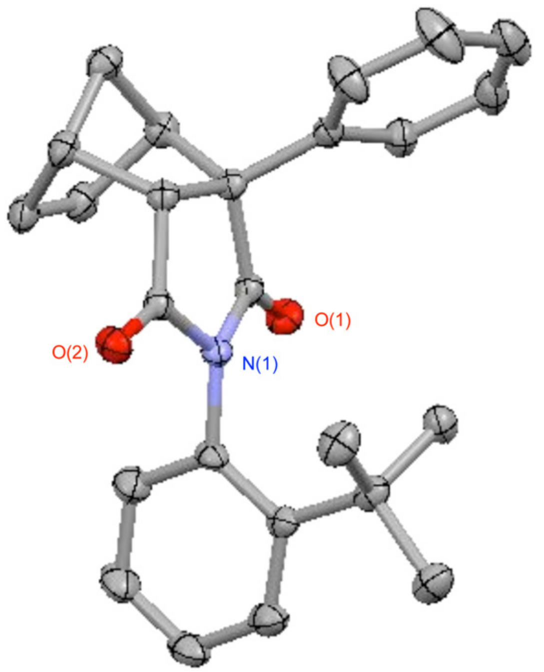

Figure 5. X-ray structure of (±)-**10** with thermal ellipsoids drawn at the 50% probability level.

3. Conclusions

We have successfully constructed chiral C–N axes by a rhodium-catalyzed asymmetric 1,4-addition. Both central chirality and axial chirality have been controlled at the same time using Rh/(*R*,*R*)-Ph-bod* catalyst with high stereoselectivity. This mode of stereoinduction has been utilized for preparing a planar-chiral ferrocene derivative as well. We have also demonstrated that the chiral C–N axes thus created can be used as a good template to control the stereochemistry in the subsequent alkylation and Diels–Alder reactions.

4. Experimental

4.1. General

All air- and moisture-sensitive manipulations were carried out with standard Schlenk techniques under nitrogen or in a glove box under argon. THF was purified by passing through a neutral alumina column under nitrogen. 1,4-Dioxane was distilled over benzophenone ketyl under nitrogen. DMF was distilled over CaH_2 under vacuum. CH_2Cl_2 was distilled over CaH_2 under nitrogen. Maleic anhydride (Nacalai Tesque), benzyl bromide (Wako Chemicals), diethyl azodicarboxylate (TCI; 40% in toluene), $LiAlH_4$ (Wako Chemicals), potassium carbonate (Kishida Reagents Chemicals), acetic acid (Wako Chemicals), and phenylboronic acid (TCI) were used as received. Other arylboronic acids were synthesized from the corresponding aryl bromides with $B(OMe)_3$ (Wako Chemicals). Cyclopentadiene was generated from dicyclopentadiene (Wako Chemicals) by pyrogenation. 1-(2-*tert*-Butylphenyl)maleimide (**1a**),[14] 4-bromo-2-*tert*-butylaniline,[16] 2-(1,1-dimethyl-2-methoxyethyl)aniline,[3b] ferrocobenzoquinone (**5**),[17] $[RhCl(C_2H_4)_2]_2$,[18] (*R*,*R*)-Bn-bod*,[8a] (*R*,*R*)-Ph-bod*,[8a] (*R*)-binap,[19] and (*R*)-phosphoramidite[20] were synthesized following the literature procedures. All other chemicals and solvents were purchased from Aldrich, Wako Chemicals, TCI, or Kanto Chemicals and used as received.

4.2. Synthesis of substrates

4.2.1. 1-(4-Bromo-2-*tert*-butylphenyl)maleimide (1b). A mixture of maleic anhydride (760 mg, 7.20 mmol) and 4-bromo-2-*tert*-butylaniline (560 mg, 2.40 mmol) in acetic acid (5.0 mL) was refluxed for 5 h. The solvent was removed under vacuum and the residue was chromatographed on silica gel with hexane/EtOAc=4/1 to afford compound **1b** as a white solid (325 mg, 1.04 mmol, 43% yield).

^{1}H NMR ($CDCl_3$): δ 7.70 (d, $^4J_{HH}$=2.1 Hz, 1H), 7.41 (dd, $^3J_{HH}$=8.2 Hz and $^4J_{HH}$=2.1 Hz, 1H), 6.89 (s, 2H), 6.77 (d, $^3J_{HH}$=8.2 Hz, 1H), 1.28 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 170.4, 151.9, 135.1, 132.9, 132.1, 130.5, 128.4, 124.2, 35.6, 31.3. Mp: 157–159 °C (Et_2O). Anal. Calcd for $C_{14}H_{14}BrNO_2$: C, 54.56; H, 4.58. Found: C, 54.79; H, 4.52.

4.2.2. 1-(2-(1,1-Dimethyl-2-methoxyethyl)phenyl)maleimide (1c). This was synthesized from 2-(1,1-dimethyl-2-methoxyethyl)aniline following the procedure for **1a**.[14] Yellow solid. Yield: 50%.

^{1}H NMR ($CDCl_3$): δ 7.58 (d, $^3J_{HH}$=8.1 Hz, 1H), 7.41 (t, $^3J_{HH}$=7.6 Hz, 1H), 7.30 (t, $^3J_{HH}$=7.6 Hz, 1H), 6.91 (d, $^3J_{HH}$=7.8 Hz, 1H), 6.89 (s, 2H), 3.35 (s, 2H), 3.27 (s, 3H), 1.30 (s, 6H). ^{13}C NMR ($CDCl_3$): δ 170.7, 146.4, 135.0, 131.4, 129.72, 129.69, 129.6, 127.6, 82.0, 59.2, 39.9, 26.5. Mp: 79–80 °C (Et_2O). Anal. Calcd for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61. Found: C, 69.74; H, 6.58.

4.3. Catalytic reactions

4.3.1. Procedure for Table 1, entry 1. A solution of $[RhCl(C_2H_4)_2]_2$ (1.9 mg, 9.8 μmol Rh) and (*R*)-binap (6.8 mg, 11 μmol) in 1,4-dioxane (0.50 mL) was stirred for 10 min at room temperature. KOH (0.10 mL, 60 μmol; 0.6 M aqueous) was added to it and the resulting solution was stirred for 3 min at room temperature. After addition of $PhB(OH)_2$ (73.2 mg, 0.60 mmol), the mixture was stirred for 3 min. Maleimide **1a** (45.9 mg, 0.20 mmol) was then added to this with additional 1,4-dioxane (0.50 mL) and the resulting mixture was stirred for 5 h at 50 °C. After passing through a pad of silica gel with EtOAc, the solvent was removed under vacuum, and the residue was purified by silica gel preparative TLC with hexane/EtOAc=4/1 to afford **3aa** as a white solid (40.1 mg, 0.13 mmol, 65% yield) and **3aa′** as a white solid (21.8 mg, 0.071 mmol, 35% yield).

The ee of **3aa** was determined on a Daicel Chiralcel OD-H column with hexane/2-propanol=80/20, flow=0.8 mL/min. Retention times: 13.7 min [(3*S*,*R*$_a$)-enantiomer], 15.3 min [(3*R*,*S*$_a$)-enantiomer]. 83% ee. The absolute configuration was assigned by analogy with Table 2, entry 5.

3aa: ^{1}H NMR ($CDCl_3$): δ 7.60 (dd, $^3J_{HH}$=8.2 Hz and $^4J_{HH}$=1.5 Hz, 1H), 7.42 (t, $^3J_{HH}$=7.0 Hz, 2H), 7.41–7.38

(m, 1H), 7.34 (d, $^3J_{HH}$=7.3 Hz, 1H), 7.32 (dd, $^3J_{HH}$=7.3 Hz and $^4J_{HH}$=1.5 Hz, 2H), 7.29 (td, $^3J_{HH}$=7.3 Hz and $^4J_{HH}$=1.5 Hz, 1H), 6.87 (dd, $^3J_{HH}$=7.9 Hz and $^4J_{HH}$=1.5 Hz, 1H), 4.19 (dd, $^3J_{HH}$=10.1 and 4.5 Hz, 1H), 3.39 (dd, $^2J_{HH}$=18.6 Hz and $^3J_{HH}$=10.1 Hz, 1H), 3.03 (dd, $^2J_{HH}$=18.6 Hz and $^3J_{HH}$=4.6 Hz, 1H), 1.35 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 177.7, 176.4, 148.0, 137.1, 130.7, 130.3, 129.8, 129.3, 128.9, 128.0, 127.4, 46.3, 37.6, 35.7, 31.6. Anal. Calcd for $C_{20}H_{21}NO_2$: C, 78.15; H, 6.89. Found: C, 77.92; H, 6.90.

The ee of **3aa′** was determined on a Daicel Chiralcel OD-H column with hexane/2-propanol=80/20, flow=0.8 mL/min. Retention times: 15.1 min [(3*S*,*S*$_a$)-enantiomer], 25.9 min [(3*R*,*R*$_a$)-enantiomer]. 75% ee. $[\alpha]_D^{20}$ +15.8 (*c* 2.02, $CHCl_3$). The absolute configuration was determined to be (3*S*,*S*$_a$) by reducing it to pyrrolidine **4** (see below).

3aa′: ^{1}H NMR ($CDCl_3$): δ 7.57 (dd, $^3J_{HH}$=7.9 Hz and $^4J_{HH}$=1.2 Hz, 1H), 7.41 (t, ^3JHH=7.3 Hz, 2H), 7.40–7.32 (m, 4H), 7.29 (td, $^3J_{HH}$=7.9 Hz and $^4J_{HH}$=1.2 Hz, 1H), 6.88 (dd, $^3J_{HH}$=7.9 Hz and $^4J_{HH}$=1.2 Hz, 1H), 4.22 (dd, $^3J_{HH}$=9.4 and 5.8 Hz, 1H), 3.36 (dd, $^2J_{HH}$=18.6 Hz and $^3J_{HH}$=9.4 Hz, 1H), 3.10 (dd, $^2J_{HH}$=18.6 Hz and $^3J_{HH}$=5.8 Hz, 1H), 1.29 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 177.2, 176.2, 148.2, 136.0, 130.83, 130.78, 129.7, 129.1, 128.6, 128.0, 127.7, 127.5, 46.5, 37.0, 35.5, 31.5. Anal. Calcd for $C_{20}H_{21}NO_3$: C, 78.15; H, 6.89. Found: C, 77.94; H, 7.00.

4.3.2. Procedure for Eq. 2. A mixture of (3*R*,*S*$_a$)-**3aa** (82.3 mg, 0.27 mmol; 83% ee) and $LiAlH_4$ (60.7 mg, 1.60 mmol) in THF (5.0 mL) was stirred for 24 h at room temperature. The reaction was quenched with water and the precipitate was filtered off through a pad of Celite with EtOAc. The solvent was removed under vacuum and the residue was purified by silica gel preparative TLC with hexane/EtOAc=20/1 to afford (*R*)-**4** as a colorless oil (23.8 mg, 0.085 mmol, 31% yield). $[\alpha]_D^{20}$ +31.1 (*c* 0.77, $CHCl_3$).

^{1}H NMR ($CDCl_3$): δ 7.44 (dd, $^3J_{HH}$=7.9 Hz and $^4J_{HH}$=1.5 Hz, 1H), 7.38–7.31 (m, 5H), 7.26–7.19 (m, 2H), 7.13 (td, $^3J_{HH}$=7.9 Hz and $^4J_{HH}$=1.5 Hz, 1H), 3.52 (quint, $^3J_{HH}$=8.5 Hz, 1H), 3.42 (dd, $^2J_{HH}$=9.1 Hz and $^3J_{HH}$=7.9 Hz, 1H), 3.27–3.20 (m, 2H), 3.12 (t, J_{HH}=8.5 Hz, 1H), 2.47–2.39 (m, 1H), 2.10 (dq, $^2J_{HH}$=12.8 Hz and $^3J_{HH}$=7.6 Hz, 1H), 1.46 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 151.4, 149.1, 144.8, 128.4, 127.4, 127.1, 127.0, 126.6, 126.2 125.7, 64.1, 57.0, 44.4, 35.4, 34.0, 31.1. Anal. Calcd for $C_{20}H_{25}N$: C, 85.97; H, 9.02. Found: C, 86.04; H, 9.28.

4.3.3. Procedure for Eq. 3. A mixture of **3aa′** (49.0 mg, 0.16 mmol, 75% ee) and $LiAlH_4$ (36.0 mg, 0.96 mmol) in THF (3.0 mL) was stirred for 60 h at room temperature. The reaction was quenched with water and the precipitate was filtered off through a pad of Celite with EtOAc. The solvent was removed under vacuum and the residue was purified by silica gel preparative TLC with hexane/EtOAc=20/1 to afford **4** as a colorless oil (11.8 mg, 0.042 mmol, 26% yield). $[\alpha]_D^{20}$ −31.0 (*c* 0.60, $CHCl_3$).

Based on the sign of the optical rotation, **4** obtained from **3aa′** has (*S*)-configuration, thereby establishing the absolute configuration of **3aa′** to be (3*S*,*S*$_a$).

4.3.4. General procedure for Table 2. A solution of $[RhCl(C_2H_4)_2]_2$ (1.9 mg, 9.8 μmol Rh) and (*R*,*R*)-Ph-bod* (2.8 mg, 11 μmol) in 1,4-dioxane (0.50 mL) was stirred for 10 min at room temperature. KOH (0.10 mL, 60 μmol; 0.6 M aqueous) was added to it and the resulting solution was stirred for 3 min at room temperature. After addition of $ArB(OH)_2$ (0.60 mmol), the mixture was stirred for 3 min. Maleimide (0.20 mmol) was then added to this with additional 1,4-dioxane (0.50 mL) and the resulting mixture was stirred for 5 h at 60 °C. After passing through a pad of silica gel with EtOAc, the solvent was removed under vacuum and the residue was purified by silica gel preparative TLC with hexane/EtOAc=4/1 to afford compound **3**.

4.3.4.1. Entry 1. White solid; 96% yield of **3aa** (dr=96/4 by crude ^{1}H NMR). 99% ee. $[\alpha]_D^{20}$ +18.6 (*c* 0.65, $CHCl_3$). The absolute configuration was assigned by analogy with Table 2, entry 5.

4.3.4.2. Entry 2. White solid; 95% yield of **3ab** (dr=98/2 by crude ^{1}H NMR). The ee was determined on a Daicel Chiralcel OD-H column with hexane/2-propanol=80/20, flow=0.8 mL/min. Retention times: 17.8 min [(3*R*,*S*$_a$)-enantiomer], 28.6 min [(3*S*,*R*$_a$)-enantiomer]. 97% ee. $[\alpha]_D^{20}$ +18.2 (*c* 1.02, $CHCl_3$). The absolute configuration was assigned by analogy with Table 2, entry 5.

^{1}H NMR ($CDCl_3$): δ 7.60 (dd, $^3J_{HH}$=8.2 Hz and $^4J_{HH}$=1.4 Hz, 1H), 7.39 (ddd, $^3J_{HH}$=8.2 and 7.3 Hz and $^4J_{HH}$=1.5 Hz, 1H), 7.28 (td, $^3J_{HH}$=7.5 Hz and $^4J_{HH}$=1.4 Hz, 1H), 7.24 (d, $^3J_{HH}$=8.8 Hz, 2H), 6.94 (d, $^3J_{HH}$=8.8 Hz, 2H), 6.85 (dd, $^3J_{HH}$=7.7 Hz and $^4J_{HH}$=1.4 Hz, 1H), 4.14 (dd, $^3J_{HH}$=9.8 and 4.6 Hz, 1H), 3.82 (s, 3H), 3.36 (dd, $^2J_{HH}$=18.6 Hz and $^3J_{HH}$=9.9 Hz, 1H), 2.97 (dd, $^2J_{HH}$=18.6 Hz and $^3J_{HH}$=4.6 Hz, 1H), 1.35 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 178.0, 176.4, 159.3, 148.0, 130.7, 130.3, 129.8, 129.0, 128.9, 128.5, 127.4, 114.7, 55.3, 45.5, 37.7, 35.7, 31.6. Anal. Calcd for $C_{21}H_{23}NO_3$: C, 74.75; H, 6.87. Found: C, 74.57; H, 6.94.

4.3.4.3. Entry 3. White solid; 92% yield of **3ac** (dr=96/4 by crude ^{1}H NMR). The ee was determined on a Daicel Chiralpak AD-H column with hexane/2-propanol=80/20, flow=0.5 mL/min. Retention times: 45.9 min [(3*R*,*S*$_a$)-enantiomer], 66.6 min [(3*S*,*R*$_a$)-enantiomer]. 98% ee. $[\alpha]_D^{20}$ +2.8 (*c* 0.62, $CHCl_3$). The absolute configuration was assigned by analogy with Table 2, entry 5.

^{1}H NMR ($CDCl_3$): δ 7.60 (dd, $^3J_{HH}$=8.2 Hz and $^4J_{HH}$=1.5 Hz, 1H), 7.40 (ddd, $^3J_{HH}$=8.2 and 7.3 Hz and $^4J_{HH}$=1.5 Hz, 1H), 7.30 (dd, $^3J_{HH}$=8.8 Hz and $^4J_{HF}$=4.9 Hz, 2H), 7.29 (td, $^3J_{HH}$=7.3 Hz and $^4J_{HH}$=1.5 Hz, 1H), 7.11 (t, ^3J=8.5 Hz, 2H), 6.85 (dd, $^3J_{HH}$=7.6 Hz and $^4J_{HH}$=1.5 Hz, 1H), 4.18 (dd, $^3J_{HH}$=10.0 and 4.9 Hz, 1H), 3.36 (dd, $^2J_{HH}$=18.6 Hz and $^3J_{HH}$=10.0 Hz, 1H), 2.97 (dd, $^2J_{HH}$=18.6 Hz and $^3J_{HH}$=4.9 Hz, 1H), 1.34 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 177.5, 176.0, 162.4 (d, $^1J_{CF}$=267 Hz), 148.0, 132.7 (d, $^4J_{CF}$=4.1 Hz), 130.7, 130.2, 129.9, 129.1 (d, $^3J_{CF}$=8.3 Hz), 129.0, 127.5, 116.2 (d, $^2J_{CF}$=21.7 Hz), 45.5, 37.5, 35.7, 31.6. Anal. Calcd for $C_{20}H_{20}FNO_2$: C, 73.83; H, 6.20. Found: C, 73.83; H, 6.19.

4.3.4.4. Entry 4. Yield: 88% of **3ad** (dr=93/7 by crude ^{1}H NMR). The ee was determined on a Daicel Chiralcel

OD-H column with hexane/2-propanol=80/20, flow=1.0 mL/min. Retention times: 13.4 min [(3*R*,*S*$_a$)-enantiomer], 22.3 min [(3*S*,*R*$_a$)-enantiomer]. 98% ee. $[\alpha]_D^{20}$ +26.4 (*c* 1.10, $CHCl_3$). The absolute configuration was assigned by analogy with Table 2, entry 5.

^{1}H NMR ($CDCl_3$): δ 7.60 (dd, $^3J_{HH}$=8.0 Hz and $^4J_{HH}$=1.2 Hz, 1H), 7.53 (d, $^3J_{HH}$=8.3 Hz, 2H), 7.40 (td, $^3J_{HH}$=8.1 Hz and $^4J_{HH}$=1.5 Hz, 1H), 7.28 (td, $^3J_{HH}$=7.6 Hz and $^4J_{HH}$=1.4 Hz, 1H), 7.20 (d, $^3J_{HH}$=8.3 Hz, 2H), 6.84 (dd, $^3J_{HH}$=7.8 Hz and $^4J_{HH}$=1.5 Hz, 1H), 4.15 (dd, $^3J_{HH}$=9.7 and 4.9 Hz, 1H), 3.37 (dd, $^2J_{HH}$=18.6 Hz and $^3J_{HH}$=9.8 Hz, 1H), 2.95 (dd, $^2J_{HH}$=18.6 Hz and $^3J_{HH}$=4.9 Hz, 1H), 1.33 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 177.2, 175.9, 147.9, 135.8, 132.3, 130.6, 130.1, 129.9, 129.1, 129.0, 127.4, 122.1, 45.6, 37.2, 35.6, 31.6. Anal. Calcd for $C_{20}H_{20}BrNO_2$: C, 62.19; H, 5.22. Found: C, 62.00; H, 4.92.

4.3.4.5. Entry 5. White solid; 88% yield of **3ae** (dr=93/7 by crude ^{1}H NMR). The ee was determined on a Daicel Chiralpak AD-H column with hexane/2-propanol=80/20, flow=1.0 mL/min. Retention times: 9.4 min [(3*R*,*S*$_a$)-enantiomer], 11.9 min [(3*S*,*R*$_a$)-enantiomer]. 96% ee. $[\alpha]_D^{20}$ +6.2 (*c* 0.41, $CHCl_3$). Recrystallization from hexane/Et_2O afforded single crystals and the absolute configuration was determined to be (3*R*,*S*$_a$) by X-ray analysis.

^{1}H NMR ($CDCl_3$): δ 7.61 (dd, $^3J_{HH}$=8.2 Hz and $^4J_{HH}$=1.5 Hz, 1H), 7.41 (td, $^3J_{HH}$=7.3 Hz and $^4J_{HH}$=1.5 Hz, 1H), 7.38–7.32 (m, 3H), 7.30 (td, $^3J_{HH}$=7.3 Hz and $^4J_{HH}$=1.2 Hz, 1H), 7.21 (dt, $^3J_{HH}$=6.7 Hz and $^4J_{HH}$=1.8 Hz, 1H), 6.87 (dd, $^3J_{HH}$=7.6 Hz and $^4J_{HH}$=1.5 Hz, 1H), 4.17 (dd, $^3J_{HH}$=10.0 and 4.8 Hz, 1H), 3.39 (dd, $^2J_{HH}$=18.6 Hz and $^3J_{HH}$=10.1 Hz, 1H), 2.99 (dd, $^2J_{HH}$=18.6 Hz and $^3J_{HH}$=4.9 Hz, 1H), 1.34 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 177.1, 175.8, 148.0, 138.8, 135.1, 130.7, 130.5, 130.1, 130.0, 129.0, 128.3, 127.9, 127.5, 125.6, 45.8, 37.3, 35.7, 31.7. Anal. Calcd for $C_{20}H_{20}ClNO_2$: C, 70.27; H, 5.90. Found: C, 70.34; H, 5.94.

4.3.4.6. Entry 6. White solid; 93% yield as a mixture of **3af**/**3af′**=97/3 (dr=96/4 by crude ^{1}H NMR). The ee was determined on a Daicel Chiralcel OD-H column with hexane/2-propanol=80/20, flow=0.8 mL/min. Retention times: 22.8 min [(3*R*,*S*$_a$)-enantiomer], 40.3 min [(3*S*,*R*$_a$)-enantiomer]. 97% ee. $[\alpha]_D^{20}$ +31.3 (*c* 0.98, $CHCl_3$). The absolute configuration was assigned by analogy with Table 2, entry 5.

^{1}H NMR ($CDCl_3$): δ 7.91 (d, $^3J_{HH}$=8.5 Hz, 1H), 7.86–7.84 (m, 2H), 7.80 (s, 1H), 7.61 (d, $^3J_{HH}$=8.2 Hz, 1H), 7.53–7.49 (m, 2H), 7.41 (t, $^3J_{HH}$=7.3 Hz, 1H), 7.40 (d, $^3J_{HH}$=8.2 Hz, 1H), 7.30 (t, $^3J_{HH}$=7.6 Hz, 1H), 6.91 (d, $^3J_{HH}$=7.6 Hz, 1H), 4.37 (dd, $^3J_{HH}$=9.7 and 4.6 Hz, 1H), 3.46 (dd, $^2J_{HH}$=18.6 Hz and $^3J_{HH}$=9.7 Hz, 1H), 3.12 (dd, $^2J_{HH}$=18.6 Hz and $^3J_{HH}$=4.6 Hz, 1H), 1.37 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 177.7, 176.4, 148.0, 134.2, 133.4, 132.8, 130.7, 130.3, 129.8, 129.4, 129.0, 127.8, 127.7, 127.5, 126.67, 126.65, 126.4, 124.8, 46.4, 37.5, 35.7, 31.7. Anal. Calcd for $C_{24}H_{23}NO_2$: C, 80.64; H, 6.49. Found: C, 80.53; H, 6.53.

4.3.4.7. Entry 7. White solid; 97% yield of **3ag** (dr=98/2 by crude ^{1}H NMR). The ee was determined on a Daicel Chiralcel OJ-H column with hexane/2-propanol=90/10, flow=0.8 mL/min. Retention times: 57.9 min [(3*S*,*R*$_a$)-enantiomer], 89.3 min [(3*R*,*S*$_a$)-enantiomer]. 97% ee. $[\alpha]_D^{20}$ +43.0 (*c* 1.0, $CHCl_3$). The absolute configuration was assigned by analogy with Table 2, entry 5.

^{1}H NMR ($CDCl_3$): δ 7.61 (dd, $^3J_{HH}$=8.2 Hz and $^4J_{HH}$=1.2 Hz, 1H), 7.41 (ddd, $^3J_{HH}$=8.2 and 7.3 Hz and $^4J_{HH}$=1.5 Hz, 1H), 7.31 (td, $^3J_{HH}$=7.3 Hz and $^4J_{HH}$=1.5 Hz, 1H), 7.26–7.24 (m, 3H), 7.18–7.15 (m, 1H), 6.91 (dd, $^3J_{HH}$=7.6 Hz and $^4J_{HH}$=1.5 Hz, 1H), 4.38 (dd, $^3J_{HH}$=10.1 and 4.5 Hz, 1H), 3.39 (dd, $^2J_{HH}$=18.6 Hz and $^3J_{HH}$=10.1 Hz, 1H), 2.87 (dd, $^2J_{HH}$=18.6 Hz and $^3J_{HH}$=4.5 Hz, 1H), 2.43 (s, 3H), 1.36 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 178.1, 176.4, 148.0, 136.3, 136.0, 131.2, 130.6, 130.4, 129.8, 129.0, 128.0, 127.5, 126.9, 126.8, 43.8, 37.5, 35.7, 31.7, 19.9. Anal. Calcd for $C_{21}H_{23}NO_2$: C, 78.47; H, 7.21. Found: C, 78.45; H, 7.15.

4.3.4.8. Entry 8. White solid; 81% yield of **3ba** (dr=91/9 by crude ^{1}H NMR). The ee was determined on a Daicel Chiralcel OD-H column with hexane/2-propanol=95/5, flow=1.0 mL/min. Retention times: 22.6 min [(3*S*,*R*$_a$)-enantiomer], 34.0 min [(3*R*,*S*$_a$)-enantiomer]. 99% ee. $[\alpha]_D^{20}$ +11.9 (*c* 0.39, $CHCl_3$). The absolute configuration was assigned by analogy with Table 2, entry 5.

^{1}H NMR ($CDCl_3$): δ 7.72 (d, $^4J_{HH}$=2.1 Hz, 1H), 7.43–7.40 (m, 3H), 7.28 (t, $^3J_{HH}$=7.3 Hz, 1H), 7.30 (d, $^3J_{HH}$=7.0 Hz, 2H), 6.74 (d, $^3J_{HH}$=8.2 Hz, 1H), 4.19 (dd, $^3J_{HH}$=9.7 and 4.6 Hz, 1H), 3.39 (dd, $^2J_{HH}$=18.6 Hz and $^3J_{HH}$=9.7 Hz, 1H), 3.02 (dd, $^2J_{HH}$=18.6 Hz and $^3J_{HH}$=4.6 Hz, 1H), 1.34 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 177.4, 176.0, 150.4, 136.8, 132.34, 132.30, 130.6, 129.5, 129.3, 128.1, 127.4, 124.2, 46.3, 37.5, 35.9, 31.4. Anal. Calcd for $C_{20}H_{20}BrNO_2$: C, 62.19; H, 5.22. Found: C, 62.39; H, 5.20.

4.3.4.9. Entry 9. White solid; 96% yield of **3ca** (dr=97/3 by crude ^{1}H NMR). The ee was determined on a Daicel Chiralcel OJ-H column with hexane/2-propanol=80/20, flow=1.0 mL/min. Retention times: 108.9 min [(3*R*,*S*$_a$)-enantiomer], 146.8 min [(3*S*,*R*$_a$)-enantiomer]. 99% ee. $[\alpha]_D^{20}$ +21.3 (*c* 0.50, $CHCl_3$). The absolute configuration was assigned by analogy with Table 2, entry 5.

^{1}H NMR ($CDCl_3$): δ 7.59 (dd, $^3J_{HH}$=8.2 Hz and $^4J_{HH}$=1.5 Hz, 1H), 7.43–7.36 (m, 3H), 7.35 (t, $^3J_{HH}$=7.3 Hz, 1H), 7.33–7.29 (m, 3H), 6.89 (dd, $^3J_{HH}$=7.9 Hz and $^4J_{HH}$=1.5 Hz, 1H), 4.19 (dd, $^3J_{HH}$=9.7 and 4.6 Hz, 1H), 3.39 (dd, $^2J_{HH}$=18.6 Hz and $^3J_{HH}$=9.7 Hz, 1H), 3.39 (s, 2H), 3.30 (s, 3H), 3.00 (dd, $^2J_{HH}$=18.6 Hz and $^3J_{HH}$=4.6 Hz, 1H), 1.36 (s, 6H). ^{13}C NMR ($CDCl_3$): δ 177.7, 176.3, 145.0, 137.1, 130.8, 129.8, 129.6, 129.3, 128.0, 127.7, 127.4, 81.9, 59.3, 46.2, 40.1, 37.6, 26.48, 26.47. Anal. Calcd for $C_{21}H_{23}NO_3$: C, 74.75; H, 6.87. Found: C, 74.70; H, 6.86.

4.3.5. Procedure for Eq. 4. A solution of $[RhCl(C_2H_4)_2]_2$ (3.0 mg, 16 μmol Rh) and (*R*,*R*)-Bn-bod* (4.8 mg, 18 μmol) in 1,4-dioxane (0.30 mL) was stirred for 10 min at room temperature. KOH (60 μL, 60 μmol; 1.0 M aqueous) was added to it and the resulting solution was stirred for 10 min at room temperature. After addition of $PhB(OH)_2$

(73.2 mg, 0.60 mmol), the mixture was stirred for 5 min. Ferrocobenzoquinone **5** (53.2 mg, 0.20 mmol) was then added to this with additional 1,4-dioxane (0.30 mL) and the resulting mixture was stirred for 48 h at 60 °C. After passing through a pad of silica gel with EtOAc, the solvent was removed under vacuum and the residue was chromatographed on silica gel with hexane/EtOAc=2/1 to afford compound **6** as a dark red solid (60.6 mg, 0.176 mmol, 88% yield (dr=94/6)). The ee value of the major diastereomer was determined on a Daicel Chiralpak AS column with hexane/2-propanol=80/20, flow=1.0 mL/min. Retention times: 16.4 min [(R,R_p)-enantiomer], 23.1 min [(S,S_p)-enantiomer]. 96% ee. $[\alpha]_D^{20}$ +75.6 (c 0.52, CH_2Cl_2). Recrystallization from hexane/CH_2Cl_2 afforded single crystals and the absolute configuration was determined to be (R,R_p) by X-ray analysis.

^{1}H NMR ($CDCl_3$): δ 7.32–7.23 (m, 5H), 5.24 (s, 2H), 4.91 (s, 1H), 4.36 (s, 5H), 4.36–4.32 (m, 1H), 3.48 (dd, $^2J_{HH}$=17.0 Hz and $^3J_{HH}$=6.1 Hz, 1H), 3.13 (dd, $^2J_{HH}$=17.1 Hz and $^3J_{HH}$=4.9 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 200.9, 200.3, 137.9, 128.8, 127.7, 127.4, 78.4, 77.8, 75.6, 72.4, 71.9, 70.5, 54.1, 44.5. Anal. Calcd for $C_{20}H_{16}FeO_2$: C, 69.79; H, 4.69. Found: C, 70.03; H, 4.64.

4.3.6. Procedure for Eq. 5. Benzyl bromide (17.8 μL, 0.15 mmol) was added to a mixture of **3aa** (30.7 mg, 0.10 mmol) and K_2CO_3 (69.1 mg, 0.50 mmol) in DMF (0.50 mL), and the resulting mixture was stirred for 12 h at room temperature. After addition of H_2O (10 mL), the mixture was extracted with EtOAc. The organic phase was washed with NaCl (saturated, aqueous), dried over $MgSO_4$, filtered, and concentrated under vacuum. The residue was purified by silica gel preparative TLC with hexane/EtOAc=5/1 to afford **7** as a white solid (34.2 mg, 0.086 mmol, 86% yield). The ee was determined on a Daicel Chiralcel OD-H column with hexane/2-propanol=95/5, flow=1.0 mL/min. Retention times: 15.0 min [(3S,S_a)-enantiomer], 18.2 min [(3R,R_a)-enantiomer]. 99% ee. $[\alpha]_D^{20}$ +28.3 (c 1.48, $CHCl_3$). Recrystallization of (±)-**7** from hexane/Et_2O afforded single crystals and the relative configuration was determined by X-ray analysis.

^{1}H NMR ($CDCl_3$): δ 7.66 (dd, $^3J_{HH}$=7.6 Hz, 2H), 7.49 (dd, $^3J_{HH}$=8.2 Hz and $^4J_{HH}$=1.2 Hz, 1H), 7.43 (t, $^3J_{HH}$=7.9 Hz, 2H), 7.37–7.34 (m, 4H), 7.32 (td, $^3J_{HH}$=7.3 Hz and $^4J_{HH}$=1.2 Hz, 1H), 7.23–7.21 (m, 2H), 7.14 (dd, $^3J_{HH}$=7.3 Hz and $^4J_{HH}$=1.5 Hz, 1H), 6.01 (dd, $^3J_{HH}$=7.9 Hz and $^4J_{HH}$=1.5 Hz, 1H), 3.61 (d, $^2J_{HH}$=13.4 Hz, 1H), 3.33 (s, 2H), 3.13 (d, $^2J_{HH}$=13.4 Hz, 1H), 1.12 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 179.1, 175.1, 148.1, 140.7, 135.4, 130.7, 130.63, 130.59, 129.6, 128.9, 128.8, 128.3, 127.73, 127.69, 127.2, 126.4, 53.5, 47.2, 40.2, 35.3, 31.4. Anal. Calcd for $C_{27}H_{27}NO_2$: C, 81.58; H, 6.85. Found: C, 81.36; H, 6.93.

A solution of **7** (30.0 mg, 0.076 mmol) in acetic acid (0.40 mL) and concd HCl (0.40 mL) was heated at 120 °C for 6 days. After cooled to room temperature, the solution was basified with NaOH (2.0 M aqueous) until pH=14, and the mixture was then washed with Et_2O. The aqueous phase was acidified with HCl (3.0 M aqueous) to pH=1, and the mixture was extracted with EtOAc. The organic phase was washed with NaCl (saturated, aqueous), dried over Na_2SO_4, filtered, and concentrated under vacuum. The residue was recrystallized from toluene to give **8** as a white solid (19.6 mg, 0.069 mmol, 90% yield). $[\alpha]_D^{20}$ −117 (c 0.93, MeOH).

^{1}H NMR ($CDCl_3$): δ 7.36–7.32 (m, 3H), 7.21 (d, $^3J_{HH}$=7.5 Hz, 2H), 7.15 (t, $^3J_{HH}$=7.3 Hz, 1H), 7.10 (t, $^3J_{HH}$=7.3 Hz, 2H), 6.59 (d, $^3J_{HH}$=7.0 Hz, 2H), 3.67 (d, $^2J_{HH}$=14.0 Hz, 1H), 3.46 (d, $^2J_{HH}$=14.0 Hz, 1H), 3.29 (d, $^2J_{HH}$=17.4 Hz, 1H), 2.89 (d, $^2J_{HH}$=17.7 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 181.3, 178.4, 139.6, 136.1, 130.5, 128.6, 127.9, 127.7, 126.7, 126.5, 52.1, 42.4, 37.1. HRMS (ESI-TOF) Calcd for $C_{17}H_{15}O_4$ (M−H$^+$): 283.0965, found: 283.0962.

4.3.7. Procedure for Eq. 6. Diethyl azodicarboxylate (68.0 μL, 0.15 mmol) was added to a mixture of **3aa** (30.7 mg, 0.10 mmol) and K_2CO_3 (69.1 mg, 0.50 mmol) in DMF (0.50 mL), and the resulting mixture was stirred for 4 h at room temperature. After addition of H_2O (10 mL), the mixture was extracted with EtOAc. The organic phase was washed with NaCl (saturated, aqueous), dried over $MgSO_4$, filtered, and concentrated under vacuum. The residue was purified by silica gel preparative TLC with hexane/EtOAc=5/1 to afford **9** as a white solid (20.2 mg, 0.066 mmol, 66% yield). The ee was determined on a Daicel Chiralcel OD-H column with hexane/2-propanol=95/5, flow=1.0 mL/min. Retention times: 12.3 min [(S)-enantiomer], 19.9 min [(R)-enantiomer]. 98% ee. $[\alpha]_D^{20}$ +19.2 (c 0.84, $CHCl_3$).

^{1}H NMR ($CDCl_3$): δ 8.00 (dd, $^3J_{HH}$=7.6 Hz and $^4J_{HH}$=2.1 Hz, 2H), 7.61 (dd, $^3J_{HH}$=7.9 Hz and $^4J_{HH}$=1.2 Hz, 1H), 7.50–7.46 (m, 3H), 7.41 (td, $^3J_{HH}$=7.3 Hz and $^4J_{HH}$=1.5 Hz, 1H), 7.29 (td, $^3J_{HH}$=7.6 Hz and $^4J_{HH}$=1.2 Hz, 1H), 6.98 (dd, $^3J_{HH}$=7.6 Hz and $^4J_{HH}$=1.2 Hz, 1H), 6.92 (s, 1H), 1.33 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 170.7, 170.5, 149.6, 144.6, 131.5, 131.4, 129.8, 129.6, 129.0, 128.8, 128.7, 128.6, 127.3, 124.6, 35.5, 31.6. Anal. Calcd for $C_{20}H_{19}NO_2$: C, 78.66; H, 6.27. Found: C, 78.40; H, 6.48.

A solution of **9** (19.4 mg, 0.063 mmol) and cyclopentadiene (37 μL, 0.44 mmol) in CH_2Cl_2 (0.50 mL) was stirred for 24 h at room temperature. After removal of the solvent under vacuum, the residue was purified by silica gel preparative TLC with hexane/EtOAc=5/1 to afford **10** as a white solid (21.8 mg, 0.058 mmol, 92% yield). The ee was determined on a Daicel Chiralpak AD-H column with hexane/2-propanol=95/5, flow=1.0 mL/min. Retention times: 13.7, 24.3 min. 98% ee. $[\alpha]_D^{20}$ +4.2 (c 0.46, $CHCl_3$). Recrystallization of (±)-**10** from Et_2O afforded single crystals and the relative configuration was determined by X-ray analysis.

^{1}H NMR ($CDCl_3$): δ 7.69 (d, $^3J_{HH}$=7.6 Hz, 2H), 7.46 (dd, $^3J_{HH}$=8.2 Hz and $^4J_{HH}$=1.2 Hz, 1H), 7.42 (t, $^3J_{HH}$=7.9 Hz, 2H), 7.35–7.30 (m, 2H), 7.23 (td, $^3J_{HH}$=7.6 Hz and $^4J_{HH}$=1.2 Hz, 1H), 6.78 (dd, $^3J_{HH}$=7.6 Hz and $^4J_{HH}$=1.5 Hz, 1H), 6.54 (dd, $^3J_{HH}$=5.5 and 3.0 Hz, 1H), 6.46 (dd, $^3J_{HH}$=5.5 and 2.7 Hz, 1H), 3.91 (d, $^3J_{HH}$=4.9 Hz, 1H), 3.65 (br s, 1H), 3.60 (br s, 1H), 1.77 (d, $^2J_{HH}$=9.1 Hz, 1H), 1.70 (d, $^2J_{HH}$=9.1 Hz, 1H), 1.08 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 178.5, 177.6, 148.0, 137.3, 136.9, 136.2, 131.3, 130.7, 129.5, 128.8, 128.2, 127.9, 127.7, 127.2, 60.6, 53.3, 50.8, 50.5, 46.0, 35.3, 31.2. Anal. Calcd for $C_{25}H_{25}NO_2$: C, 80.83; H, 6.78. Found: C, 80.99; H, 6.78.

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