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# Preparation of indole-phosphine oxazoline (IndPHOX) ligands and their application in allylic alkylation

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ABSTRACT

Two classes of indole-phosphine oxazoline ligands have been prepared from readily available starting materials in good overall yields. These modular ligands include an indole skeleton with either a phosphine moiety or an oxazoline ring at the 2- or 3-position, respectively. The utility of these ligands was demonstrated in a catalytic asymmetric reaction: the palladium-catalyzed allylic alkylation of 1,3-diphenyl-2-propenyl acetate with dimethyl malonate was performed with enantioselectivities as high as 98%.



## 1. Introduction

Asymmetric synthesis is a vital and challenging field due to the need for enantiomerically pure compounds in pharmaceuticals, biochemical research, and agrochemicals. Asymmetric induction via metal catalysts and chiral ligands is one of the most elegant and effective methods. Among the diverse chiral ligands reported to date, the oxazoline ring-containing ligands are one of the most versatile and widely used classes.[1] The large majority of these are synthesized from readily available chiral amino alcohols, and the stereogenic carbon atom is located next to the nitrogen atom coordinating with metals, thus having a direct influence on the stereochemistry.[1]

A classic representative of oxazoline ligands is phosphino-oxazoline (PHOX) ligand (Fig. 1), pioneered by Pfaltz,[2a] Helmchen,[2b] and Williams.[2c] These outstanding and tunable class of chiral *P,N*-ligands have been utilized in several metal-catalyzed transformations, such as Heck reactions,[3] allylic substitutions,[4,5] and hydrogenations.[6,7] Due to the success of the PHOX ligands, a variety of derivatives have been prepared and used extensively in catalytic applications (Fig. 2).[8] A successful strategy has been the replacement of the phenyl ring with a heterocycle bearing an oxazoline moiety. Several highly effective hetero PHOX (Het-PHOX) ligands have been prepared (Fig. 3), and utilized in asymmetric allylic alkylations,[9a,9b] Heck reactions,[9c] hydrogenations,[9d,9e] and hydrosilylations.[9f]

Although the indole core has been investigated for over a century, it has gained attention as a ligand only very recently. Excellent results for the utility of achiral indolylphosphine ligands in Pd-catalyzed reactions, such as Suzuki-Miyaura couplings,[10] Hiyama cross-couplings,[11] cross-couplings utilizing organotitanium nucleophiles,[12] and aminations[13] have been reported. Moreover,

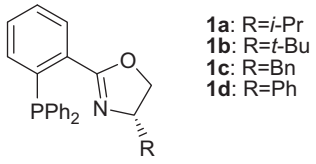
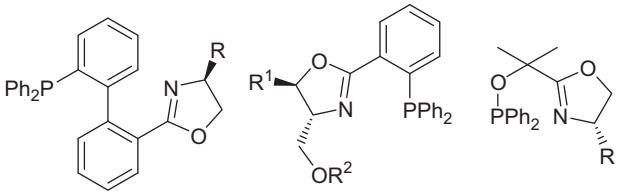



**Figure 1.** Phosphinooxazoline (PHOX) ligands.




**2**[8a] **3**[8b] **4**[8c]

**Figure 2.** Some PHOX ligand derivatives.

only a few chiral indole ligands have been prepared,[14–16] and only three of them have been utilized in catalytic asymmetric reactions until now (Fig. 4).[15,16a,17] In comparison with other benzofused heterocycles, the selective modification methods for indole are much more diverse and thus offer more possibilities for tuning the electronic and steric properties. Due to the accessible diversity, tunability, and potential activity in asymmetric reactions, we envisioned that indole-phosphine oxazoline (IndPHOX) ligands[18] could be valuable additions to PHOX and Het-PHOX derivatives. Herein, we report the synthesis and application of eight novel IndPHOX ligands (Fig. 5), which were conveniently prepared from commercially available starting materials in good overall yields.

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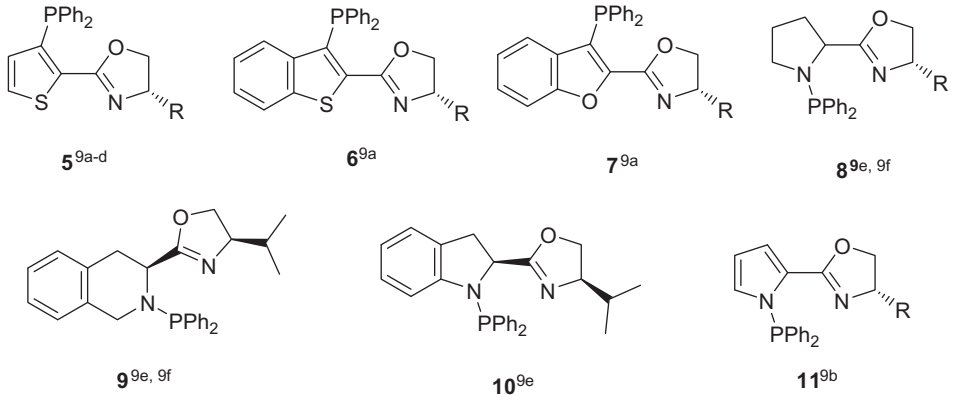



**Figure 3.** Examples of Het-PHOX ligands.

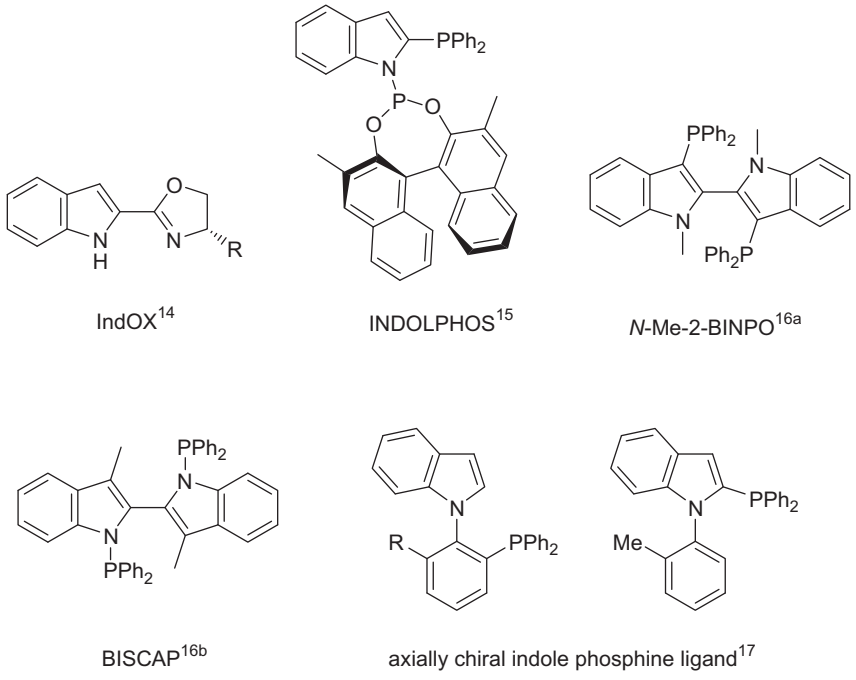



**Figure 4.** Indole based ligands with chirality.

## 2. Results and discussion

Indole-2-carboxylic acid was converted into the corresponding acid chloride using oxalyl chloride with a catalytic amount of DMF, and the subsequent amidation with L-valinol provided **22**. Oxazoline formation was accomplished by treatment of MsCl in the presence of DMAP under basic conditions to yield **23**.[14] Following N-functionalization with methyl or MOM group, the corresponding compounds were treated with *sec*-BuLi and TMEDA, followed by electrophilic quenching by $ClPPh_2$ or $ClPCy_2$, respectively. The desired products **13** and **14** were not formed, indicating that direct lithiation at the 3-postion was unsuccessful (**Route A**, Scheme 1). A literature survey revealed that the 3-position could be modified by a more powerful *P*-electrophile.[19] Thus we treated the lithiated **24a** and **24b** with diphenylphosphinic chloride, and **25a** and **25b** were obtained in good yields. Reduction of **25a** and **25b** by trichlorosilane in the presence of $Et_3N$ afforded ligands **13** and **14** in moderate yields (**Route B**).

In order to attempt the preparation of **15** and **16** by halogen–lithium exchange, compound **23** was brominated with NBS in $CHCl_3$ in 82% yield. After the N-functionalization, the bromine–lithium exchange of **27**, and treatment with $ClPCy_2$, ligands **15** and **16** were obtained (**Route C**).

Recently a new synthetic approach for PHOX ligands was reported by Tani et al.[20] The P–C bond was formed by an Ullman-type coupling developed by Buchwald.[21] With compound **28a** in hand, we investigated this method preliminarily for IndPHOX ligand **13** (**Route D**). Although the yield was poor (14%), our opinion is that this methodology could offer a wide range of possibilities in the future. A similar synthetic strategy was utilized for ligand class II (Scheme 2). Indole-3-carboxylic acid **29** was prepared from indole in good yield.[22] The 'acid chloride-approach' was found unsuitable for the preparation of **30**, and L-valinol was coupled to indole-3-carboxylic acid by EDC-activation, and **30** was obtained in 75% yield. Oxazoline formation at the 3-position was not accomplished in $CH_2Cl_2$, probably due to poor solubility, so the addition of DMF was found necessary. After optimization, **31** was obtained in 77% yield. After N-functionalization, direct lithiation at the 2-position and $ClPR_2$ treatment, ligands **17**–**20** were obtained.

Synthesized ligands **13**–**20** were investigated for the asymmetric allylic alkylation of 1,3-diphenyl-2-propenyl acetate **33** with dimethyl malonate [a standard model reaction for evaluation of

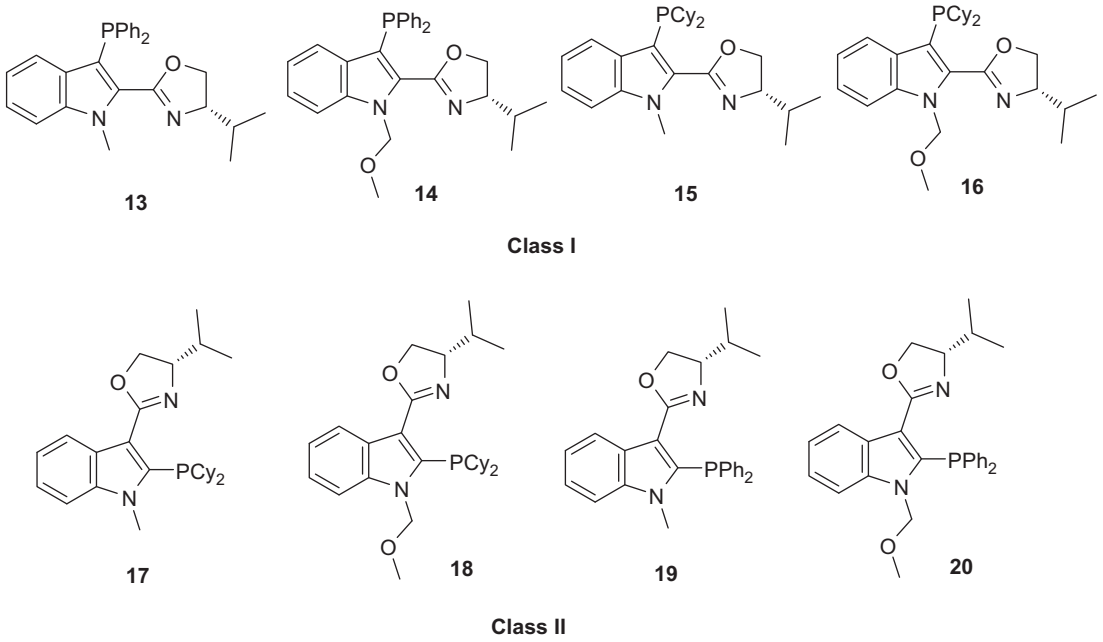



**Figure 5.** Indole-phosphine oxazoline ligands synthesized.

novel chiral ligands (Scheme 3)], and the results are summarized in Table 1.

For class I-type ligands, **13** and **14** with a diphenylphosphine-group greatly increased the reaction rate compared to ligands **15** and **16** with dicyclohexylphosphine. All of the ligands provided excellent enantiomeric excess. In contrast, the different phosphorus substituents of class II have a bigger influence on the results than class I. Although ligands **17** and **18** resulted in good ee%, the yields were poor, while ligands **19** and **20** increased the yield, reaction rate, and enantioselectivity. The opposite configured ligand (*R*)-**20** was synthesized utilizing the developed route from D-valinol. When (*R*)-**20** was subjected to the alkylation reaction, **34** was obtained with an (*R*)-configuration (Table 1). Recrystallization of product **34** with *n*-hexane/diethyl ether further improved the enantiomeric excesses from 97% to 99%.

Compared to other Het-PHOX ligands utilized in the asymmetric allylic alkylation, most IndPHOX ligands provided similar yields and higher ee% at room temperature. The requirement for lower temperature, needed for ligands **5a**–**7a**, was found unnecessary. Ligands **13**, **14,** and **20** also greatly increased the reaction rate in comparison with other Het-PHOX ligands. In addition, compared to PHOX ligand **1a**, the IndPHOX ligands with diphenylphosphine achieved equally excellent ee values (Table 1).

## 3. Conclusion

In conclusion, we have designed and prepared two classes of novel chiral indole-phosphine oxazoline ligands. Ligands could conveniently be synthesized from commercially available starting materials in good overall yields. The ligands were utilized in the Pd-catalyzed allylic alkylation of 1,3-dipheny-2-propenyl acetate with dimethyl malonate resulting in high enantioselectivities of up to 98%. IndPHOX ligands are in our opinion superior to the present related Het-PHOX ligands available for the Pd-catalyzed allylic alkylation. Our best results, when taking reaction time, yield, and enantiomeric purity into account, were achieved when the indole core was combined with a diphenylphosphine functionality. Further modification of the IndPHOX ligands and their applications in other asymmetric reactions are currently underway in our laboratory.

## 4. Experimental

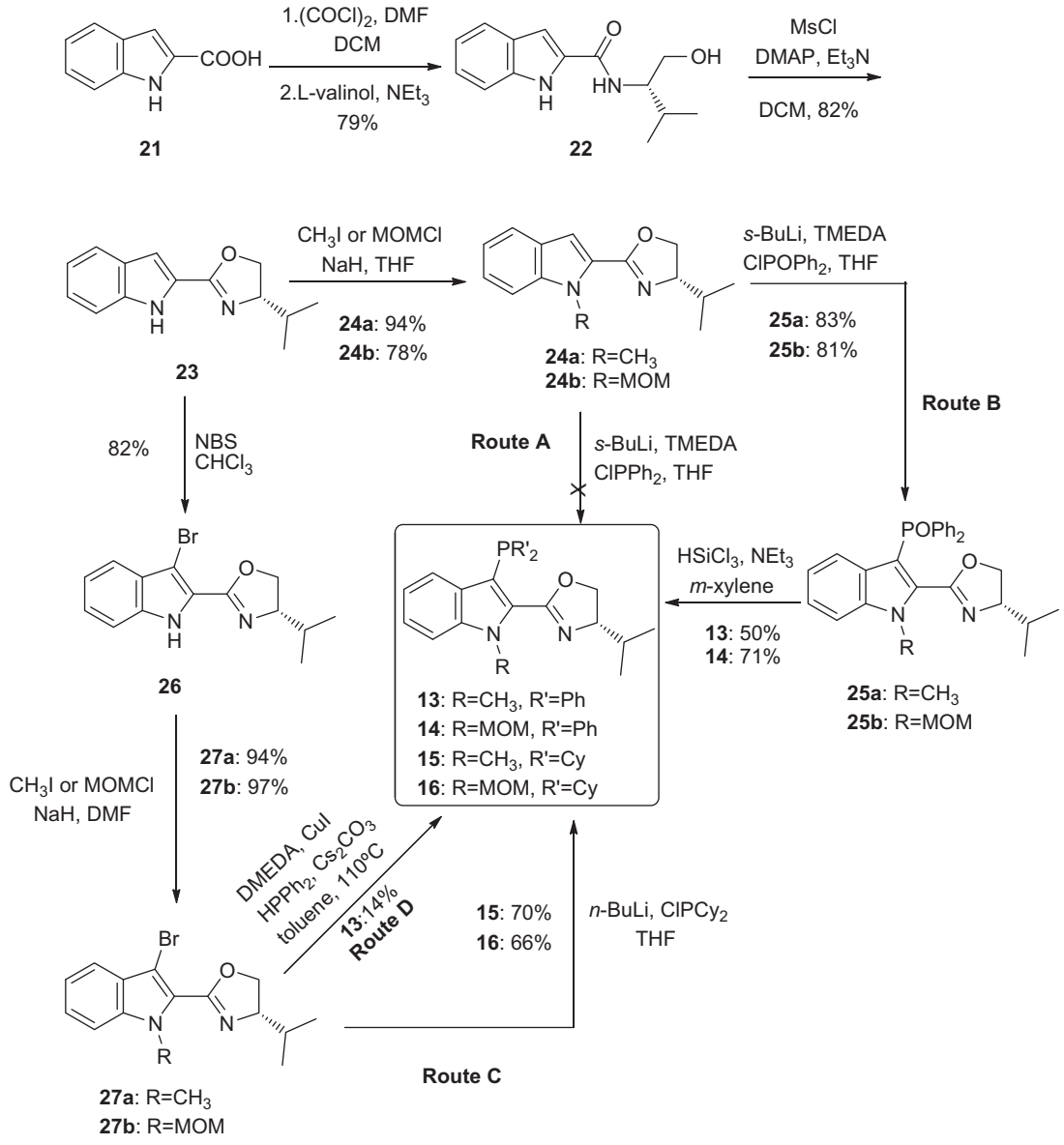
### 4.1. General

Solvent THF was distilled over sodium and benzophenone ketyl before use. Other solvents and reagents were used as received. TLC was performed on precoated (Silica Gel 60 F254) aluminum plates and visualization was performed by UV-light. Silica Gel 60, particle size 0.040–0.063 nm was used for column chromatography. $^{1}H$, $^{13}C$ and $^{31}P$ NMR spectra were measured at 300, 75 and 121 MHz, respectively, using $CDCl_3$ or DMSO-$d_6$ as solvents. Chemical shifts are reported in $\delta$ values (ppm) relative to tetramethylsilane. Melting points were not corrected.

### 4.2. Preparation of ligands 13–16

#### 4.2.1. (*S*)-*N*-(1-Hydroxy-3-methylbutan-2-yl)-1*H*-indole-2-carboxamide 22

To a suspension of indole-2-carboxylic acid **21** (1.61 g, 10.0 mmol) in $CH_2Cl_2$ (10 ml), oxalyl chloride (10 ml 2 mol/L, 20.0 mmol), and DMF (0.15 ml, 2.0 mmol) were added dropwise at 0 °C and further stirred 2.5 h at rt. The solvent was removed in vacuo. The crude acid chloride was dissolved in $CH_2Cl_2$ (15 ml), and added dropwise to a solution of L-valinol (1.08 g, 10.5 mmol) and $Et_3N$ (2.8 ml, 20.0 mmol) in $CH_2Cl_2$ (15 ml) at 0 °C. After stirring for 3 h at rt, 1 M HCl was added. The aqueous phase was extracted with $CH_2Cl_2$ and the combined organic layers were washed with brine and dried over $MgSO_4$. The solvent was removed and the crude product was triturated with cold $CH_2Cl_2$ to afford a light yellow solid (1.54 g). An additional amount of product (0.40 g) was obtained from the filtrate after silica chromatography (*n*-hexane/ethyl acetate = 2:1 to 1:1). Combined yield 79%. Mp 158–159 °C; $[\alpha]_D^{20} = -46.3$ (*c* 1.0, MeOH); $^{1}H$ NMR (300 MHz, DMSO-$d_6$): $\delta$ = 0.89–0.94 (2 × d, *J* = 6.9 Hz, 6H), 1.91–1.98 (m, 1H), 3.52–3.56 (m, 2H), 3.84–3.87 (m, 1H), 4.65 (t, *J* = 5.5 Hz, 1H), 7.00–7.05 (m, 1H), 7.14–7.20 (m, 1H), 7.21–7.22 (m, 1H), 7.43 (dd, *J* = 8.2, 0.8 Hz, 1H), 7.61 (d, *J* = 8.0 Hz, 1H), 7.97 (d, *J* = 9.0 Hz, 1H), 11.5 (br, 1H); $^{13}C$ NMR (75 MHz, DMSO-$d_6$): 19.6, 20.7, 29.6, 57.1, 62.3, 103.7, 113.2, 120.6, 122.4, 124.1, 128.0, 133.0, 137.3,




**Scheme 1.** Synthesis of ligands **13**–**16** of class I.

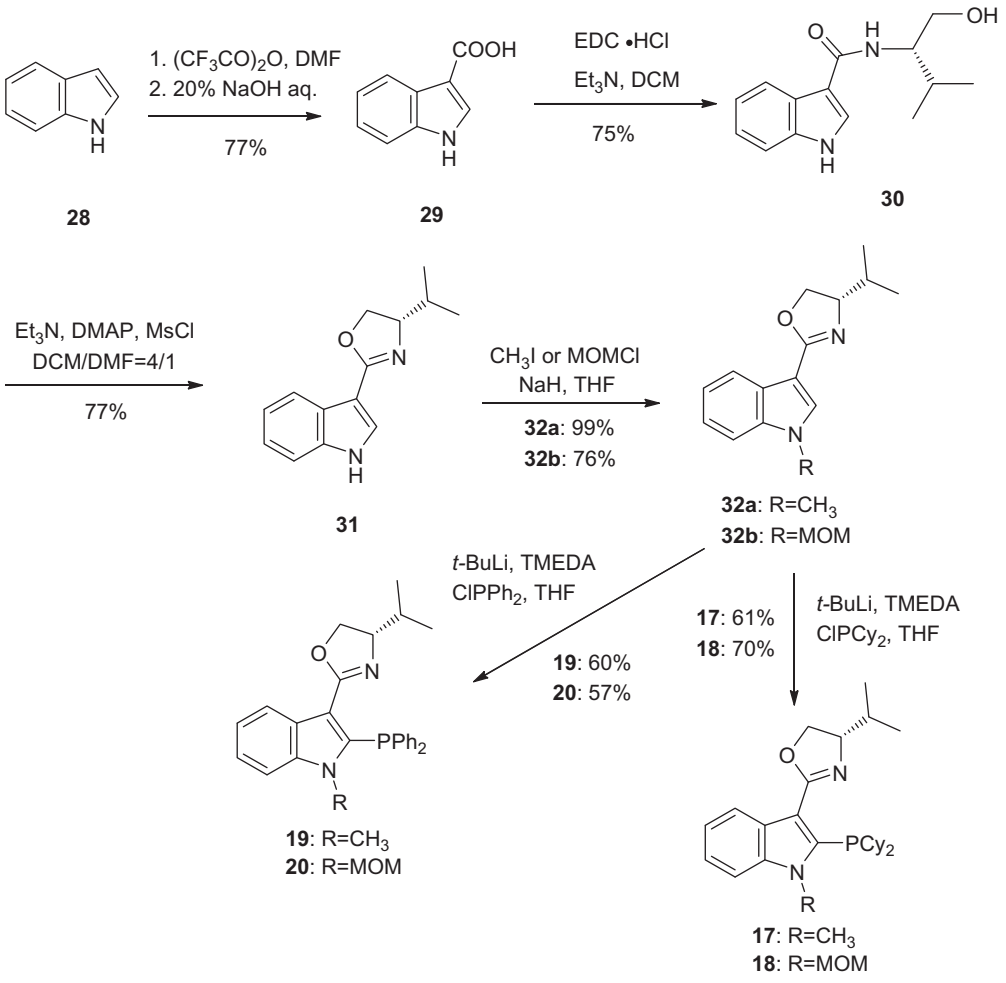
162.0. HRMS-ESI (*m*/*z*) for $C_{14}H_{18}N_2O_2Na$, $(M+Na)^+$ found 269.1276, calcd 269.1266.

#### 4.2.2. (*S*)-2-(4-Isopropyl-4,5-dihydrooxazol-2-yl)-1*H*-indole 23

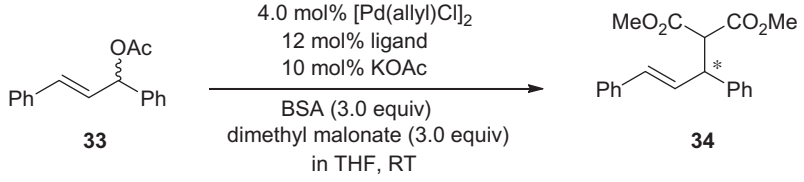
At first, MsCl (0.42 ml, 5.4 mmol) was added to a cooled mixture (0 °C) of **22** (1.21 g, 4.9 mmol), $Et_3N$ (5.4 ml, 39.2 mmol) and DMAP (0.12 g, 0.98 mmol) in $CH_2Cl_2$ (20 ml). After 2 h at rt, the starting material was consumed according to TLC. The reaction was quenched with water and extracted with $CH_2Cl_2$. The extracts were washed with brine and dried over $MgSO_4$. The solvent was removed in vacuo and the residue was purified by column chromatography (*n*-hexane/ethyl acetate = 5:1) to afford **23** as a light yellow solid (0.92 g, 82%). Mp 81–82 °C; $[\alpha]_D^{20} = +52.0$ (*c* 1.0, DCM); $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 0.95 (d, *J* = 6.8 Hz, 3H), 1.00 (d, *J* = 6.7 Hz, 3H), 1.83–1.89 (m, 1H), 4.29–4.35 (m, 2H), 4.55–4.59 (m, 1H), 7.10 (d, *J* = 1.0 Hz, 1H), 7.16 (td, *J* = 8.0, 1.0 Hz, 1H), 7.30 (td, *J* = 8.2, 1.0 Hz, 1H), 7.38 (d, *J* = 7.9, 1H), 7.72 (d, *J* = 8.0 Hz, 1H), 11.5 (br, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$): 18.5, 33.4, 71.0, 72.0, 106.4, 111.9, 120.3, 122.1, 124.4, 125.7, 127.9, 137.9, 159.8.

#### 4.2.3. (*S*)-2-(4-Isopropyl-4,5-dihydrooxazol-2-yl)-1-methyl-1*H*-indole 24a

Compound **23** (1.10 g, 4.8 mmol) in THF (10 ml) was added to a suspension of NaH (0.29 g, 7.2 mmol) in THF (10 ml) at 0 °C. After stirring for 1 h at rt, the solution was recooled to 0 °C, and $CH_3I$ (0.36 ml, 5.8 mmol) was added. After 2 h at rt, the reaction was quenched with water, and extracted with $Et_2O$. The organic layer was washed with brine and dried over $MgSO_4$. After concentration in vacuo, the crude product was filtered through a pad of silica using $Et_2O$ as eluent. The product was obtained as a light yellow solid after concentration (1.09 g, 94%). Mp 91–92 °C; $[\alpha]_D^{20} = -55.8$ (*c* 1.0, DCM); $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 0.95 (d, *J* = 6.7 Hz, 3H), 1.05 (d, *J* = 6.7 Hz, 3H), 1.83–1.89 (m, 1H), 4.04–4.18 (m, 5H), 4.35 (td, *J* = 8.0, 1.4 Hz, 1H), 7.07 (d, *J* = 0.6 Hz, 1H), 7.12 (ddd, *J* = 6.8, 5.6, 1.2 Hz, 1H), 7.28–7.38 (m, 2H), 7.64 (dt, *J* = 8.0, 0.9 Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$): 19.2, 19.3, 32.1, 33.3, 69.2, 73.6, 107.4, 110.2, 120.4, 122.2, 124.1, 126.8, 127.2, 139.7, 158.2. HRMS-ESI (*m*/*z*) for $C_{15}H_{19}N_2O$, $(M+H)^+$ found 243.1483, calcd 243.1473.




**Scheme 2.** Synthesis of ligands **17**–**20** of class II.




**Scheme 3.** Enantioselective allylic alkylation.

#### 4.2.4. (*S*)-2-(4-Isopropyl-4,5-dihydrooxazol-2-yl)-1-(methoxymethyl)-1*H*-indole 24b

Compound **23** (0.68 g, 3.0 mmol) in THF (5 ml) was added to a suspension of NaH (0.18 g, 4.5 mmol) in THF (10 ml) at 0 °C. After stirring for 1 h at rt, the solution was recooled to 0 °C, and MOMCl (0.27 ml, 3.6 mmol) was added. After 2 h at rt, the reaction was quenched with water and extracted with $Et_2O$. The organic layer was washed with brine and dried over $MgSO_4$. The solvent was removed in vacuo and the residue was purified by column chromatography (*n*-hexane/ethyl acetate = 5:1) to afford **24b** as a light yellow oil (0.64 g, 78%). $[\alpha]_D^{20} = -37.3$ (*c* 1.0, DCM); $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 0.97 (d, $J$ = 6.7 Hz, 3H), 1.06 (d, $J$ = 6.7 Hz, 3H), 1.82–1.88 (m, 1H), 3.29 (s, 3H), 4.04–4.17 (m, 2H), 4.34–4.39 (m, 1H), 6.13 (A, $J_{AB}$ = 10.6 Hz, 1H), 6.19 (B, $J_{AB}$ = 10.6 Hz, 1H), 7.12 (d, $J$ = 0.8 Hz, 1H), 7.17 (ddd, $J$ = 7.1, 7.0, 1.0 Hz, 1H), 7.33 (ddd, $J$ = 7.1, 7.0, 1.2 Hz, 1H), 7.54–7.57 (m, 1H), 7.66 (dt, $J$ = 7.9, 1.1 Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$): 19.0, 19.3, 33.4, 56.10, 69.5, 73.7, 75.0, 109.4, 111.3, 121.3, 122.2, 124.8, 127.1, 127.2, 139.7, 157.8. HRMS-ESI (*m*/*z*) for $C_{16}H_{20}N_2O_2Na$, $(M+Na)^+$ found 295.1419, calcd 295.1422.

#### 4.2.5. (*S*)-3-(Diphenylphosphoryl)-2-(4-isopropyl-4,5-dihydrooxazol-2-yl)-1-methyl-1*H*-indole 25a

Compound **24a** (1.00 g, 4.1 mmol) was dissolved in THF (10 ml) with TMEDA (0.80 ml, 5.3 mmol) and treated with *s*-BuLi (4.1 ml 1.4 mol/L, 5.7 mmol) at −78 °C. After 0.5 h under the same temperature, diphenylphosphinic chloride (1.1 ml, 5.7 mmol) was added. The cooling bath was removed after 0.5 h, and the reaction was allowed to warm to rt with stirring overnight. The reaction was quenched with a saturated solution of $NH_4Cl$ and extracted with ethyl acetate. The extracts were washed with brine and dried over $MgSO_4$. The solvent was removed in vacuo and the residue was purified by column chromatography (*n*-hexane/ethyl acetate = 2:1 to 1:2) to afford a light yellow solid (1.50 g, 83%). Mp 172–174 °C;

**Table 1**
Asymmetric allylic alkylation with various ligands[a]

| Entry | Ligand | Time(h) | Isolated yield (%) | ee[b] (%) | Configuration |
|---|---|---|---|---|---|
| 1 | **13** | 2 | 77[c] | 97 | (*S*)[d] |
| 2 | **14** | 2 | 79[c] | 97 | (*S*) |
| 3 | **15** | 24 | 42 | 93 | (*S*) |
| 4 | **16** | 24 | 63 | 90 | (*S*) |
| 5 | **17** | 24 | 17 | 72 | (*S*) |
| 6 | **18** | 24 | 17 | 86 | (*S*) |
| 7 | **19** | 24 | 55 | 97 | (*S*) |
| 8 | **20** | 0.5 | 95[c] | 98 | (*S*) |
| 9 | (*R*)-**20** | 0.5 | 77[c] | 98 | (*R*)[e] |
| 10[f] | **1a** | 1 | 98 | 98 | (*S*) |
| 11[g] | **5a** | 14 | 83 | 75 | (*S*) |
| 12[g] | **6a** | 14 | 86 | 88 | (*S*) |
| 13[g] | **7a** | 14 | 89 | 86 | (*S*) |

[a] See the Experimental for details concerning the reaction conditions.
[b] Determined by chiral HPLC.
[c] The conversion was 100%.
[d] $[\alpha]_D^{20} = -17.8$ (*c* 1.0, DCM).
[e] $[\alpha]_D^{20} = +22.1$ (*c* 1.05, DCM).
[f] See Ref. 4h.
[g] Reaction at −10 °C. See Ref. 9a.

$[\alpha]_D^{20} = -88.9$ (*c* 1.0, DCM); $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 0.82 (d, *J* = 6.7 Hz, 3H), 0.96 (d, *J* = 6.7 Hz, 3H), 1.54–1.59 (m, 1H), 3.38–3.45 (m, 1H), 3.48–3.58 (m, 2H), 3.98 (s, 3H), 7.03 (ddd, *J* = 7.0, 5.9, 1.1 Hz, 1H), 7.26–7.51 (m, 9H), 7.81–7.88 (m, 4H); $^{13}$C NMR (75 MHz, $CDCl_3$): 19.0, 19.2, 31.8, 32.8, 69.9, 73.3, 105.8, 107.4, 110.3 (d, $J_{CP}$ = 1.0 Hz), 121.7 (d, $J_{CP}$ = 0.7 Hz), 122.8 (d, $J_{CP}$ = 1.1 Hz), 124.2, 128.3 (2d, $J_{CP}$ = 2.4, 3.3 Hz), 129.2 (d, $J_{CP}$ = 8.5 Hz), 131.3–131.8 (7 lines), 132.8 (d, $J_{CP}$ = 16.17 Hz), 134.0 (d, $J_{CP}$ = 1.1 Hz), 135.5 (d, $J_{CP}$ = 1.1 Hz), 138.4 (d, $J_{CP}$ = 10.8 Hz), 156.4 (d, $J_{CP}$ = 1.1 Hz); $^{31}$P NMR (121 MHz, $CDCl_3$): 20.7. HRMS-ESI (*m*/*z*) for $C_{27}H_{27}N_2O_2PNa$, $(M+Na)^+$ found 465.1716, calcd 465.1708.

#### 4.2.6. (*S*)-3-(Diphenylphosphoryl)-2-(4-isopropyl-4,5-dihydrooxazol-2-yl)-1-(methoxymethyl)-1*H*-indole 25b

Compound **24b** (1.00 g, 3.7 mmol) was dissolved in THF (10 ml) with TMEDA (0.72 ml, 4.8 mmol) and treated with *s*-BuLi (3.7 ml 1.4 mol/L, 5.1 mmol) at −78 °C. After 0.5 h at the same temperature, diphenylphosphinic chloride (1.0 ml, 5.1 mmol) was added. The cooling bath was removed after 0.5 h, and the reaction was allowed to warm to rt with stirring overnight. The reaction was quenched with a saturated solution of $NH_4Cl$ and extracted with ethyl acetate. The extracts were washed with brine and dried over $MgSO_4$. The solvent was removed in vacuo and the residue was purified by column chromatography (*n*-hexane/ethyl acetate = 2:1 to 1:2) to afford a light yellow solid (1.40 g, 81%). Mp 123–124 °C; $[\alpha]_D^{20} = -79.5$ (*c* 1.0, DCM); $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 0.80 (d, *J* = 6.7 Hz, 3H), 0.96 (d, *J* = 6.7 Hz, 3H), 1.50–1.54 (m, 1H), 3.23 (s, 3H), 3.40–3.48 (m, 3H), 5.78 (A, $J_{AB}$ = 10.9 Hz, 1H), 5.86 (B, $J_{AB}$ = 10.9 Hz, 1H), 7.06 (ddd, *J* = 7.2, 7.1, 1.0 Hz, 1H), 7.30 (ddd, *J* = 7.2, 7.1, 1.0 Hz, 1H), 7.40–7.50 (m, 7H), 7.55–7.58 (m, 1H), 7.80–7.89 (m, 4H); $^{13}$C NMR (75 MHz, $CDCl_3$): 18.9, 19.3, 32.8, 56.2, 70.1, 73.3, 75.2, 107.8, 109.4, 111.1 (d, $J_{CP}$ = 1.0 Hz), 122.2 (d, $J_{CP}$ = 0.7 Hz), 122.9 (d, $J_{CP}$ = 1.1 Hz), 124.7, 128.3 (2d, $J_{CP}$ = 12.4, 2.8 Hz), 129.4 (d, $J_{CP}$ = 8.5 Hz), 131.5–131.9 (8 lines), 132.5 (d, $J_{CP}$ = 16.3 Hz), 133.6 (d, $J_{CP}$ = 3.8 Hz), 135.0 (d, $J_{CP}$ = 3.9 Hz), 137.9 (d, $J_{CP}$ = 10.6 Hz), 156.2 (d, $J_{CP}$ = 1.2 Hz); $^{31}$P NMR (121 MHz, $CDCl_3$): 21.2. HRMS-ESI (*m*/*z*) for $C_{28}H_{29}N_2O_3PNa$, $(M+Na)^+$ found 495.1822, calcd 465.1814.

#### 4.2.7. (*S*)-3-(Diphenylphosphino)-2-(4-isopropyl-4,5-dihydrooxazol-2-yl)-1-methyl-1*H*-indole 13

To a mixture of **25a** (0.88 g, 2.0 mmol) and $Et_3N$ (1.1 ml, 8.0 mmol) in *m*-xylene (25 ml), trichlorosilane (0.81 ml, 8.0 mmol) was added dropwise at 0 °C. The mixture was heated to 90 °C for 3 h. The mixture was cooled on ice-bath, and the pH was adjusted to 10 by the addition of 2 M NaOH. The solution was extracted with ethyl acetate, and the organic layers were washed with brine and dried over $MgSO_4$. The solvent was removed in vacuo and the residue was purified by column chromatography (*n*-hexane/ethyl acetate = 5:1) to afford a light yellow oil (0.43 g, 50%). $[\alpha]_D^{20} = -59.4$ (*c* 1.0, DCM); $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 0.94 (d, *J* = 6.7 Hz, 3H), 1.04 (d, *J* = 6.7 Hz, 3H), 1.79–1.84 (m, 1H), 4.00 (s, 3H), 4.04–4.08 (m, 2H), 4.21–4.28 (m, 1H), 6.82–6.87 (m, 2H), 7.17–7.49 (m, 12H); $^{13}$C NMR (75 MHz, $CDCl_3$): 18.9, 19.3, 32.0, 33.2, 70.2, 73.4, 110.5, 120.6, 122.92 (d, $J_{CP}$ = 2.2 Hz), 123.8, 128.1 (d, $J_{CP}$ = 12.4 Hz), 128.4–128.5 (4 lines), 129.4 (d, $J_{CP}$ = 2.0 Hz), 132.7, 133.0 (d, $J_{CP}$ = 1.8 Hz), 133.2, 134.0, 134.5, 138.1 (d, $J_{CP}$ = 9.8 Hz), 138.1 (d, $J_{CP}$ = 9.8 Hz), 139.5 (d, $J_{CP}$ = 2.6 Hz), 158.0 (d, $J_{CP}$ = 1.0 Hz); $^{31}$P NMR (121 MHz, $CDCl_3$): −25.2. HRMS-ESI (*m*/*z*) for $C_{27}H_{28}N_2OP$, $(M+H)^+$ found 427.1946, calcd 427.1939.

#### 4.2.8. (*S*)-3-(Diphenylphosphino)-2-(4-isopropyl-4,5-dihydrooxazol-2-yl)-1-(methoxymethyl)-1*H*-indole 14

To a mixture of **25b** (0.71 g, 1.5 mmol) and $Et_3N$ (0.83 ml, 6.0 mmol) in *m*-xylene (20 ml), trichlorosilane (0.61 ml, 6.0 mmol) was added dropwise at 0 °C. The mixture was heated to 90 °C for 3 h. The mixture was cooled on ice-bath, and the pH was adjusted to 10 by the addition of 2 M NaOH. The solution was extracted with ethyl acetate, and the organic layers were washed with brine and dried over $MgSO_4$. The solvent was removed in vacuo and the residue was purified by column chromatography (*n*-hexane/ethyl acetate = 5:1) to provide light yellow oil (0.49 g, 71%). $[\alpha]_D^{20} = -53.1$ (*c* 1.0, DCM); $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 0.93 (d, *J* = 6.7 Hz, 3H), 1.04 (d, *J* = 6.7 Hz, 3H), 1.76–1.80 (m,1H), 3.24 (s, 3H), 3.96–4.04 (m, 2H), 4.20–4.23 (m, 1H), 5.83 (A, $J_{AB}$ = 10.8 Hz, 1H), 5.90 (B, $J_{AB}$ = 10.8 Hz, 1H), 6.83–6.89 (m, 2H), 7.15–7.54 (m, 12H); $^{13}$C NMR (75 MHz, $CDCl_3$): 19.0, 19.3, 33.2, 56.2, 70.3, 73.4, 75.3, 111.3, 112.6 (d, $J_{CP}$ = 16.6 Hz), 121.3, 123.0 (d, $J_{CP}$ = 2.0 Hz), 124.3, 128.2 (d, $J_{CP}$ = 11.0 Hz), 128.4–128.5 (4 lines), 129.8 (d, $J_{CP}$ = 2.0 Hz), 132.7, 133.0 (d, $J_{CP}$ = 1.4 Hz), 133.2, 133.6, 134.1, 137.7 (d, $J_{CP}$ = 10.0 Hz), 137.9 (d, $J_{CP}$ = 10.0 Hz), 139.2 (d, $J_{CP}$ = 2.4 Hz), 157.7 (d, $J_{CP}$ = 1.0 Hz); $^{31}$P NMR (121 MHz, $CDCl_3$): −24.9. HRMS-ESI (*m*/*z*) for $C_{28}H_{30}N_2O_2P$, $(M+H)^+$ found 457.2051, calcd 457.2045.

#### 4.2.9. (*S*)-3-Bromo-2-(4-isopropyl-4,5-dihydrooxazol-2-yl)-1*H*-indole 26

Compound **23** (1.70 g, 7.4 mmol) was dissolved in chloroform (30 ml), and NBS (1.32 g, 7.4 mmol) was added at 0 °C. The mixture was stirred further at the same temperature for 2 h. After concentration, water was added, followed by $Et_2O$ extraction. The organic layers were washed with brine and dried over $MgSO_4$. The solvent was removed in vacuo and the residue was triturated with *n*-hexane/ethyl acetate (5:1) to afford a light yellow solid (1.46 g). An additional amount of product (0.40 g) was obtained from the filtrate after silica chromatography (*n*-hexane/ethyl acetate = 20:1 to 5:1). Combined yield 82%. Mp 122–124 °C; $[\alpha]_D^{20} = +60.4$ (*c* 1.0, DCM); $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ = 0.87 (d, *J* = 6.7 Hz, 3H), 0.96 (d, *J* = 6.7 Hz, 3H), 1.75–1.79 (m, 1H), 4.05–4.19 (m, 2H), 4.42–4.48 (m, 1H), 7.15 (ddd, *J* = 7.0, 6.9, 0.9 Hz, 1H), 7.27 (ddd, *J* = 7.2, 7.0, 1.1 Hz, 1H), 7.44–7.46 (m, 1H), 7.47–7.48 (m, 1H), 12.03 (br, 1H); $^{13}$C NMR (75 MHz, DMSO-$d_6$): 19.1, 19.6, 33.2, 70.9, 72.6, 93.7, 113.6, 120.4, 121.7, 123.7, 125.8, 128.0, 136.8, 157.3. HRMS-ESI (*m*/*z*) for $C_{14}H_{15}N_2OBrNa$, $(M+Na)^+$ found 329.0251, calcd 329.0265.

#### 4.2.10. (*S*)-3-Bromo-2-(4-isopropyl-4,5-dihydrooxazol-2-yl)-1-methyl-1*H*-indole 27a

Compound **26** (0.86 g, 2.8 mmol) in DMF (10 ml) was added to suspension of NaH (0.17 g, 4.2 mmol) in DMF (5 ml) at 0 °C. After

stirring for 1 h at rt, the solution was recooled to 0 °C, and $CH_3I$ (0.21 ml, 3.4 mmol) was added. After 2 h at rt, the reaction was quenched with water, and the precipitate was filtered and triturated with water. Compound **27a** was obtained as a white solid (0.85 g, 94%). Mp 72–73 °C; $[\alpha]_D^{20} = -59.9$ (*c* 1.0, DCM); $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 0.95 (d, *J* = 6.8 Hz, 3H), 1.03 (d, *J* = 6.8 Hz, 3H), 1.80–1.86 (m, 1H), 3.97 (s, 3H), 4.10–4.14 (m, 2H), 4.34–4.42 (m, 1H), 7.16 (ddd, *J* = 5.9, 5.8, 2.1 Hz, 1H), 7.26–7.31 (m, 2H), 7.60 (dt, *J* = 8.4, 1.0 Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$): 18.7, 19.2, 32.8, 33.2, 70.0, 73.0, 95.7, 110.4, 120.9, 121.1, 124.9, 125.2, 127.2, 138.2, 157.3. HRMS-ESI (*m*/*z*) for $C_{15}H_{17}N_2OBrNa$, $(M+Na)^+$ found 343.0406, calcd 343.0422.

#### 4.2.11. (*S*)-3-Bromo-2-(4-isopropyl-4,5-dihydrooxazol-2-yl)-1-(methoxymethyl)-1*H*-indole 27b

Compound **26** (0.61 g, 2 mmol) in DMF (10 ml) was added to suspension of NaH (0.12 g, 3.0 mmol) in DMF (5 ml), at 0 °C. After stirring for 1 h at rt, the solution was recooled to 0 °C, and MOMCl (0.18 ml, 2.4 mmol) was added. After 2 h at rt, the reaction was quenched with water, and the precipitate was filtered and triturated with water. Compound **27b** was obtained as a white solid (0.68 g, 97%). Mp 55–57 °C; $[\alpha]_D^{20} = -46.0$ (*c* 1.0, DCM); $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 0.99 (d, *J* = 6.8 Hz, 3H), 1.07 (d, *J* = 6.8 Hz, 3H), 1.86–1.90 (m, 1H), 3.23 (s, 3H), 4.14–4.20 (m, 2H), 4.41–4.50 (m, 1H), 5.96 (A, $J_{AB}$ = 10.7 Hz, 1H), 6.03 (B, $J_{AB}$ = 10.8 Hz, 1H), 7.25 (ddd, *J* = 7.0, 6.9, 0.9 Hz 1H), 7.37 (ddd, *J* = 7.1, 7.0, 1.2 Hz 1H), 7.45 (d, *J* = 8.0, 1H), 7.65(d, *J* = 6.8 Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$): 18.8, 19.2, 33.3, 56.3, 70.1, 73.0, 75.7, 98.6, 111.3, 121.1, 122.0, 125.9, 127.7, 129.6, 138.1, 157.1. HRMS-ESI (*m*/*z*) for $C_{16}H_{19}N_2O_2BrNa$, $(M+Na)^+$ found 373.0517, calcd 373.0528.

#### 4.2.12. (*S*)-3-(Dicyclohexylphosphino)-2-(4-isopropyl-4,5-dihydrooxazol-2-yl)-1-methyl-1*H*-indole 15

A cooled solution (−78 °C) of **27a** (0.64 g, 2.0 mmol) in THF (10 ml) was treated with *n*-BuLi (0.96 ml, 2.5 mol/L, 2.4 mmol). After 0.5 h under the same temperature, chlorodicyclohexylphosphine (0.55 ml, 2.4 mmol) was added. The temperature was allowed to gradually reach rt with stirring overnight. The reaction was quenched with a saturated solution of $NH_4Cl$ and extracted with ethyl acetate. The extracts were washed with brine and dried over $MgSO_4$. The solvent was removed in vacuo and the residue was purified by silica chromatography (*n*-hexane/ethyl acetate = 10:1 to 5:1) to afford a colorless oil (0.61 g, 70%). $[\alpha]_D^{20} = -36.5$ (*c* 1.0, DCM); $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 1.00–1.96 (m, 27H), 2.20–2.36 (m, 2H), 3.86 (s, 3H), 4.15–4.18 (m, 2H), 4.44–4.53 (m, 1H), 7.14 (ddd, *J* = 6.8, 6.8, 1.3 Hz, 1H), 7.28 (td, *J* = 6.7, 1.0 Hz 1H), 7.34 (m, 1H), 7.89 (d, *J* = 8.0 Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$): 19.0, 19.5, 26.6 (d, $J_{CP}$ = 1.3 Hz), 27.4–27.6 (8 lines), 30.4, 30.6 (d, $J_{CP}$ = 2.6 Hz), 30.7, 31.8, 32.0 (d, $J_{CP}$ = 7.5 Hz), 32.3 (d, $J_{CP}$ = 7.5 Hz), 33.3, 34.2, 34.3 (d, $J_{CP}$ = 4.1 Hz), 34.5, 70.3, 73.5, 109.8 (d, $J_{CP}$ = 21.8 Hz), 110.4, 120.4, 122.9 (d, $J_{CP}$ = 3.0 Hz), 123.4, 139.0 (d, $J_{CP}$ = 2.2 Hz), 158.8; $^{31}$P NMR (121 MHz, $CDCl_3$): −15.1. HRMS-ESI (*m*/*z*) for $C_{27}H_40N_2OP$, $(M+H)^+$ found 439.2875, calcd 439.2878.

#### 4.2.13. (*S*)-3-(Dicyclohexylphosphino)-2-(4-isopropyl-4,5-dihydrooxazol-2-yl)-1-(methoxy-methyl)-1*H*-indole 16

A cooled solution (−78 °C) of **27b** (0.53 g, 1.5 mmol) in THF (5 ml) was treated with *n*-BuLi (0.72 ml, 2.5 mol/L, 1.8 mmol). After 0.5 h under the same temperature, chlorodicyclohexylphosphine (0.41 ml, 1.8 mmol) was added. The temperature was allowed to gradually reach rt with stirring overnight. The reaction was quenched with a saturated solution of $NH_4Cl$ and extracted with ethyl acetate. The extracts were washed with brine and dried over $MgSO_4$. The solvent was removed in vacuo and the residue was purified by silica chromatography (*n*-hexane/ethyl acetate = 10:1 to 5:1) to afford a colorless oil (0.47 g, 66%). $[\alpha]_D^{20} = -33.8$ (*c* 1.0, DCM); $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 1.00–2.00 (m, 27H), 2.29–2.34 (m, 2H), 3.17 (s, 3H), 4.12–4.20 (m, 2H), 4.47–4.51 (m, 1H), 5.71 (A, $J_{AB}$ = 10.9 Hz, 1H), 5.76 (B, $J_{AB}$ = 10.9 Hz, 1H), 7.18 (ddd, *J* = 7.2, 7.0, 1.0 Hz, 1H), 7.30 (ddd, *J* = 7.1, 7.1, 1.1 Hz 1H), 7.53 (d, *J* = 8.2 Hz, 1H), 7.89 (d, *J* = 8.0 Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$): 19.1, 19.6, 26.6 (d, $J_{CP}$ = 1.5 Hz), 27.3–27.5 (5 lines), 30.4, 30.6 (d, $J_{CP}$ = 1.6 Hz), 30.7, 32.1 (d, $J_{CP}$ = 4.9 Hz), 32.4 (d, $J_{CP}$ = 7.8 Hz), 33.3, 34.2, 34.4 (d, $J_{CP}$ = 2.9 Hz), 34.5, 56.1, 70.4, 73.6, 75.2, 111.3, 112.0 (d, $J_{CP}$ = 23.5 Hz), 121.2, 122.9 (d, $J_{CP}$ = 2.8 Hz), 124.0, 138.7 (d, $J_{CP}$ = 2.0 Hz), 158.5; $^{31}$P NMR (121 MHz, $CDCl_3$): −15.4. HRMS-ESI (*m*/*z*) for $C_{28}H_{42}N_2O_2P$, $(M+H)^+$ found 469.2980, calcd 469.2984.

### 4.3. Preparation of ligands 17–20

#### 4.3.1. Indole-3-carboxylic acid 29

At first, indole (2.34 g, 20 mmol) was dissolved in DMF (10 ml) and trifluoroacetic anhydride (4.2 ml, 30 mmol) was added dropwise at 0 °C. After stirring for 3 h at rt, water was added and the pink solid was filtered. The collected solid was treated with 20% NaOH (40 ml, 0.2 mol) at 50 °C overnight. After cooling to rt, the solution was extracted with $Et_2O$. The aqueous phase was acidified with concd HCl and the product was filtered. Compound **29** was obtained as a light yellow solid (2.47 g, 77%). Mp 194–196 °C (decomposed); $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 7.14–7.33 (m, 2H), 7.46–7.50 (m, 1H), 8.00–8.06 (m, 2H), 11.85–11.97 (m, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$): 108.4, 113.2, 121.6, 122.0, 123.2, 127.0, 133.3, 137.5, 167.0.

#### 4.3.2. (*S*)-*N*-(1-Hydroxy-3-methylbutan-2-yl)-1*H*-indole-3-carboxamide 30

The EDC hydrochloride (2.30 g, 12 mmol) was added to a mixture of **29** (1.61 g, 10 mmol) and $Et_3N$ (2.8 ml, 20 mmol) in $CH_2Cl_2$ (30 ml), and stirred for 0.5 h under rt. Next, L-valinol (1.24 g, 12 mmol) in $CH_2Cl_2$ (5 ml) was added dropwise and the mixture was stirred overnight at rt. The precipitate formed was filtered and triturated with 1 M HCl and $CH_2Cl_2$. Compound **30** was obtained as a white solid (1.85 g, 75%). Mp 193–195 °C (decomposed); $[\alpha]_D^{20} = -37.8$ (*c* 1.0, MeOH); $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ = 0.89–0.93 (2 × d, *J* = 6.7 Hz, 6H), 1.90–1.97 (m, 1H), 3.50–3.54 (m, 2H), 3.80–3.82 (m, 1H), 4.60 (t, *J* = 5.5 Hz, 1H), 7.06–7.16 (2 × td, *J* = 7.1, 1.4 Hz, 2H), 7.35 (d, *J* = 8.9 Hz, 1H), 7.41 (dd, *J* = 7.0, 1.6 Hz, 1H), 8.11–8.13 (m, 2H), 11.5 (br, 1H); $^{13}$C NMR (75 MHz, DMSO-$d_6$): 19.6, 20.7, 29.5, 56.3, 62.6, 111.8, 112.7, 121.1, 122.0, 122.7, 127.2, 128.6, 137.0, 165.5. HRMS-ESI (*m*/*z*) for $C_{14}H_{18}N_2O_2Na$, $(M+Na)^+$ found 269.1254, calcd 269.1266.

#### 4.3.3. (*S*)-3-(4-Isopropyl-4,5-dihydrooxazol-2-yl)-1*H*-indole 31

At first, MsCl (2.3 ml, 29.2 mmol) was added to a cooled mixture (0 °C) of **30** (2.88 g, 11.7 mmol), $Et_3N$ (13.0 ml, 93.6 mmol), and DMAP (0.28 g, 2.3 mmol) in $CH_2Cl_2$/DMF (40 ml:10 ml). After 3 h at rt, the starting material was consumed. The reaction was quenched with water and extracted with $CH_2Cl_2$. The extracts were washed with brine and dried over $MgSO_4$. The solvent was removed in vacuo and the residue was purified by column chromatography (*n*-hexane/ethyl acetate = 3:1 to 2:1) to afford **31** as a white solid (2.05 g, 77%). Mp 139–140 °C; $[\alpha]_D^{20} = -29.7$ (*c* 1.0, DCM); $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 0.97 (d, *J* = 6.8 Hz, 3H), 1.11 (d, *J* = 6.8 Hz, 3H), 1.86–1.92 (m, 1H), 4.13–4.20 (m, 2H), 4.37–4.41 (m, 1H), 7.19–7.31 (m, 3H), 7.62 (d, *J* = 2.7 Hz, 1H), 8.24 (dd, *J* = 6.2, 2.7 Hz, 1H), 10.44 (br, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$): 18.4, 19.2, 33.3, 69.6, 72.1, 104.8, 112.0, 121.4, 121.6, 123.0, 126.0, 128.6, 136.6, 162.0.

#### 4.3.4. (*S*)-3-(4-Isopropyl-4,5-dihydrooxazol-2-yl)-1-methyl-1*H*-indole 32a

Compound **31** (0.57 g, 2.5 mmol) in THF (5 ml) was added to a suspension of NaH (0.12 g, 3.0 mmol) in THF (5 ml) at 0 °C. After stirring for 1 h at rt, the solution was recooled to 0 °C, and $CH_3I$ (0.17 ml, 2.8 mmol) was added. After 2 h at rt, the reaction was quenched with water and extracted with $Et_2O$. The organic layer was washed with brine and dried over $MgSO_4$. The solvent was removed in vacuo and the residue was purified by column chromatography (*n*-hexane/ethyl acetate = 5:1 to 2:1) to afford **32a** as a light yellow oil (0.60 g, 99%). $[\alpha]_D^{20} = -35.0$ (*c* 0.8, DCM); $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 0.95 (d, *J* = 6.8 Hz, 3H), 1.06 (d, *J* = 6.8 Hz, 3H), 1.84–1.88 (m, 1H), 3.80 (s, 3H), 4.04–4.11 (m, 2H), 4.32–4.38 (m, 1H), 7.22–7.34 (m, 3H), 7.60 (s, 1H), 8.21–8.25 (m, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$): 18.5, 19.3, 33.4, 33.5, 69.3, 72.8, 104.2, 109.7, 121.4, 122.1, 122.8, 126.7, 132.1, 137.4, 160.6. HRMS-ESI (*m*/*z*) for $C_{15}H_{19}N_2O$, $(M+H)^+$ found 243.1486, calcd 243.1497.

#### 4.3.5. (*S*)-3-(4-Isopropyl-4,5-dihydrooxazol-2-yl)-1-(methoxymethyl)-1*H*-indole 32b

Compound **31** (0.91 g, 4 mmol) in THF (10 ml) was added to a suspension of NaH (0.24 g, 6 mmol) in THF (10 ml) at 0 °C. After stirring for 1 h at rt, the solution was recooled to 0 °C, and MOMCl (0.36 ml, 4.8 mmol) was added. After 2 h at rt, the reaction was quenched with water and extracted with $Et_2O$. The organic layers were washed with brine and dried over $MgSO_4$. The solvent was removed in vacuo and the residue was purified by column chromatography (*n*-hexane/ethyl acetate = 3:1) to provide **32b** as a light yellow oil (0.83 g, 76%). $[\alpha]_D^{20} = -31.2$ (*c* 1.0, DCM); $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 0.96 (d, *J* = 6.8 Hz, 3H), 1.08 (d, *J* = 6.8 Hz, 3H), 1.85–1.89 (m, 1H), 3.23 (s, 3H), 4.05–4.15 (m, 2H), 4.33–4.36 (m, 1H), 5.42 (A, $J_{AB}$ = 11.0 Hz, 1H), 5.44 (B, $J_{AB}$ = 11.0 Hz, 1H), 7.27–7.32 (m, 2H), 7.47–7.50 (m, 1H), 7.70 (s, 1H), 8.25–8.29 (m, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$): 18.6, 19.3, 33.4, 56.3, 69.4, 72.9, 78.1, 105.7, 110.5, 122.1, 122.3, 123.4, 127.2, 131.2, 136.8, 160.3. HRMS-ESI (*m*/*z*) for $C_{16}H_{21}N_2O_2$, $(M+H)^+$ found 273.1592, calcd 273.1603.

#### 4.3.6. (*S*)-2-(Dicyclohexylphosphino)-3-(4-isopropyl-4,5-dihydrooxazol-2-yl)-1-methyl-1*H*-indole 17

A cooled solution (−78 °C) of **32a** (0.48 g, 2 mmol) and TMEDA (0.36 ml, 2.4 mmol) in THF (8 ml) was treated with *t*-BuLi (1.4 ml, 2.4 mmol). After 0.5 h under the same temperature, chlorodicyclohexylphosphine (0.59 ml, 2.6 mmol) was added. The temperature was allowed to reach rt with stirring overnight. The reaction was quenched with saturated solution of $NH_4Cl$ and extracted with ethyl acetate. The extracts were washed with brine and dried over $MgSO_4$. The solvent was removed in vacuo and the residue was purified by column chromatography (*n*-hexane/ethyl acetate = 20:1) to afford a white solid (0.54 g, 61%). Mp 90–91 °C; $[\alpha]_D^{20} = -21.0$ (*c* 1.0, DCM); $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 0.88–1.98 (m, 27H), 2.68–2.77 (m, 2H), 4.00 (s, 3H), 4.04–4.13 (m, 2H), 4.36–4.44 (m, 1H), 7.15–7.28 (m, 2H), 7.31–7.34 (m, 1H), 8.20–8.23 (m, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$): 19.1, 19.6, 26.5 (d, $J_{CP}$ = 1.7 Hz), 27.0–27.3 (6 lines), 30.9, 31.0 (d, $J_{CP}$ = 1.2 Hz), 32.2, 32.5 (d, $J_{CP}$ = 5.0 Hz), 32.8 (d, $J_{CP}$ = 4.7 Hz), 33.1, 33.6, 34.4, 34.5 (d, $J_{CP}$ = 1.8 Hz), 34.7, 69.5, 73.1, 109.9 (d, $J_{CP}$ = 1.2 Hz), 121.2, 121.9, 122.8, 127.9 (d, $J_{CP}$ = 1.0 Hz), 138.7 (d, $J_{CP}$ = 2.8 Hz), 161.3; $^{31}$P NMR (121 MHz, $CDCl_3$): −16.2. HRMS-ESI (*m*/*z*) for $C_{27}H_{40}N_2OP$ $(M+H)^+$ found 439.2871, calcd 439.2878.

#### 4.3.7. (*S*)-2-(Dicyclohexylphosphino)-3-(4-isopropyl-4,5-dihydrooxazol-2-yl)-1-(methoxy-methyl)-1*H*-indole 18

A cooled solution (−78 °C) of **32b** (0.11 g, 0.4 mmol) and TMEDA (0.07 ml, 0.48 mmol) in THF (2.5 ml) was treated with *t*-BuLi (0.28 ml, 0.48 mmol). After 0.5 h at the same temperature, chlorodicyclohexylphosphine (0.12 ml, 0.42 mmol) was added. The temperature was allowed to reach rt with stirring overnight. The reaction was quenched with saturated solution of $NH_4Cl$ and extracted with ethyl acetate. The extracts were washed with brine and dried over $MgSO_4$. The solvent was removed in vacuo and the residue was purified by column chromatography (*n*-hexane/ethyl acetate = 20:1) to afford a colorless oil (0.13 g, 70%). $[\alpha]_D^{20} = -20.1$ (*c* 1.0, DCM); $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 0.85–2.00 (m, 27H), 2.63–2.80 (m, 2H), 3.28 (s, 3H), 4.07–4.15 (m, 2H), 4.39–4.42 (m, 1H), 5.94 (app d, *J* = 3.7 Hz, 2H), 7.20–7.28 (2 × td, *J* = 7.0, 1.5 Hz, 2H), 7.51 (dd, *J* = 7.0, 1.7 Hz, 1H), 8.20 (dd, *J* = 7.0, 1.7 Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$): 19.1, 19.5, 26.5 (d, $J_{CP}$ = 1.6 Hz), 27.1–27.4 (5 lines), 30.8, 31.0 (d, $J_{CP}$ = 1.4 Hz), 32.5, 32.8 (d, $J_{CP}$ = 4.1 Hz), 33.1, 33.6, 34.8, 34.9, 35.0, 55.8, 69.6, 73.1, 74.6 (d, $J_{CP}$ = 24.1 Hz), 110.6 (d, $J_{CP}$ = 1.7 Hz), 121.9 (d, $J_{CP}$ = 2.8 Hz), 123.4, 128.2, 138.6 (d, $J_{CP}$ = 2.5 Hz), 140.0 (d, $J_{CP}$ = 24.1 Hz), 161.1; $^{31}$P NMR (121 MHz, $CDCl_3$): −17.1. HRMS-ESI (*m*/*z*) for $C_{28}H_{42}N_2O_2P$ $(M+H)^+$ found 469.2989, calcd 469.2984.

#### 4.3.8. (*S*)-2-(Diphenylphosphino)-3-(4-isopropyl-4,5-dihydrooxazol-2-yl)-1-methyl-1*H*-indole 19

A cooled solution (−78 °C) of **32a** (0.34 g, 1.4 mmol) and TMEDA (0.25 ml, 1.7 mmol) in degassed THF (5 ml) was treated with *t*-BuLi (1.0 ml, 1.7 mol/L, 1.7 mmol). After 0.5 h at the same temperature, chlorodiphenylphosphine (0.32 ml, 1.8 mmol) was added. The temperature was allowed to reach rt with stirring overnight. The reaction was quenched with saturated solution of $NH_4Cl$ and extracted with ethyl acetate. The extracts were washed with brine and dried over $MgSO_4$. The solvent was removed in vacuo and the residue was purified by column chromatography (*n*-hexane/ethyl acetate = 10:1) to afford a white solid (0.36 g, 60%). Mp 52–53 °C; $[\alpha]_D^{20} = -75.6$ (*c* 1.0, DCM); $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 0.89 (d, *J* = 6.7 Hz, 3H), 1.01 (d, *J* = 6.7 Hz, 3H), 1.68–1.73 (m, 1H), 3.49 (s, 3H), 3.52–3.82 (m, 3H), 7.21–8.15 (m, 13H), 8.17 (d, *J* = 7.9 Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$): 18.9, 19.4, 32.6 (d, $J_{CP}$ = 11.2 Hz), 33.4, 69.5, 72.7, 109.6 (d, $J_{CP}$ = 1.0 Hz), 121.4, 121.9 (d, $J_{CP}$ = 0.9 Hz), 123.9, 127.7 (d, $J_{CP}$ = 4.9 Hz), 128.4, 128.8 (d, $J_{CP}$ = 6.7 Hz), 128.9, 132.2–133.2 (4 lines), 135.1 (d, $J_{CP}$ = 10.0 Hz), 135.4 (d, $J_{CP}$ = 10.0 Hz), 139.7 (d, $J_{CP}$ = 1.7 Hz), 160.6; $^{31}$P NMR (121 MHz, $CDCl_3$): −24.1. HRMS-ESI (*m*/*z*) for $C_{27}H_{28}N_2OP$ $(M+H)^+$ found 427.1941, calcd 427.1939.

#### 4.3.9. (*S*)-2-(Diphenylphosphino)-3-(4-isopropyl-4,5-dihydrooxazol-2-yl)-1-(methoxymethyl)-1*H*-indole 20

A cooled solution (−78 °C) of **32b** (0.46 g, 1.7 mmol) and TMEDA (0.38 ml, 2.5 mmol) in degassed THF (5 ml) was treated with *t*-BuLi (1.5 ml, 1.7 mol/L, 2.5 mmol). After 0.5 h at the same temperature, chlorodiphenylphosphine (0.47 ml, 2.5 mmol) was added. The temperature was allowed to reach rt with stirring overnight. The reaction was quenched with a saturated solution of $NH_4Cl$ and extracted with ethyl acetate. The extracts were washed with brine and dried over $MgSO_4$. The solvent was removed in vacuo and the residue was purified by column chromatography (*n*-hexane/ethyl acetate = 10:1) to afford a white solid (0.44 g, 57%). Mp 89–90 °C; $[\alpha]_D^{20} = -77.6$ (*c* 1.0, DCM); $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 0.84 (d, *J* = 6.8 Hz, 3H), 0.98 (d, *J* = 6.8 Hz, 3H), 1.58–1.63 (m, 1H), 2.91 (s, 3H), 3.42–3.46 (m, 2H), 3.53–3.57 (m, 1H), 5.68 (app d, *J* = 2.6 Hz, 2H), 7.21–7.32 (m, 9H), 7.38–7.55 (m, 4H), 8.07–8.10 (m, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$): 19.3, 19.4, 33.2, 55.5 (d, $J_{CP}$ = 1.3 Hz), 69.3, 72.5, 75.4 (d, $J_{CP}$ = 17.0 Hz), 110.6 (d, $J_{CP}$ = 1.6 Hz), 114.0 (d, $J_{CP}$ = 2.2 Hz), 121.6, 122.0, 124.3, 128.0–128.9 (8 lines), 132.6 (d, $J_{CP}$ = 20.6 Hz), 133.7 (d, $J_{CP}$ = 20.4 Hz), 134.3 (d, $J_{CP}$ = 6.4 Hz), 135.0 (d, $J_{CP}$ = 6.2 Hz), 136.6 (d, $J_{CP}$ = 19.3 Hz), 139.2 (d, $J_{CP}$ = 2.5 Hz), 160.1; $^{31}$P NMR (121 MHz, $CDCl_3$): −23.1. HRMS-ESI (*m*/*z*) for $C_{28}H_{30}N_2O_2P$ $(M+H)^+$ found 457.2035, calcd 457.2045.

#### 4.3.10. (*R*)-2-(Diphenylphosphino)-3-(4-isopropyl-4,5-dihydrooxazol-2-yl)-1-(methoxymethyl)-1*H*-indole (*R*)-20

Mp 89–90 °C; $[\alpha]_D^{20} = +79.5$ (*c* 1.0, DCM); $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 0.83 (d, *J* = 6.7 Hz, 3H), 0.97 (d, *J* = 6.7 Hz, 3H), 1.58–1.61 (m, 1H), 2.90 (s, 3H), 3.42–3.46 (m, 2H), 3.56–3.59 (m, 1H), 5.68 (app d, *J* = 2.6 Hz, 2H), 7.20–7.56 (m, 13H), 8.08–8.11 (m, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$): 18.9, 19.3, 33.1, 55.5 (d, $J_{CP}$ = 1.3 Hz), 69.3, 72.5, 75.2 (d, $J_{CP}$ = 17.0 Hz), 110.6 (d, $J_{CP}$ = 1.6 Hz), 114.0 (d, $J_{CP}$ = 2.2 Hz), 121.5, 122.0, 124.3, 128.0–128.8 (8 lines), 132.6 (d, $J_{CP}$ = 19.1 Hz), 133.7 (d, $J_{CP}$ = 20.3 Hz), 134.2 (d, $J_{CP}$ = 6.4 Hz), 134.9 (d, $J_{CP}$ = 6.3 Hz), 136.5 (d, $J_{CP}$ = 19.4 Hz), 139.1 (d, $J_{CP}$ = 2.5 Hz), 160.0; $^{31}$P NMR (121 MHz, $CDCl_3$): −23.2. HRMS-ESI (*m*/*z*) for $C_{28}H_{30}N_2O_2P$ $(M+H)^+$ found 457.2039, calcd 457.2045.

### 4.4. General procedure for allylic alkylation

IndPHOX ligand (4.8 mmol %), $[Pd(allyl)Cl]_2$ (1.6 mmol %), KOAc (4 mmol %), and 2 mL of THF were added into the flask, and stirred for 0.5 h at rt. Then **33** (0.10 g, 0.4 mmol) in 2 mL of THF, BSA (0.30 ml, 1.2 mmol), and dimethyl malonate (0.14 ml, 1.2 mmol) were added separately. After stirring at rt for 1–24 h, the solvent was removed in vacuo and the residue was purified by column chromatography (*n*-hexane/ethyl acetate = 20:1) to afford **34** as a colorless oil. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 3.51 (s, 3H), 3.70 (s, 3H), 3.96 (d, *J* = 10.9 Hz, 1H), 4.27 (dd, *J* = 8.5, 10.9 Hz, 1H), 6.33 (dd, *J* = 15.8, 8.5 Hz, 1H), 6.48 (d, *J* = 15.8 Hz, 1H), 7.19–7.34 (m, 10H); $^{13}$C NMR (75 MHz, $CDCl_3$): 49.5, 52.8, 52.9, 57.9, 126.7, 127.5, 127.9, 128.2, 128.8, 129.0, 129.4, 132.1, 137.1, 140.4, 168.1, 168.5. The enantiomeric excess was determined by HPLC using a Chiralpak IA column: *i*-PrOH/hexane: 5:95; flow rate: 1 mL/min; UV at 254 nm; $t_{R1}$ = 18.6 min, $t_{R2}$ = 23.6 min.

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