Chiral Brønsted acid catalyzed asymmetric Friedel–Crafts alkylation reaction of indoles with α,β-unsaturated ketones: short access to optically active 2- and 3-substituted indole derivatives

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The asymmetric Friedel–Crafts alkylation reaction of indoles with α,β-unsaturated ketones catalyzed by chiral phosphoric acid is reported. A wide range of indoles and 4,7-dihydroindoles were allowed to react with α,β-unsaturated ketones to give the corresponding 1,4-adducts in good to high chemical yields and with excellent enantioselectivities.

Introduction

The indole skeleton is frequently encountered in biologically active compounds and pharmaceuticals, such as rhazinoline, (−)-eudistomin C, scholarisine A, and (+)-vinblastine (Fig. 1).[1] Because of their important biological activities, the development of new approaches for the synthesis of *enantio*-enriched indole derivatives has been emphasized.[2] The enantioselective Friedel–Crafts alkylation reaction of indole constitutes an important method for the preparation of optically active 3-substituted indole derivatives.[3] Recently, the asymmetric Friedel–Crafts reaction of indole with α,β-unsaturated carbonyl compounds, in particular, has attracted much attention and a range of reactions exploiting transition metal catalysts and organocatalysts have been developed.[4,5]

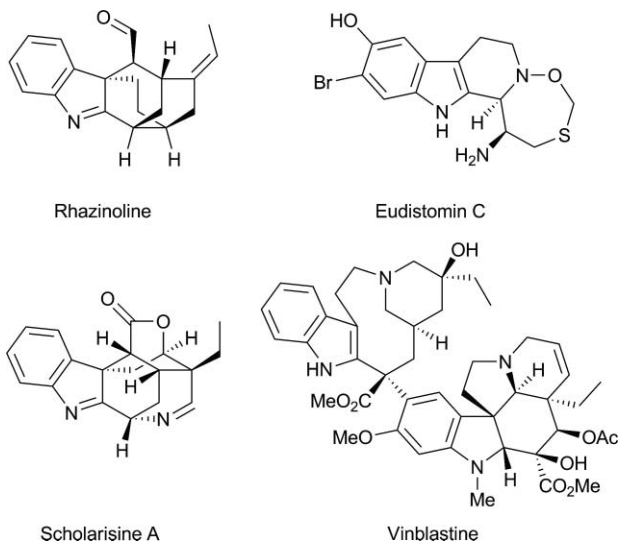


Fig. 1 Bioactive molecules bearing indole skeleton.

We found that chiral phosphoric acids **3** synthesized from (*R*)-BINOL worked as efficient chiral catalysts for the reaction with imines, thereby demonstrating that **3** are efficient activators of imines (Fig. 2).[6] Since then, phosphoric acid chemistry has been extensively studied with its main focus being on the reaction with imines.[7,8] Recent studies have shown that aziridine, enecarbamate, nitroalkene, and carbonyl compounds are also suitable substrates.[9]

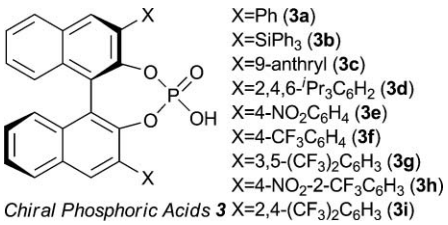
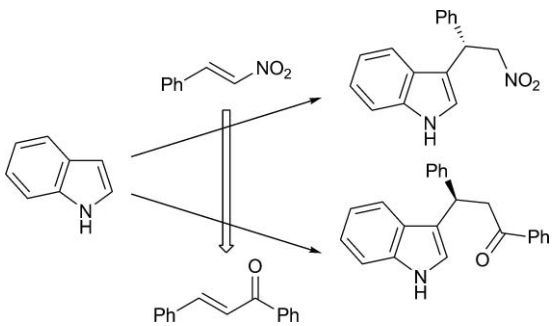


Fig. 2 Chiral phosphoric acid catalysts.

Encouraged by our success in the Friedel–Crafts reaction of indoles with nitroalkenes,[9g] we envisioned that 1,3-diaryl α,β-unsaturated ketone would be a promising carbonyl reaction partner (Scheme 1).[5]



Scheme 1 This work.

Although Zhou and co-workers already reported the asymmetric Friedel–Crafts alkylation reaction of indole derivatives with 1,3-diaryl α,β-unsaturated ketones catalyzed by **3**, the yields and enantiomeric excess (ee) were not satisfactory (up to 56% ee).[5a,5b] Rueping and co-workers also achieved a highly enantioselective Friedel–Crafts reaction. However, a β,γ-unsaturated α-ketoester possessing high electrophilic activity had to be employed as a reaction partner.[5c] We describe herein a chiral phosphoric acid catalyzed highly enantioselective Friedel–Crafts alkylation reaction of indoles with simple α,β-unsaturated ketones.

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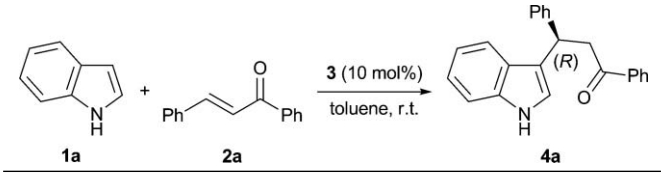
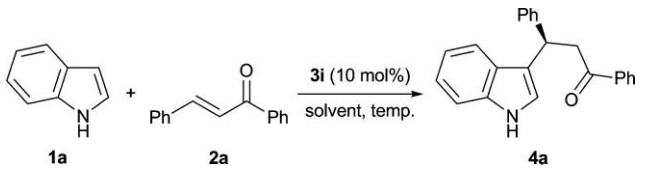
Table 1 Effect of phosphoric acid



Entry	Catalyst	Time/h	Yield (%)[a]	ee (%)[b]
1	**3a**	7	76	30
2	**3b**	36	23	49
3	**3c**	31.5	47	−16
4	**3d**	49.5	19	20
5	**3e**	22.5	quant.	50
6	**3f**	46.5	70	55
7	**3g**	26	quant.	58
8	**3h**	35	quant.	67
9	**3i**	22	quant.	76

[a] Isolated yield. [b] Determined by HPLC on a chiral stationary phase using Daicel Chiralpak AD-H column.

Table 2 Optimization of the reaction conditions



Entry	Solvent	Temp./°C	Time/h	Yield (%)[a]	ee (%)[b]
1	Toluene	rt	22	quant.	76
2	THF	rt	48	4	40
3	CH_2Cl_2	rt	39	84	73
4	$ClCH_2CH_2Cl$	rt	34	96	75
5	Benzene	rt	18	quant.	72
6	Mesitylene	rt	18	quant.	77
7	Mesitylene	−40	137	69	87
8	Mesitylene/$(CH_2Cl)_2$ = 1/1	−40	137	79	91
9[c]	Mesitylene/$(CH_2Cl)_2$ = 1/1	−40	48	87(61)	92(>99)[d]

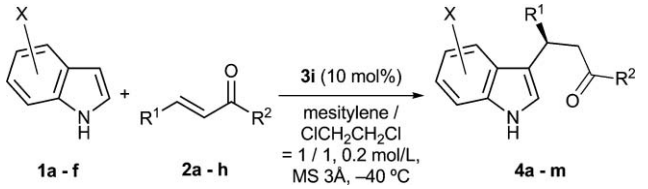
[a] Isolated yield. [b] Determined by HPLC on a chiral stationary phase using Daicel Chiralpak AD-H column. [c] MS 3 Å was employed. [d] After recrystallization.

Results and discussion

At the outset, we studied the effects of chiral phosphoric acid catalysts **3** on the reaction of indole **1** with chalcone **2** (Table 1). Adduct **4** was obtained in good yield with moderate ee using catalyst **3a** bearing a phenyl group at 3,3′-position (entry 1, 76%, 30% ee). Further screening of the catalysts revealed that the catalysts with electron-withdrawing groups gave better results in term of chemical yield and enantioselectivity (entries 2–5). Of note was that phosphoric acid **3i** (Ar = 2,4-$(CF_3)_2C_6H_3$) gave **4a** in excellent yield and high enantioselectivity (entry 9, quant., 76% ee).

Table 2 lists the results of investigation of the reaction conditions for the further enhancement of enantioselectivity. Although the reaction was sluggish in THF (entry 2), non-polar solvents, such as CH_2Cl_2, $ClCH_2CH_2Cl$, and benzene, gave **4a** in almost quantitative yields with high ee (entries 3–5). Mesitylene turned out to be the solvent of choice (entry 6). Low-temperature experiment (−40 °C) in mesitylene improved the enantioselectivity to 87% ee, but this was accompanied by a decrease of the chemical yield and a long reaction time (entry 7, 137 h). The ee could be further enhanced to 91% by employing the mixed solvent system of mesitylene and dichloroethane (entry 8). We were pleased to find that the addition of MS 3 Å accelerated the reaction, affording **4a** in 87% yield within 48 h (entry 9). Enantiomerically pure adduct **4a** could be obtained by single recrystallization from ethanol. The absolute configuration of **4a** was determined to be *R* by comparison of the optical rotation with that of the reported data.[10]

Table 3 Friedel–Crafts alkylation reaction to give 3-substituted indole analogues



Entry	X	R^1	R^2	4	Time/h	Yield (%)[a]	ee (%)[b]
1	H(**1a**)	Ph	Ph(**2a**)	**4a**	48	87	92
2	5-MeO(**1b**)	Ph	Ph	**4b**	48	98	91
3	5-BnO(**1c**)	Ph	Ph	**4c**	34	94	91
4	5-Cl(**1d**)	Ph	Ph	**4d**	167	53	90
5	5-Br(**1e**)	Ph	Ph	**4e**	167	42	89
6	7-Me(**1f**)	Ph	Ph	**4f**	40	97	88
7	H	2-ClC_6H_4	Ph(**2b**)	**4g**	48	90	86
8	H	3-ClC_6H_4	Ph(**2c**)	**4h**	48	79	90
9[c]	H	4-ClC_6H_4	Ph(**2d**)	**4i**	48	74	90
10[c]	H	4-BrC_6H_4	Ph(**2e**)	**4j**	48	67	91
11	H	4-FC_6H_4	Ph(**2f**)	**4k**	96	94	90
12	H	Ph	Me(**2g**)	**4l**	48	37	91
13	H	Me	Ph(**2h**)	**4m**	15	94	58

[a] Isolated yield. [b] Determined by HPLC on a chiral stationary phase using Daicel Chiralpak AD-H, AS-H column, and Daicel Chiralcel OD-H column. [c] Mesitylene/$ClCH_2CH_2Cl$ = 3/5, 0.25 mol L^{-1}, −20 °C.

Under the optimized conditions, the scope of the reaction was examined (Table 3). In all cases of indole derivatives, excellent ees were achieved while the chemical yields dramatically changed depending on the substituent on the indoles. Electron-rich indoles were obtained in excellent yields (entries 2 and 3). Indoles bearing electron-withdrawing substituents (Cl, Br) had moderate chemical yields and the reaction time was long (entries 4, 5, 167 h). It should be noted that 7-methylindole adduct **4f** had excellent ee (88% ee) although 7-methylindole had low ee in the asymmetric Friedel–Crafts reaction with α,β-unsaturated acyl phosphonates (19% ee).[5f]

The substituents on α,β-unsaturated ketones were well tolerated. 2-Chloro-, 3-chloro-, and 4-fluorochalcone gave adducts **4** in high yields with high enantioselectivities (entries 7, 8, and 11). On the other hand, 4-chloro- and 4-bromochalcone exhibited low reactivities (20%) under the same conditions. By tuning the reaction conditions (concentration, solvent ratio, and temperature), the chemical yields were improved to 74% and 67%, respectively, and the ees remained high (entries 9 and 10). While the chemical yield of alkyl-substituted adduct **4l** (R^2 = Me) was moderate due to the low reactivity, its ee was excellent (entry 12). 1-Phenylbut-2-en-1-one gave the corresponding adduct **4m** with

lower enantioselectivity (entry 13). The absolute configurations of the adducts (**4b–4l**) were surmised by analogy with **4a**.

We also studied the utility of the enantioselective Friedel–Crafts reaction for the construction of the optically active 2-substituted indole skeleton. Recently, the asymmetric syntheses of 2-substituted indole were developed by taking advantage of the pyrrole-like reactivity of 4,7-dihydroindole (Fig. 3).[11] Wang and You explored the organocatalytic enantioselective reactions of 4,7-dihydroindole.[12] Although You and co-workers thoroughly studied the chiral phosphoric acid catalyzed asymmetric Friedel–Crafts alkylation reaction of 4,7-dihydroindole with imine, nitroalkene, β,γ-unsaturated α-ketoester, and α,β-unsaturated aldehyde,[12b–d] the reaction with α,β-unsaturated ketone remains to be investigated.

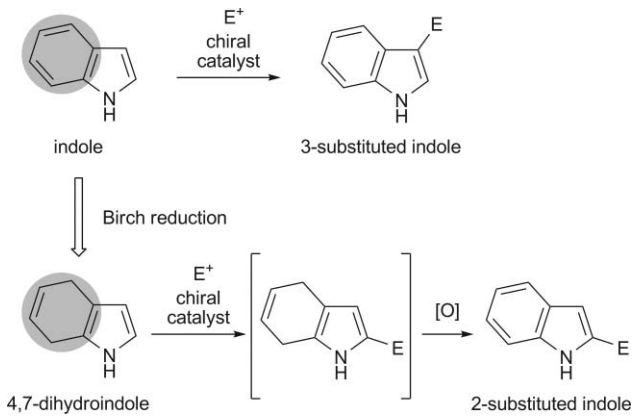
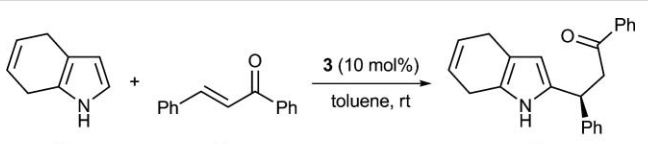


Fig. 3 Reactivity of 4,7-dihydroindole.

First, we studied the Friedel–Crafts reaction of **5** under the optimized conditions (Table 3) to give corresponding 2-adduct **6a** with moderate enantioselectivity (quant., 50% ee). The search for the most effective catalyst yielded fascinating knowledge: while the electronic factor of a catalyst is important for the Friedel–Crafts reaction of an indole, the steric factor governs the selectivity in this case. Both the reaction temperature and some additives turned out to be critical factors affecting ee, as in the case of indole: when the reaction was performed at −78 °C in the presence of MS 4 Å, enantioselectivity was improved to 85% ee (Table 4,[13] entry 6).

Table 4 Screening for catalysts for the reaction of 4,7-dihydroindole

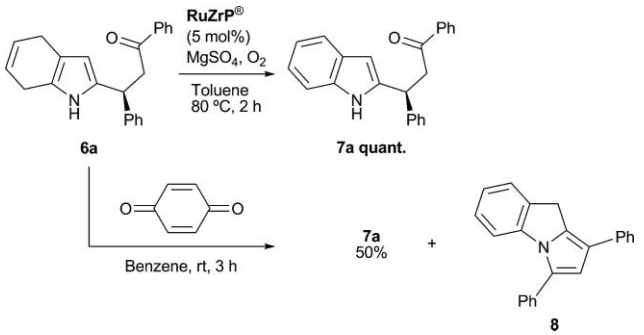


5 **2a** **6a**

Entry	Catalyst	Time/h	Yield (%)[a]	ee (%)[b]
1	**3b**	2	91	10
2	**3c**	1	93	56
3	**3d**	3.5	86	42
4	**3e**	3	77	23
5	**3i**	1	80	53
6[c]	**3c**	48	79	85

[a] NMR yield of a mixture of **6a** and corresponding indole **7a**. [b] Determined by HPLC on a chiral stationary phase using Daicel Chiralpak AS-H column. [c] The reaction was performed in the presence of MS 4 Å at −78 °C.

Although You and co-workers reported the successful oxidation of dihydroindole by employing benzoquinone as an oxidant,[12] the oxidation of **6a** by benzoquinone or DDQ gave **7a** in only 50% yield, accompanied by the formation of byproduct **8** (Scheme 2). The dihydroquinone that was produced after oxidation induced dehydrative condensation followed by double bond isomerization[14] to afford **8**. We found that treatment with 5 mol% of RuZrP®[15] at molecular oxygen atmosphere gave **7a** in quantitative yield.



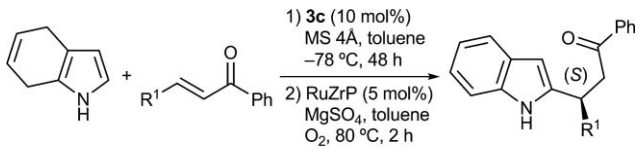
Scheme 2 Oxidation to 2-substituted indole **7a**.

This method could also be applied to various α,β-unsaturated ketones (Table 5). The asymmetric Friedel–Crafts alkylation reaction and the subsequent oxidation afforded **7** with high enantioselectivities regardless of the substituent on the phenyl group at the 3-position of **2** (entries 2–5, 82–85% ee).

Interestingly, although the same (*R*)-phosphoric acid catalysts were employed in both Friedel–Crafts reactions, the absolute configuration of the corresponding adducts was switched. In the case of dihydroindole, the enriched enantiomer was the (*S*)-enantiomer,[16] while the (*R*)-isomer was the major indole in the Friedel–Crafts reaction.

To gain insight into the reaction mechanism we examined the reaction of *N*-Me indole with chalcone under the optimized reaction conditions. As expected, both the chemical yield and enantioselectivity diminished (25%, 56% ee).[9g] The plausible transition states of these reactions are illustrated in Fig. 4.[17] The

Table 5 Friedel–Crafts alkylation reaction to give 2-substituted indole analogues



5 **2** **7a - f**

Entry	R^1	**7**	Yield (%)[a]	ee (%)[b]
1	Ph	**7a**	90	87
2	4-ClC_6H_4	**7b**	51	84
3	4-BrC_6H_4	**7c**	65	85
4	4-FC_6H_4	**7d**	69	82
5	4-$MeOC_6H_4$	**7e**	58	85
6	Me	**7f**	79[c]	79[d]

[a] Isolated yield. [b] Determined by HPLC on a chiral stationary phase using Daicel Chiralpak AS-H and AD-H column. [c] 10 h. [d] *S*-isomer was obtained.

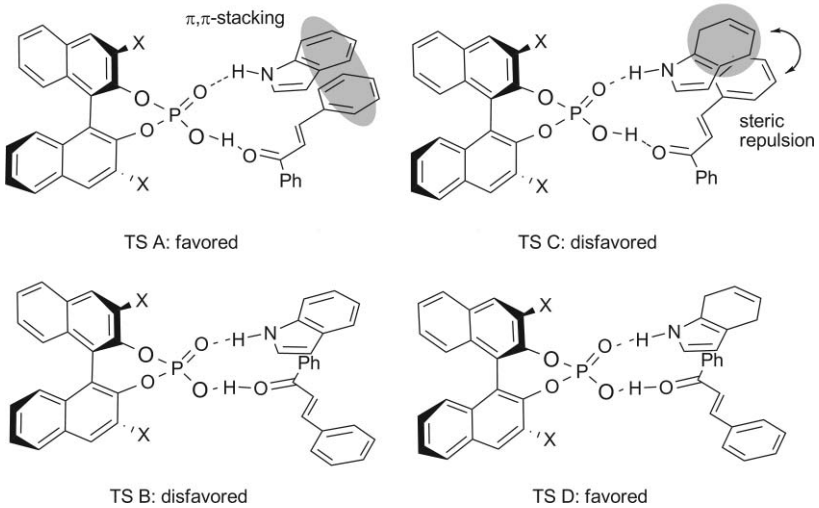


Fig. 4 Plausible transition states.

reversal of facial selectivity is ascribed to the difference in the direction of the α,β-unsaturated ketone. In the case of indole, TS A was preferred over TS B because of the π,π-stacking between the indole benzene ring and the benzene ring at the 3-position of the chalcone moiety. On the other hand, in the case of 4,7-dihydroindole, the collapse of aromaticity brought about severe steric repulsion (Fig. 4), which led to TS D being the predominant transition state.

In summary, we have developed the phosphoric acid catalyzed asymmetric Friedel–Crafts alkylation reaction of indole with α,β-unsaturated ketone. Futhermore, we have established an effective method for the synthesis of 2-substituted indole analogues using 4,7-dihydroindole.

Experimental

1. General details

NMR spectra were recorded on Unity Inova 400 instrument (Varian Inc., 400 MHz for ^{1}H, 100 MHz for ^{13}C, 376 MHz for ^{19}F, 189 MHz for ^{31}P) using $CDCl_3$ as a solvent. Tetramethylsilane (TMS) ($\delta = 0$) or $CHCl_3$ ($\delta = 7.27$) served as an internal standard for ^{1}H NMR spectroscopy. H_3PO_4 was used as an external standard ($\delta = 0$) for ^{31}P NMR. C_6F_6 was used as an internal standard ($\delta = 0$) for ^{19}F NMR. IR spectra were recorded on a Shimadzu FT-IR 8600 spectrometer. EI Mass spectra were measured by JMS-AX505HA (JEOL) at an ionizing voltage of 70 eV. Purification of the products was performed by column chromatography on silica gel (Fuji sylisia D60L or PSQ-60B). All solvents were purified according to the standard procedures. Elemental analysis (EA) was carried out on EA1110 instrument (Amco Inc.).

2. Friedel–Crafts alkylation

(*R*)-3-(1*H*-Indol-3-yl)-1,3-diphenylpropan-1-one (4a)[5a]. To a dry 20 mL flask with activated MS 3 Å (20 mg) under nitrogen were added phosphoric acid **3e** (15.5 mg, 0.02 mmol), chalcone **2a** (62.5 mg, 0.3 mmol), mesitylene (0.5 mL), and 1,2-dichloroethane (0.5 mL). The solution was cooled to –40 °C, and indole **1a** (23.4 mg, 0.2 mmol) was added. After completion of the reaction, the mixture was purified directly by flash silica gel chromatography (hexane–ethyl acetate = 20/1, and then hexane–ethyl acetate–dichloromethane = 1/1/8) to afford adduct **4a** as a white solid.

Solid, mp 159–160 °C (EtOH); $[\alpha]_D^{27}$ –47 (*c* 1.0, $CHCl_3$, 91% ee), $[\alpha]_D^{26}$ –57 (*c* 1.0, $CHCl_3$, 100% ee (EtOH)); R_f 0.10 (hexane: ethyl acetate = 5 : 1), ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.97 (brs, 1 H), 7.93–7.91 (m, 2 H), 7.53 (dddd, 1 H, *J* = 7.5, 7.3, 1.3, 1.3 Hz), 7.44–7.40 (m, 3 H), 7.34 (d, 2 H, *J* = 7.7 Hz), 7.30 (ddd, 1 H, *J* = 8.2, 0.9, 0.7 Hz), 7.24 (dd, 2 H, *J* = 7.3, 6.6 Hz), 7.17–7.11 (m, 2 H), 7.01 (ddd, 1 H, *J* = 7.1, 7.0, 1.1 Hz), 6.97 (dd, 1 H, *J* = 2.4, 0.7 Hz), 5.06 (dd, 1 H, *J* = 7.0, 7.7 Hz), 3.81 (dd, 1 H, *J* = 16.7, 7.0 Hz), 3.72 (dd, 1 H, *J* = 16.7, 7.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 198.6, 144.2, 137.2, 136.6, 133.0, 128.6, 128.4, 128.1, 127.8, 126.6, 126.3, 122.1, 121.4, 119.6, 119.4, 119.3, 111.1, 45.2, 38.3; HPLC: Daicel Chiralpak AD-H, Hexane/*i*PrOH = 5/1, Flow rate = 0.5 mL min^{-1}, UV = 254 nm, t_R = 40.6 min (major), t_R = 47.1 min (minor).

(*R*)-3-(5-Benzyloxy-1*H*-indol-3-yl)-1,3-diphenylpropan-1-one (4c). Mp 61–62 °C; $[\alpha]_D^{25}$ –4.6 (*c* 1.0, $CHCl_3$, 91% ee); R_f 0.10 (hexane: ethyl acetate = 5 : 1), ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.93–7.90 (m, 2 H), 7.90 (brs, 1 H), 7.52 (dddd, 1 H, *J* = 7.5, 7.3, 1.3, 1.3 Hz), 7.43–7.39 (m, 4 H), 7.35–7.32 (m, 4 H), 7.29–7.22 (m, 3 H), 7.18–7.14 (m, 1 H), 7.15 (d, 1 H, *J* = 8.8 Hz), 6.93 (d, 1 H, *J* = 2.4 Hz), 6.89 (d, 1 H, *J* = 2.2 Hz), 6.86 (dd, 1 H, *J* = 8.8, 2.4 Hz), 4.99 (dd, 1 H, *J* = 7.7, 7.0 Hz), 4.96 (s, 2 H), 3.75 (dd, 1 H, *J* = 16.8, 7.0 Hz), 3.68 (dd, 1 H, *J* = 16.8, 7.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 198.6, 152.9, 144.1, 137.6, 137.1, 135.0, 133.0, 132.5, 131.9, 128.5, 128.4, 128.1, 127.8, 127.7, 127.6, 126.9, 126.3, 122.2, 119.0, 113.0, 111.8, 103.1, 70.8, 45.0, 38.1; IR ($CHCl_3$) 3479, 3012, 1685, 1582, 1481, 1452, 1288, 1267, 1222, 1184, 1080, 1022 cm^{-1}; MS (EI) *m*/*z* 431 (M^++1, 24), 431 (M^+, 71), 340 (23), 312 (53), 220 (100), 192 (30), 165 (9), 105 (37), 91 (31), 77 (14), 69 (8); Found: C, 83.55; H, 5.72; N, 3.30%. Calcd for $C_{30}H_{25}NO_2$: C, 83.50; H, 5.84; N, 3.25%; HPLC: Daicel Chiralcel OD-H, Hexane/EtOH = 9/1. Flow rate = 1.0 mL min^{-1}, UV = 254 nm, t_R = 26.1 min (major), t_R = 30.7 min (minor).

(*R*)-3-(5-Chloro-1*H*-indol-3-yl)-1,3-diphenylpropan-1-one (4d). Mp 165–166 °C; $[\alpha]_D^{24}$ −35 (*c* 0.50, $CHCl_3$, 90% ee); R_f 0.15 (hexane: ethyl acetate = 5 : 1) ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.00 (brs, 1 H), 7.94–7.92 (m, 2 H), 7.55 (dddd, 1 H, *J* = 7.5, 7.3, 1.3, 1.3 Hz), 7.44 (dd, 2 H, *J* = 7.7, 7.5 Hz), 7.38 (d, 1 H, *J* = 2.0 Hz), 7.33 (m, 2 H), 7.29–7.25 (m, 2 H), 7.23 (d, 1 H, *J* = 8.6 Hz), 7.18 (dddd, 1 H, *J* = 7.3, 7.1, 1.3, 1.3 Hz), 7.09 (dd, 1 H, *J* = 8.6, 2.0 Hz), 7.04 (d, 1 H, *J* = 2.4 Hz), 5.00 (dd, 1 H, *J* = 7.3, 7.1 Hz), 3.78 (dd, 1 H, *J* = 16.7, 7.3 Hz), 3.70 (dd, 1 H, *J* = 16.7, 7.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 198.3, 143.8, 137.0, 134.9, 133.1, 128.6, 128.6, 128.1, 127.8, 127.7, 126.5, 125.2, 122.7, 122.5, 119.1, 119.0, 112.1, 45.2, 38.0. IR ($CHCl_3$) 3477, 1686, 1599, 1464, 1448, 1377, 1362, 1223, 1209, 1101 cm^{-1}; MS (EI) *m*/*z* 361 (M^++1, 8), 359 (M^+-1, 26), 284 (2), 254 (18), 242 (32), 240 (100), 204 (17), 176 (5), 151 (3), 105 (17), 77 (16), 69 (9).; Found: C, 76.87; H, 4.82; N, 3.87%. Calcd for $C_{23}H_{18}ClNO$: C, 76.77; H, 5.04; N, 3.89%; HPLC: Daicel Chiralcel OD-H, Hexane/EtOH = 10/1. Flow rate = 1.0 mL min^{-1}, UV = 254 nm, t_R = 19.5 min (major), t_R = 24.4 min (minor).

(*R*)-3-(4-Fluorophenyl)-3-(1*H*-indol-3-yl)-1-phenylpropan-1-one (4k). Mp 149–150 °C; $[\alpha]_D^{27}$ −43 (*c* 1.0, $CHCl_3$, 90% ee); R_f 0.10 (hexane: ethyl acetate = 5 : 1), ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.99 (brs, 1 H), 7.94–7.91 (m, 2 H), 7.55 (dddd, 1 H, *J* = 7.5, 7.3, 1.3, 1.3 Hz), 7.44 (dd, 2 H, *J* = 7.9, 7.3 Hz), 7.40 (d, 1 H, *J* = 7.9 Hz), 7.34 (ddd, 1 H, *J* = 8.2, 0.9, 0.7 Hz), 7.30 (dd, 2 H, *J* = 8.6 Hz, J_{H-F} = 5.5 Hz), 7.16 (ddd, 1 H, *J* = 7.1, 6.9, 1.1 Hz), 7.03 (ddd, 1 H, *J* = 7.1, 7.0, 1.1 Hz), 7.00 (d, 1 H, *J* = 2.2 Hz), 6.93 (dd, 2 H, J_{H-F} = 8.8, 8.6 Hz), 5.05 (dd, 1 H, *J* = 6.4, 8.1 Hz), 3.80 (dd, 1 H, *J* = 16.7, 6.4 Hz), 3.70 (dd, 1 H, *J* = 16.7, 8.1 Hz).; ^{19}F-NMR (376 MHz, $CDCl_3$) δ = 44.8 (m).; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 198.4, 161.3 (d, *J* = 244.4 Hz), 139.9, 139.8, 137.0, 136.6, 133.1, 129.2 (d, *J* = 7.7 Hz), 128.6, 128.0, 126.4, 122.2, 121.3, 119.4 (d, *J* = 4.6 Hz), 119.2, 115.1 (d, *J* = 21.1 Hz), 111.2, 45.2, 37.5. IR ($CHCl_3$) 3479, 3010, 1684, 1599, 1508, 1456, 1448, 1337, 1229, 1157, 1096, 1014 cm^{-1}; MS (EI) *m*/*z* 343 (M^+, 18), 238 (13), 224 (100), 97 (11), 83 (18), 69 (23).; Found: C, 80.23; H, 5.36; N, 3.81%. Calcd for $C_{23}H_{18}FNO$: C, 80.45; H, 5.28; N, 4.08%; HPLC: Daicel Chiralpak AD-H, Hexane/EtOH = 1/1. Flow rate = 0.5 mL min^{-1}, UV = 254 nm, t_R = 12.4 min (major), t_R = 13.8 min (minor).

(*S*)-3-(1*H*-Indol-3-yl)-1-phenylbutan-1-one (4m)[18]. Amorphous, $[\alpha]_D^{26}$ −8.1 (*c* 1.2, $CHCl_3$, 58% ee) (lit. (*R*)-isomer, $[\alpha]_D^{25}$ +24.2 (*c* 0.4, $CHCl_3$));[18] R_f 0.20 (hexane: ethyl acetate = 5 : 1), ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.97–7.94 (m, 3 H), 7.68 (dd, 1 H, *J* = 7.8, 1.0 Hz), 7.54 (dddd, 1 H, *J* = 7.4, 7.2, 1.4, 1.4 Hz), 7.46–7.41 (m, 2 H), 7.36 (ddd, 1 H, *J* = 8.0, 1.0, 1.0 Hz), 7.19 (ddd, 1 H, *J* = 8.0, 7.0, 1.2 Hz), 7.12 (ddd, 1 H, *J* = 7.0, 7.0, 1.0 Hz), 7.04–7.03 (m, 1 H), 3.83 (ddq, 1 H, *J* = 8.8, 4.9, 6.9 Hz), 3.48 (dd, 1 H, *J* = 16.4, 4.9 Hz), 3.24 (dd, 1 H, *J* = 16.4, 8.8 Hz), 1.45 (d, 3 H, *J* = 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 199.7, 137.3, 136.5, 132.9, 128.5, 128.1, 126.3, 122.0, 121.6, 120.2, 119.3, 119.2, 111.2, 46.4, 27.1, 21.0; HPLC: Daicel Chiralcel OD-H, Hexane/EtOH = 5/1, Flow rate = 1.0 mL min^{-1}, UV = 254 nm, t_R = 9.3 min (major), t_R = 11.8 min (minor).

(*S*)-3-(1*H*-Indol-2-yl)-1,3-diphenylpropan-1-one (7a)[11]. To a dry 20 mL flask under nitrogen were added phosphoric acid **3c** (14.0 mg, 0.02 mmol), chalcone **2a** (62.5 mg, 0.3 mmol), and toluene (1.0 mL). The solution was cooled to −78 °C, and 4,7-dihydroindole **5** (23.8 mg, 0.2 mmol) was added. After being stirred at the temperature for 48 h, the mixture was quenched with $NaHCO_3$, and extracted with AcOEt(×3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under vacuo to dryness. The residue was purified by *p*-TLC (hexane–ethyl acetate = 5/1) to obtain **6a** as yellow solid. This material was subjected to RuZrP oxidation (25 mg, 5 mol% against **5**) under O_2 at 80 °C in toluene. As a result, corresponding adduct **7a** was obtained with high yield and good ee.

Mp 136–137 °C (*i*-PrOH); $[\alpha]_D^{26}$ −50 (*c* 1.0, $CHCl_3$, 87% ee); R_f 0.40 (hexane: ethyl acetate = 5 : 1), ^{1}H NMR(400 MHz, $CDCl_3$) δ = 8.23 (brs, 1 H), 7.99–7.97 (m, 2 H), 7.58 (dddd, 1 H, *J* = 7.5, 7.3, 1.8, 1.3 Hz), 7.50–7.45 (m, 3 H), 7.36–7.31 (m, 4 H), 7.29–7.24 (m, 2 H), 7.10 (ddd, 1 H, *J* = 7.1, 7.1, 1.1 Hz), 7.03 (ddd, 1 H, *J* = 7.1, 7.1, 1.1 Hz), 6.19 (m, 1 H), 4.95 (dd, 1 H, *J* = 8.2, 5.3 Hz), 3.93 (dd, 1 H, *J* = 17.6, 8.2 Hz), 3.68 (dd, 1 H, *J* = 17.6, 8.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 198.5, 142.2, 141.5, 136.6, 136.0, 133.3, 128.6, 128.6, 128.1, 128.0, 128.0, 127.0, 121.3, 119.9, 119.5, 110.6, 99.7, 44.7, 39.6. HPLC: Daicel Chiralpak AS-H, Hexane/*i*PrOH = 9/1. Flow rate = 1.0 mL min^{-1}, UV = 254 nm, t_R = 13.9 min (major), t_R = 16.3 min (minor).

(*S*)-3-(4-Chlorophenyl)-3-(1*H*-indol-2-yl)-1-phenylpropan-1-one (7b). Mp 122–123 °C; $[\alpha]_D^{25}$ −8.0 (*c* 1.0, $CHCl_3$, 84% ee); R_f 0.25 (hexane: ethyl acetate = 5 : 1), ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.22 (brs, 1 H), 7.99–7.96 (m, 2 H), 7.59 (dddd, 1 H, *J* = 7.3, 7.3, 1.3, 1.1 Hz), 7.50–7.45 (m, 3 H), 7.32–7.25 (m, 5 H), 7.11 (ddd, 1 H, *J* = 8.1, 7.1, 1.3 Hz), 7.04 (ddd, 1 H, *J* = 8.1, 7.0, 1.1 Hz), 6.18–6.18 (m, 1 H), 4.92 (dd, 1 H, *J* = 7.9, 5.7 Hz), 3.90 (dd, 1 H, *J* = 17.6, 7.9 Hz), 3.65 (dd, 1 H, *J* = 17.6, 5.7 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 198.3, 141.0, 140.2, 136.5, 136.1, 133.5, 132.8, 129.5, 128.8, 128.7, 128.1, 128.0, 121.6, 120.1, 119.7, 110.7, 100.0, 44.6, 39.0.; IR ($CHCl_3$) 3464, 3020, 2401, 1686, 1597, 1521, 1490, 1456, 1418, 1340, 1300, 1209, 1092, 1015, 928, 731, 669 cm^{-1}; MS (EI) *m*/*z* 361 (M^++2, 10), 359 (M^+, 29), 256 (38), 255 (26), 254 (100), 237 (10), 236 (25), 111 (16), 105 (21), 77 (16); Found: C, 76.77; H, 5.04; N, 3.89%. Calcd for $C_{23}H_{18}ClNO$: C, 76.94; H, 5.12; N, 3.85%; HPLC: Daicel Chiralpak AD-H, Hexane/*i*PrOH = 1/1. Flow rate = 0.5 mL min^{-1}, UV = 254 nm, t_R = 14.1 min (minor), t_R = 17.7 min (major).

(*S*)-3-(4-Bromophenyl)-3-(1*H*-indol-2-yl)-1-phenylpropan-1-one (7c). Mp 170–171 °C; $[\alpha]_D^{26}$ −9.1 (*c* 0.99, $CHCl_3$, 85% ee); R_f 0.35 (hexane: ethyl acetate = 5 : 1), ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.22 (brs, 1 H), 7.99–7.96 (m, 2 H), 7.59 (dddd, 1 H, *J* = 7.5, 7.3, 1.3, 1.3 Hz), 7.50–7.44 (m, 5 H), 7.27–7.22 (m, 3 H), 7.12 (ddd, 1 H, *J* = 8.2, 7.0, 1.3 Hz), 7.05 (ddd, 1 H, *J* = 8.1, 7.0, 1.1 Hz), 6.18–6.18 (m, 1 H), 4.91 (dd, 1 H, *J* = 7.9, 5.7 Hz), 3.90 (dd, 1 H, *J* = 17.6, 7.9 Hz), 3.65 (dd, 1 H, *J* = 17.6, 5.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 198.2, 141.3, 141.0, 136.6, 136.1, 133.6, 131.9, 129.9, 128.7, 128.1, 128.1, 121.7, 121.0, 120.1, 119.8, 110.7, 110.1, 44.7, 39.1; IR ($CHCl_3$) 3686, 3618, 3464, 3020, 2401, 1684, 1597, 1521, 1489, 1420, 1340, 1217, 1074, 1045, 1013, 930, 731, 669 cm^{-1}; MS (EI) *m*/*z* 404 (M^+, 25), 402 (M^+, 27), 300 (18), 299 (98), 298 (100), 285 (17), 283 (19), 183 (13), 181 (13), 105 (16) 77 (15); Found: C, 68.33; H, 4.49; N, 3.46%. Calcd for $C_{23}H_{18}BrNO$: C, 68.39; H, 4.31; N, 3.45%; Daicel Chiralpak AD-H, Hexane/*i*PrOH = 1/1. Flow rate = 0.5 mL min^{-1}, UV = 254 nm, t_R = 15.5 min (minor), t_R = 20.6 min (major).

(*S*)-3-(4-Fluorophenyl)-3-(1*H*-indol-2-yl)-1-phenylpropan-1-one (7d). Mp 75–77 °C; $[\alpha]_D^{25}$ −39 (*c* 1.0, $CHCl_3$, 82% ee); R_f 0.30 (hexane: ethyl acetate = 5 : 1), ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.21 (brs, 1 H), 7.99–7.96 (m, 2 H), 7.59 (dddd, 1 H, *J* = 7.4, 7.4, 1.4, 1.0 Hz), 7.52–7.45 (m, 3 H), 7.32 (dd, 2 H, *J* = 8.6 Hz, J_{H-F} = 5.3 Hz), 7.27–7.25 (m, 1 H), 7.11 (ddd, 1 H, *J* = 8.2, 7.0, 1.0 Hz), 7.06–7.00 (m, 3 H), 6.18 (m, 1 H), 4.94 (dd, 1 H, *J* = 7.8, 5.7 Hz), 3.90 (dd, 1 H, *J* = 17.6, 7.8 Hz), 3.66 (dd, 1 H, *J* = 17.6, 5.7 Hz); ^{19}F-NMR (376 MHz, $CDCl_3$) δ = 46.2 (m).; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 198.4, 161.7 (d, *J* = 245.3 Hz), 141.4, 138.0 (d, *J* = 3.0 Hz), 136.6, 136.1, 133.5, 129.6 (d, *J* = 7.5 Hz), 128.7, 128.5, 128.1, 121.6, 120.0, 119.7, 115.5 (d, *J* = 21.7 Hz), 110.6, 99.9, 44.8, 38.9. IR ($CHCl_3$) 3464, 3032, 3009, 2928, 2855, 1686, 1601, 1508, 1458, 1412, 1342, 1296, 1219, 1180, 1157, 1099, 980, 918, 837, 787, 760, 729, 691, 667, 548, 436 cm^{-1}; MS (EI) *m*/*z* 343 (M^+, 18), 325 (35), 324 (17), 239 (18), 238 (100), 224 (22), 222 (15), 121 (29), 77 (14).; Found: C, 80.45; H, 5.11; N, 4.05%. Calcd for $C_{23}H_{18}FNO$: C, 80.45; H, 5.28; N, 4.08%; HPLC: Daicel Chiralpak AD-H, Hexane/*i*PrOH = 1/1. Flow rate = 0.5 mL min^{-1}, UV = 254 nm, t_R = 13.0 min (minor), t_R = 14.7 min (major).

(*S*)-3-(1*H*-Indol-2-yl)-3-(4-methoxyphenyl)-1-phenylpropan-1-one (7e). Mp 48–49 °C; $[\alpha]_D^{28}$ −54 (*c* 1.0, $CHCl_3$, 85% ee); R_f 0.30 (hexane: ethyl acetate = 5 : 1), ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.20 (brs, 1 H), 7.99–7.97 (m, 2 H), 7.59 (dddd, 1 H, *J* = 7.5, 7.3, 1.3, 1.3 Hz), 7.50–7.45 (m, 3 H), 7.27–7.23 (m, 3 H), 7.10 (ddd, 1 H, *J* = 8.1, 7.1, 1.3 Hz), 7.03 (ddd, 1 H, *J* = 7.9, 7.1, 1.1 Hz), 6.87 (dd, 2 H, *J* = 9.5, 2.2 Hz), 6.19–6.18 (m, 1 H), 4.90 (dd, 1 H, *J* = 8.1, 5.7 Hz), 3.89 (dd, 1 H, *J* = 17.6, 8.1 Hz), 3.80 (s, 3 H), 3.65 (dd, 1 H, *J* = 17.6, 5.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 198.7, 158.6, 142.0, 136.8, 136.1, 134.3, 133.4, 129.1, 128.7, 128.2, 128.1, 121.4, 120.0, 119.6, 114.1, 110.6, 99.7, 55.2, 45.0, 38.9. IR ($CHCl_3$) 3684, 3618, 3462, 3020, 2401, 1684, 1611, 1599, 1582, 1512, 1458, 1420, 1302, 1209, 1180, 1036, 928, 731, 669 cm^{-1}; MS (EI) *m*/*z* 356 (M^++1, 12), 355 (M^+, 45), 251 (21), 250 (100), 237 (21), 236 (73), 135 (15), 133 (58), 107 (12), 105 (32), 77 (24).; Found: C, 81.10; H, 5.96; N, 3.94%. Calcd for $C_{24}H_{21}NO_2$: C, 80.15; H, 5.84; N, 4.00%; HPLC: Daicel Chiralpak AD-H, Hexane/*i*PrOH = 1/1. Flow rate = 0.5 mL min^{-1}, UV = 254 nm, t_R = 20.3 min (minor), t_R = 23.9 min (major).

(*S*)-3-(1*H*-Indol-2-yl)-1-phenylbutan-1-one (7f)[14]. Amorphous, $[\alpha]_D^{27}$ +31 (*c* 1.0, CH_2Cl_2, 79% ee) (lit. (*R*)-isomer, $[\alpha]_D^{25}$ −16.7 (*c* 0.87, CH_2Cl_2, 71% ee));[14] R_f 0.40 (hexane: ethyl acetate = 5 : 1), ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.62 (brs, 1 H), 7.97–7.94 (m, 2 H), 7.57 (dddd, 1 H, *J* = 7.4, 7.4, 1.4, 1.2 Hz), 7.52 (dd, 1 H, *J* = 7.0, 0.8 Hz), 7.48–7.44 (m, 2 H), 7.31 (dd, 1 H, *J* = 8.0, 0.8 Hz), 7.11 (ddd, 1 H, *J* = 8.0, 7.2, 1.4 Hz), 7.04 (ddd, 1 H, *J* = 8.2, 7.2, 1.2 Hz), 6.28 (m, 1 H), 3.74 (ddq, 1 H, *J* = 8.0, 4.7, 7.1 Hz), 3.41 (dd, 1 H, *J* = 18.0, 8.0 Hz), 3.31 (dd, 1 H, *J* = 18.0, 4.7 Hz), 1.52 (d, 3 H, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 200.1, 144.2, 136.7, 135.7, 133.4, 128.6, 128.2, 128.0, 121.2, 119.8, 119.4, 110.6, 97.5, 47.0, 27.9, 19.9; HPLC: Daicel Chiralpak AS-H, Hexane/*i*PrOH = 10/1, Flow rate = 0.5 mL min^{-1}, UV = 254 nm, t_R = 23.0 min (major), t_R = 24.9 min (minor).

1,3-Diphenyl-9*H*-pyrrolo[1,2-*a*]indole (8). Amorphous, R_f 0.40 (hexane: ethyl acetate = 10 : 1), ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.63–7.59 (m, 4 H), 7.50–7.45 (m, 3 H), 7.44–7.38 (m, 3 H), 7.23–7.19 (m, 1 H), 7.15–7.07 (m, 3 H), 6.68 (s, 1 H), 4.15 (s, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 141.2, 135.3, 134.9, 133.2, 132.8, 130.9, 129.0, 128.7, 128.3, 127.5, 127.1, 125.7, 125.2, 125.1, 123.1, 117.5, 111.9, 111.8, 30.2.; Found: C, 89.74; H, 5.30; N, 4.55%. Calcd for $C_{23}H_{17}N$: C, 89.87; H, 5.57; N, 4.56%.

3. Preparation of phosphoric acid

(*R*)-3,3′-Bis(2,4-bis(trifluoromethyl)phenyl)-1,1′-binaphth-2,2′-diol (precursor of 3i). To a three-necked round flask with a condenser were added barium hydroxide octahydrate (15 mmol), tetrakis(triphenylphosphine)palladium(0) (0.25 mmol), a 1,4-dioxane/H_2O solution (3/1, 75 mL), 2,2′-(2,2′-bis(methoxymethoxy)-1,1′-binaphthyl-3,3′-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane), and 2,4-bis(trifluoromethyl)bromobenzene (11 mmol). The mixture was refluxed for 24 h and quenched with 1 M aq. HCl. After extraction of this solution with CH_2Cl_2(×3), the combined organic layers were successively washed 1 N aq. HCl, brine, sat. $NaHCO_3$ aq., and brine. The organic layers were dried over Na_2SO_4, and concentrated *in vacuo* to give crude product.

A 1,4-dioxane/conc. HCl (= 3/1) solution of the crude mixture in a flask with a condenser was stirred for 5 h at 70 °C. After cooling down to room temperature, the solution was extracted with CH_2Cl_2(×3). The organic layers were combined, dried over Na_2SO_4, and concentrated to give a crude product, which was purified by column chromatography (hexane–ethyl acetate = 20/1) to give the precursor of **3i**.

Mp 122–123 °C, $[\alpha]_D^{24}$ +50 (*c* 1.0, $CHCl_3$, 100% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.06 (d, 2 H, *J* = 8.2 Hz), 7.93–7.88 (m, 6 H), 7.72–7.62 (m, 2 H), 7.47–7.41 (m, 4 H), 7.27–7.19 (m, 2 H), 5.13–5.09 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 150.5, 150.3, 150.2, 140.3, 135.8, 133.7, 133.5, 133.4, 133.3, 133.2, 133.1, 131.9, 131.4, 131.3, 131.2, 130.9, 130.8, 130.8, 130.7, 130.5, 130.4, 130.4, 130.3, 130.0, 130.0, 129.9, 128.9, 128.8, 128.7, 128.5, 128.5, 128.3, 128.2, 128.1, 127.5, 127.3, 127.1, 125.3, 125.0, 124.9, 24.1, 124.0, 123.9, 123.6, 121.7, 121.6, 118.1, 118.0, 118.0, 111.2, 111.0, 110.9, 110.8; ^{19}F-NMR (376 MHz, $CDCl_3$) δ = 102.58, 102.57, 102.5, 102.4, 98.94, 98.92; IR ($CHCl_3$) 3531, 3020,1710, 1628, 1603, 1578, 1501, 1439, 1346, 1298, 1279, 1267, 1220, 1209, 1180, 1140, 1084, 1063, 912, 862, 847 cm^{-1}; MS (EI) *m*/*z* 711 (M^++1, 10), 709 (M^+-1, 100), 670 (35), 669 (70), 347 (24), 149 (31); Found: C, 60.86; H, 2.55%. Calcd for $C_{36}H_{18}F_{12}O_2$: C, 60.62; H, 2.68%.

(*R*)-3,3′-Bis(2,4-bis(trifluoromethyl)phenyl)-1,1′-binaphth-2,2′-yl phosphate (3i). Phosphoryl chloride (2.8 mmol) was added to a pyridine (20 mL) solution of (*R*)-3,3′-bis(2,4-bis(trifluoromethyl)phen-yl)-1,1′-binaphth-2,2′-diol (2 mmol) in a dry flask equipped with a condenser under nitrogen at 0 °C. After being refluxed for 3 h, the reaction mixture was cooled to 0 °C and excess pure water was added, and then the mixture was warmed to room temperature. After being stirred at the temperature for 1 h, the reaction mixture was quenched with 6 N HCl and CH_2Cl_2, and extracted with CH_2Cl_2 (×3). The combined organic layers were washed with 6 N HCl, dried over Na_2SO_4, and concentrated *in vacuo* to give crude product. Reprecipitation with MeOH/6N HCl gave phosphoric acid **3i**, which was dried *in vacuo* at 50 °C with P_2O_5 in another flask to remove water.

Amorphous, $[\alpha]_D^{24}$ +17 (*c* 1.0, $CHCl_3$, 100% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.00–7.88 (m, 6 H), 7.64–7.54 (m, 6 H), 7.48–7.34 (m, 4 H), 6.93 (brs, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$)

δ = 176.9, 149.5, 144.1, 144.0, 143.9, 143.8, 143.4, 143.3, 143.2, 143.1, 138.6, 138.2, 138.1, 133.7, 133.6, 132.6, 132.6, 132.4, 132.3, 132.2, 132.0, 131.9, 131.8, 131.4, 131.3, 131.0, 131.0, 130.9, 130.8, 130.6, 130.6, 130.5, 130.4, 130.2, 130.2, 130.1, 129.8, 129.7, 129.6, 129.4, 129.4, 129.2, 129.1, 128.8, 128.8, 128.6, 128.5, 128.0, 127.9, 127.7, 127.5, 127.3, 127.2, 127.1, 127.0, 126.7, 126.6, 125.7, 125.6, 125.1, 125.0, 124.9, 124.5, 124.3, 122.9, 122.9, 122.8, 122.4, 122.4, 122.2, 122.2, 121.7, 121.6, 121.6, 121.6, 121.5, 121.5, 121.4, 121.4, 121.4, 121.3, 121.3, 117.8, 117.7; ^{19}F-NMR (376 MHz, $CDCl_3$) δ = 105.6, 105.4, 102.4, 102.3, 98.5, 98.4, 98.3; ^{31}P NMR (189 MHz, $CDCl_3$) δ = 5.67, 4.76, 4.17. IR ($CHCl_3$) 3649, 3063, 2253, 1711, 1628, 1499, 1418, 1346, 1298, 1281, 1269, 1221, 1180, 1140, 1082, 1063, 1020, 999, 970, 908, 847, 822 cm^{-1}; MS (EI) *m*/*z* 772 (M^+, 69), 771 (100), 770 (55), 691 (46), 369 (45), 368 (78), 129 (46), 111 (48), 97 (69), 83 (85), 77 (43), 69 (95).; Found: C, 55.97; H, 2.22%. Calcd for $C_{36}H_{17}F_{12}O_4P$: C, 55.98; H, 2.49%.

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