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Indole-olefin-oxazoline (IndOlefOx)-ligands: synthesis and utilization in asymmetric Rh-catalyzed conjugate addition

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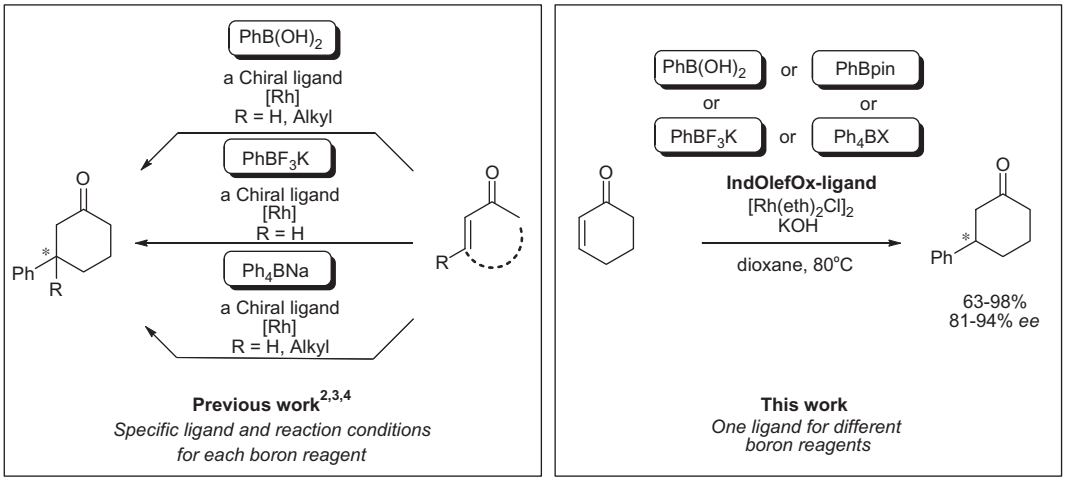
ABSTRACT

The synthesis and utility of novel indole-olefin-oxazoline (IndOlefOx)-ligands are described. The use of these ligands was demonstrated in rhodium catalyzed asymmetric conjugate additions between 2-cyclopentenone, 2-cyclohexenone, and 2-cycloheptenone with different boron reagents with good yields and enantioselectivities of up to 94%.

1. Introduction

The transition metal catalyzed conjugate addition of organometallic reagents to electron-deficient alkenes is a widely used process in organic chemistry. The stability and chemoselective nature of organoboron compounds make these handy tools for this reaction.[1] Despite the many examples of this transformation, the examples are usually restricted to the utilization of only one certain boron reagent with a specific substrate and ligand (Scheme 1).[2–4] Liao et al.[4a] have reported a rhodium catalyzed addition reaction in the presence of a chiral bis-sulfoxide ligand, where a challenging substrate, chromenone, was used as an enone. In this example, the phenylboronic acid produced the 1,4-addition product in low yield (32%), whereas the use of sodium tetraphenylborate as a coupling partner improved the yield to 75%. In a study on stereogenic quaternary carbon centers, Hayashi et al.[4b] noticed a similar phenomenon. The desired products were obtained only by utilizing sodium tetraphenylborate in the addition reaction. It was discovered later that a different Rh-source and ligand allowed the use of phenylboroxine as well.[5] Recently, Glorius et al.[2a] reported the utilization of an oxazoline based ligand (OlefOx) in a conjugate addition. These ligands enabled the use of phenylboronic



Scheme 1. Asymmetric addition of boron compounds to enones.

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acid in the construction of quaternary carbon centers for the first time. However, the use of other boron reagents was not investigated. Our recent interest toward oxazolines and indoles as ligand scaffolds[6] inspired us to synthesize a series of novel indole-olefin-oxazoline ligands in order to investigate the conjugate addition between an α,β-unsaturated enone and different boron reagents (Scheme 1).

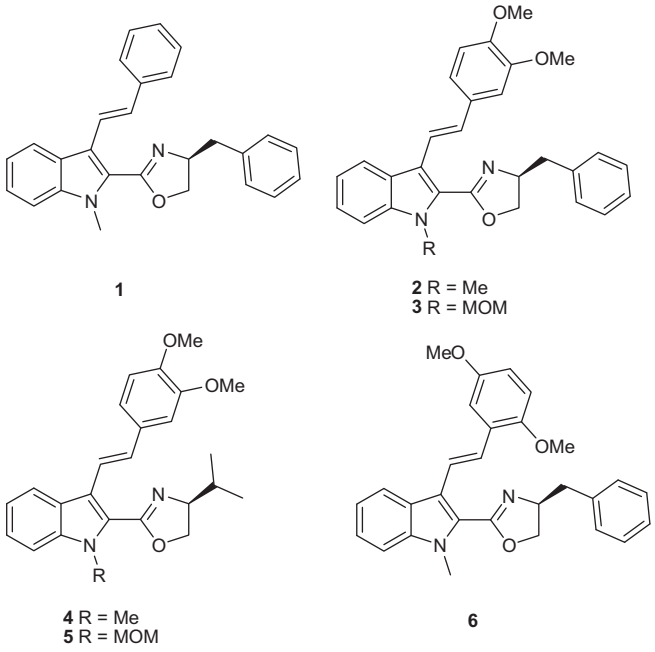
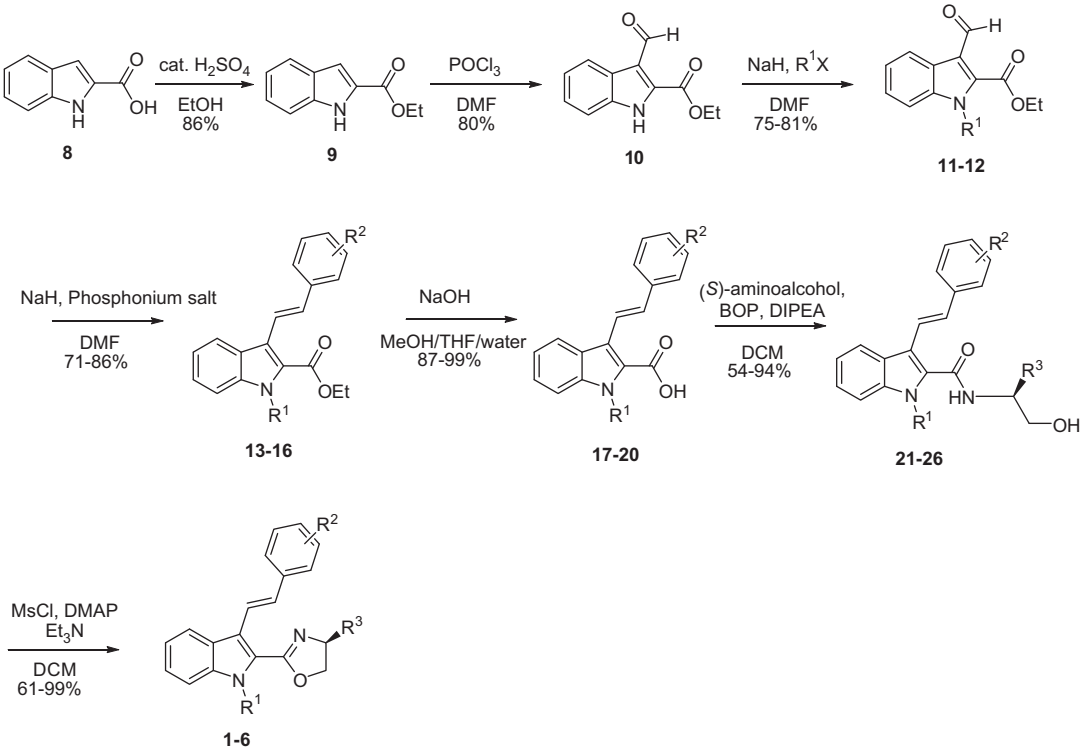


Figure 1. Structures of the prepared IndOlefOx-ligands **1**–**6**.

2. Results and discussion

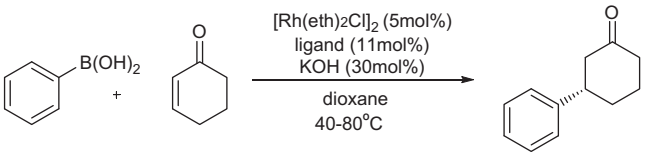
IndOlefOx-ligands **1**–**6** (Fig. 1) were synthesized according to Scheme 2. Compounds **11** and **12** were obtained from commercially available 2-indolecarboxylic acid **8** (52% and 56% yields, over 3 steps). The aldehydes were then subjected to a Wittig reaction with phosphonium salts to provide the olefinic compounds **13**–**16** in good yields (71–86%). After hydrolysis, acids **17**–**20** were subjected to BOP mediated amide formation with aminoalcohols.[7] Finally, amido alcohols **21**–**26** were treated with MsCl in the presence of DMAP to give the desired IndOlefOx ligands **1**–**6** (Fig. 1) in acceptable overall yields (13–26%, over 7 steps). All purifications were carried out by recrystallization and there was no need for column chromatography.

To evaluate the utility of the IndOlefOx-ligands, the conjugate addition of phenylboronic acid to 2-cyclohexenone was chosen as the model reaction (Table 1). With ligand **1**, the reaction proceeded smoothly and the addition product was obtained in 98% yield and 64% ee (Table 1, entry 1). Glorius et al.[2a] noticed that electron-donating methoxy groups in their structurally similar ligands increased the enantioselectivity. Also in our case, ligands **2**–**5** with a 3,4-dimethoxy motif gave the highest enantioselectivities (Table 1, entries 2–5). Methoxy groups at the 2- and 5-positions in ligand **6,** however, reduced both the yield and enantioselectivity (Table 1, entry 6). We believe that the proximity of the methoxy substituent at the *ortho*-position affects complex formation in a negative manner. The oxazoline-moieties of ligands **2**–**5** were derived either from phenylalaninol (ligands **2** and **3**) or valinol (ligands **4** and **5**). The ligands derived from phenylalaninol (Table 1, entries 2 and 3) gave better results than those derived from valinol (Table 1, entries 4 and 5) in terms of yield and ee%. We also compared the ligands with different substituents at the indole nitrogen. When ligands **4** and **5** were compared, higher yields and ee% were obtained when the ligand bore a methyl-group at the 1-position (Table 1, entries 4 and 5). Although ligands **2** and **3** both



Scheme 2. Synthesis route to IndOlefOx-ligands **1**–**6**.

Table 1
Screening of ligands **1–7** in 1,4-addition of phenylboronic acid to 2-cyclohexenone[a]



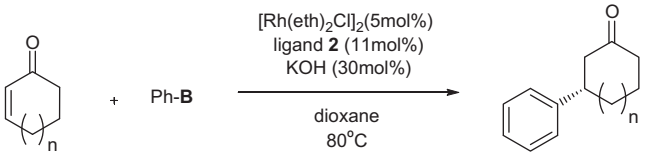
Entry	Ligand	Temp (°C)	Time (h)	Yield[b] (%)	ee[c] (%)
1	**1**	80	4	98	64
2	**2**	80	2	87	89
3	**3**	80	24	57	89
4	**4**	80	24	72	89
5	**5**	80	24	44	74
6	**6**	80	24	68	61
7	**7**[d]	80	24	46	0
8	**2**	60	21	78	92
9	**2**	40	24	43	94
10	—	80	24	33	—

[a] General procedure: ligand (0.057 mmol) and $[Rh(eth)_2Cl]_2$ (0.026 mmol) were stirred in dioxane (1.6 ml) 10 min. Next, $PhB(OH)_2$ (0.78 mmol) was added to the reaction followed by 1 M KOH (aq) (0.16 ml) and cyclohexenone (0.52 mmol). The reaction mixture was stirred until TLC showed an absence of starting material (max 24 h).
[b] Yield of isolated product.
[c] Determined by HPLC analysis with chiral stationary phase column (Chiralpak IA).
[d] See Ref. 8.

induced good enantioselectivities, the yield with ligand **3** was much lower (Table 1, entries 2 and 3). When the reactions were performed with ligand **2** (at reduced temperatures), higher enantioselectivity was achieved at the expense of yield and reaction times (Table 1, entries 8 and 9). To prove the indispensability of the olefinic moiety in the ligand structure, the double bond in ligand **4** was reduced to afford ligand **7**.[8] Conjugate addition reactions with this ligand gave a racemic mixture with low yield (Table 1, entry 7). The reaction without any ligand produced a racemic product in 33% yield (Table 1, entry 10). In conclusion, we have discovered that ligand **2** was found to be the most practical ligand for this reaction, when taking into account reaction time, yield and enantioselectivity.

After the successful reaction with phenylboronic acid, we turned our attention to different boron reagents. All reactions were performed with the most promising ligand **2** at 80 °C. With all the tested organoboron compounds, moderate to excellent yields (63–98%) and good enantioselectivities (83–94%) were achieved (Table 2, entries 1–7). In addition to the commercially available boron reagents, we also investigated the suitability of triethylammonium tetra-arylborates[9] (TEATAB) in the reaction (Table 2, entries 6 and 7). Tetra-arylborates are noteworthy coupling partners, which can transfer all four aryl groups from the substrate to the product efficiently.[9,10] A literature survey revealed that usually 2–4 equiv of tetra-arylborate are needed for successful conjugate additions.[4] We found that the amount of tetra-arylborate can be decreased even to 0.5 equiv and, therefore, better atom-economy can be achieved (Table 2, entries 5 and 7). In addition, enones with different ring sizes were tested in the reaction (Table 2, entries 8 and 9).

Table 2
Rhodium-catalyzed 1,4-addition of phenylboron reagents to cyclic enones[a]



Entry	Enone	Ph-B	Equiv	Time (h)	Yield[b] (%)	ee[c,d] (%)
1	$n = 1$	$PhB(OH)_2$	1.2	2	87	89
2	$n = 1$	PhBpin	1.2	24	78	94
3	$n = 1$	$PhBF_3K$	1.2	24	63	86
4	$n = 1$	Ph_4BNa	1.2	4	79	90
5	$n = 1$	Ph_4BNa	0.5	6	66	90
6	$n = 1$	Ph_4BNHEt_3	1.2	22	67	81
7	$n = 1$	Ph_4BNHEt_3	0.5	22	98	83
8	$n = 0$	PhBpin	1.2	24	94	91
9	$n = 2$	PhBpin	1.2	24	89	75

[a] General procedure: ligand **2** (0.057 mmol) and $[Rh(eth)_2Cl]_2$ (0.026 mmol) were stirred in dioxane (1.6 ml) for 10 min. Next, the phenylboron reagent (0.78 mmol) was added to the reaction followed by 1 M KOH (aq) (0.16 ml) and the cyclic enone (0.52 mmol). The reaction mixture was stirred until TLC showed an absence of starting material (max 24 h).
[b] Yield of isolated product.
[c] Determined by HPLC analysis with a chiral stationary phase column (Chiralpak IA/Chiralpak IC).
[d] The specific rotation has been determined for the products obtained.

3. Conclusion

In conclusion, we have designed and synthesized six indole-olefin-oxazoline (IndOlefOx)-ligands. These ligands were prepared conveniently in acceptable overall yields without chromatographic purification. We have demonstrated that these ligands enabled the utilization of all common organoboron reagents for a Rh-catalyzed asymmetric 1,4-addition reaction with good yield and enantioselectivity.

4. Experimental

4.1. General

All solvents and chemicals were used as received. Dioxane and 1 M KOH (aq) solutions were bubbled with argon before use. TLC was performed on precoated (Silica Gel 60 F254) aluminum plates and visualization was performed by UV-light or using Hanessian's stain (5 g $CeSO_4$, 25 g $(NH_4)Mo_7O_{24}{\cdot}4H_2O$, 450 ml water, 50 ml conc H_2SO_4) Silica Gel 60, particle size 0.040–0.063 nm was used for chromatography. ^1H and ^{13}C NMR spectra were measured at 300 and 75 MHz, respectively, using $CDCl_3$ or DMSO-d_6 as solvents. Chemical shifts are reported in δ values (ppm) relative to tetramethylsilane.

4.2. Preparation of compounds 9–12

4.2.1. Ethyl-1*H*-indole-2-carboxylate 9

A solution of indole-2-carboxylic acid **8** (25 g, 0.16 mol) and concentrated H_2SO_4 (2 ml) in EtOH (250 ml) was refluxed for 18 h. The reaction mixture was allowed to cool at room temperature, concentrated and filtered. The crude product was washed with water and recrystallized from EtOH. Product **9** was obtained as a yellow solid (20.5 g, 80%). Mp 122–123 °C; ^1H NMR (300 MHz, DMSO-d_6) δ: 11.91 (br s, 1H), 7.66 (d, 1H, J = 8.3 Hz), 7.49 (d, 1H, J = 8.0 Hz), 7.16 (s, 1H) 7.26 (t, 1H, J = 7.6 Hz), 7.07 (t, 1H, J = 7.6 Hz), 4.34 (q, 2H, J = 7.1 Hz), 1.33 (t, 3H, J = 7.1 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 161.4, 137.5, 127.4, 126.8, 124.7, 122.1, 120.2, 112.7, 107.7, 60.5, 14.3. HRMS-ESI (m/z) for $C_{11}H_{11}NO_2Na$, (M+Na) found 212.0676, calcd 212.0687.

4.2.2. Ethyl-3-formyl-1*H*-indole-2-carboxylate[11] 10

At first, $POCl_3$ (9.8 ml, 0.11 mol) was added dropwise to DMF (30 ml) at 0 °C to obtain the chloroiminium ion. A solution of

ethyl-1*H*-indole-2-carboxylate **9** (19 g, 0.10 mol) in DMF (30 ml) was added to the vessel containing the formylating agent and the resulting mixture was stirred at room temperature for 1 h and at 70 °C for 6 h. The reaction mixture was poured into cold water (400 ml) and neutralized with 2 M NaOH. The yellow precipitate was collected by filtration to give product **10** as a yellow powder (18 g, 86%). Mp 187–188 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 12.84 (s, 1H), 10.62 (s, 1H), 8.26 (d, 1H, J = 8.07 Hz), 7.58 (dt, 1H, J = 8.23, 0.94 Hz), 7.41 (ddd, 1H, J = 9.0, 6.0, 1.3 Hz), 7.31 (ddd, 1H, J = 8.0, 7.0, 1.1 Hz), 4.46 (q, 2H, J = 7.1 Hz), 1.41 (t, 3H, J = 7.1 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 187.6, 160.2, 135.8, 132.8, 126.0, 124.8, 123.6, 122.4, 118.4, 113.2, 61.8, 14.1. HRMS-ESI (m/z) for $C_{12}H_{11}NO_3Na$, (M+Na) found 240.0636, calcd 240.0637.

4.3. General procedure for compounds 11 and 12

A solution of ethyl-3-formyl-1*H*-indole-2-carboxylate **10** (5 g, 23 mmol) in DMF (60 ml) was added dropwise under argon to an ice-cooled suspension of NaH (1.4 g, 35 mmol) in DMF (30 ml). After stirring at 0 °C for 20 min, the alkyl halide (28 mmol) was added dropwise and the reaction mixture was allowed to reach the room temperature and stirred for 1.5 h. The reaction mixture was poured into ice-water and slightly yellow solid was collected by filtration to give the product.

4.3.1. Ethyl-3-formyl-1-methyl-indole-2-carboxylate 11

Solid (4.0 g, 75%). Mp 108 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 10.64 (s, 1H), 8.50 (dt, 1H, J = 8.0, 1.0 Hz), 7.46–7.32 (m, 3H), 4.51 (q, 2H, J = 7.1 Hz), 4.05 (s, 3H), 1.47 (t, 3H, J = 7.1); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 188.6, 161.3, 138.4, 133.8, 126.4, 124.9, 124.3, 124.0, 120.0, 110.6, 62.4, 32.6, 14.5. HRMS-ESI (m/z) for $C_{13}H_{13}NO_3Na$ (M+ Na) found 254.0781, calcd 254.0793.

4.3.2. Ethyl-3-formyl-1-(methoxymethyl)-indole2-carboxylate 12

Solid (4.9 g, 81%). Mp 66–68 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.51 (d, 1H, J = 8.0 Hz), 7.59 (d, 1H, J = 9.0 Hz), 7.48–7.35 (m, 2H), 5.95 (s, 2H), 4.54 (q, 2H, J = 7.1 Hz), 3.31 (s, 3H), 1.48 (t, 3H, J = 7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 188.9, 163.9, 138.4, 132.6, 126.9, 124.9, 124.7, 124.1, 121.3, 111.4, 75.6, 62.6, 56.6, 14.5. HRMS-ESI (m/z) for $C_{14}H_{15}NO_4Na$ (M+Na) found 284.0910, calcd 284.0899.

4.4. General procedure for the Wittig reaction 13–16

The phosphonium salts[12] (20 mmol) were dissolved in DMF (95 ml) under argon and cooled to 0 °C. Sodium hydride (1.04 g, 26.0 mmol) was added and reaction mixtures were stirred at 0 °C for 20 min. Immediately, after the addition of NaH, a deep red solution was obtained. Indole aldehyde **11** or **12** (3.0 g, 13 mmol) in DMF (30 ml) was added dropwise and the reaction mixtures were allowed to stir at rt for 2.5 h. The reaction mixtures were poured in to 0.5 M HCl (300 ml) and a yellow solid was collected by filtration. The crude products **13**–**16** were recrystallized from *i*-PrOH.

4.4.1. (*E*)-Ethyl 3-styryl-1-methyl-indole-2-caboxylate 13

Compound **13** was prepared according to the reaction conditions described above using benzyltriphenylphosphonium bromide (4.3 g, 9.7 mmol), sodium hydride (0.5 g, 13.0 mmol) and indole-aldehyde **11** (1.5 g, 6.50 mmol) as the starting materials. Yellow solid (1.28 g, 65%). Mp 88–90 °C; ^{1}H NMR ($CDCl_3$) δ: 8.11 (d, 1H,, J = 8.2 Hz), 7.93 (d, 1H, J = 16.7 Hz), 7.56 (d, 2H, J = 7.59 Hz), 7.41–7.35 (m, 4H), 7.28–7.22 (m, 4H), 4.46 (q, 2H, J = 7.1 Hz), 4.04 (s, 3H), 1.48 (t, 3H, J = 7.1 Hz) (16% of Z-isomer); ^{13}C NMR ($CDCl_3$) δ: 162.9, 139.5, 138.6, 130.7, 128.9, 127.5, 126.6, 126.4, 125.7, 124.9, 122.9, 122.7, 121.3, 110.7, 61.2, 32.5, 12.7 (also small peaks from *Z*-isomer). HRMS-ESI (m/z) for $C_{20}H_{19}NO_2Na$, (M+Na) found 328.1315, calcd 328.1313.

4.4.2. (*E*)-Ethyl 3-(3,4-dimethoxystyryl)-1-methyl-indole-2-caboxylate 14

Yellow solid (3.3 g, 71%). 114–115 °C; ^{1}H NMR ($CDCl_3$) δ: 8.12 (d, 1H, J = 8.1 Hz), 7.80 (d, 1H, J = 16.6 Hz), 7.40–7.38 (m, 2H), 7.26–7.08 (m, 4H), 6.88 (d, 1H, J = 8.2 Hz), 4.45 (q, 2H, J = 7.1 Hz), 4.01 (s, 3H), 3.97 (s, 3H), 3.91 (s, 3H), 1.49 (t, 3H, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$) δ: 162.7, 149.2, 148.7, 139.3, 131.6, 130.4, 125.5, 124.6, 122.5, 121.4, 120.9, 120.8, 119.5, 111.3, 110.5, 108.4, 60.9, 55.9, 55.8, 32.3, 14.5. HRMS-ESI (m/z) for $C_{22}H_{23}NO_4Na$, (M+Na) found 388.1501, calcd 388.1525.

4.4.3. (*E*)-Ethyl 3-(3,4-dimethoxystyryl)-1-(methoxymethyl)-1*H*-indole-2-carboxylate 15

Compound **15** was prepared according to the general procedure above using (3,4-dimethoxybenzyl)triphenylphosphonium bromide (8.0 g, 16 mmol), sodium hydride (0.86 g, 22 mmol) and indole aldehyde **12** (2.82 g, 11 mol) as starting materials. The reaction was quenched using satd NH_4Cl (300 ml). Yellow solid (2.6 g, 56%). Mp 94–96 °C; ^{1}H NMR ($CDCl_3$) δ: 8.11 (d, 1H, J = 8.1 Hz), 7.77 (d, 1H, J = 16.6 Hz), 7.57 (d, 1H, J = 8.4 Hz), 7.43 (t, 1H, J = 9.0 Hz), 7.30–7.10 (m, 4H), 6.89 (d, 1H, J = 8.0 Hz), 5.95 (s, 2H), 4.47 (q, 2H, J = 7.1 Hz), 3.96 (s, 3H), 3.92 (s, 3H), 3.28 (s, 3H), 1.50 (t, 3H, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$) δ: 162.6, 149.3, 149.0, 139.7, 131.7, 131.4, 126.2, 125.3, 123.4, 122.6, 121.8, 120.5, 119.8, 111.4, 111.3, 108.6, 75.2, 61.2, 56.1 (2C), 55.9, 14.6. HRMS-ESI for $C_{23}H_{25}NO_5Na$, (M+Na) found 418.1626, calcd 418.1630.

4.4.4. (*E*)-Ethyl 3-(2,5-dimethoxystyryl)-1-methyl-indole-2-caboxylate 16

Compound **16** was prepared according to the reaction conditions described above using (2,5-dimethoxybenzyl)triphenylphosphonium bromide (3.03 g, 6.15 mmol) in DMF (100 ml), sodium hydride (0.33 g, 8.20 mmol) and indole-aldehyde **11** (0.95 g, 4.10 mmol) in DMF (20 ml) as starting materials. Yellow solid (1.00 g, 67%). Mp 101–103 °C; ^{1}H NMR ($CDCl_3$) δ: 8.16 (d, 1H, J = 8.2 Hz), 7.88 (d, 2H, J = 16.8 Hz), 7.60 (d, 2H, J = 16.8 Hz), 7.40 (d, 2H, J = 3.7 Hz), 7.27–7.21 (m, 2H), 6.88–6.78 (m, 2H), 4.46 (q, 2H, J = 7.1), 4.04 (s, 3H), 3.86 (s, 3H), 3.83 (s, 3H), 1.49 (t, 3H, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$) δ: 162.9, 154.1, 151.6, 139.6, 128.6, 126.0, 125.6, 125.4, 124.9, 123.2, 122.9, 121.9, 121.3, 113.7, 112.6, 111.2, 110.6, 61.1, 56.4, 56.0, 32.5, 14.7. HRMS-ESI (m/z) for $C_{22}H_{23}NO_4Na$, (M+Na) found 388.1550, calcd 388.1525.

4.5. General procedure for ester hydrolysis 17–20

The ester **13**–**16** (8.76 mmol) was dissolved in a MeOH/THF/water (2:2:1) solvent mixture. Next, NaOH (1.81 g, 45.3 mmol) was added and the reaction mixture stirred for 1 h at 80 °C. The solvents were removed and the residue diluted with water. The reaction mixture was acidified using conc. HCl (aq) and the yellow solids (**17**–**20**) were collected by filtration.

4.5.1. (*E*)-3-Styryl-1-methyl-1*H*-indole-2-carboxylic acid 17

Compound **17** was prepared according to the reaction conditions described above using ester **13** (1.28 g, 4.19 mmol) as starting material. Yellow solid (0.90 g, 97%). Mp 167–169 °C; ^{1}H NMR (DMSO-d_6) δ: 8.16, (d, 1H, J = 8.1 Hz), 7.95 (d, 1H, J = 16.8 Hz), 7.63–7.57 (m, 3H), 7.41–7.24 (m, 6H), 4.00 (s, 3H); ^{13}C NMR (DMSO-d_6) δ: 163.4, 138.8, 138.2, 128.9, 128.8, 127.3, 127.2, 126.0, 125.3, 123.8, 122.6, 122.1, 121.3, 119.2, 111.3, 32.3. HRMS-ESI (m/z) for $C_{18}H_{15}NO_2Na$, (M+Na) found 300.1018, calcd 300.1000.

4.5.2. (*E*)-3-(3,4-Dimethoxystyryl)-1-methyl-1*H*-indole-2-carboxylic acid 18

Compound **18** was prepared according to the reaction conditions described above using ester **14** (3.20 g, 8.76 mmol) as a starting material. Yellow solid (2.56 g, 87%). Mp 185–187 °C; ^{1}H NMR (DMSO-d_6) δ: 8.15 (d, 1H, J = 8.2 Hz), 7.81 (d, 1H, J = 16.8 Hz), 7.61 (d, 1H, J = 8.4 Hz), 7.40 (td, 1H, J = 9.0, 1.0 Hz), 7.27–7.12 (m, 4H), 6.98 (d, 1H, J = 8.4 Hz), 3.98 (s, 3H), 3.82 (s, 3H), 3.78 (s, 3H); ^{13}C NMR (DMSO- d_6) δ: 164.09, 149.6, 149.1, 139.4, 131.8, 129.7, 127.4, 125.8, 124.4, 122.8, 121.7, 121.2, 120.3, 119.1, 112.7, 111.8, 110.4, 56.2, 56.1, 32.8. HRMS-ESI for $C_{20}H_{19}NO_4Na$, (M+Na) found 360.1224, calcd 360.1212.

4.5.3. (*E*)-3-(3,4-Dimethoxystyryl)-1-(methoxymethyl)-1*H*-indole-2-carboxylic acid 19

Compound **19** was prepared according to the reaction conditions described above using ester **15** (2.57 g, 6.50 mmol) as a starting material. Yellow solid (2.30 g, 97%). Mp 133–135 °C; ^{1}H NMR (DMSO-d_6) δ: 8.16 (d, 1H, J = 8.1 Hz), 7.77 (d, 1H, J = 16.9 Hz), 7.73 (d, 1H, J = 9.6 Hz), 7.42 (t, 1H, J = 7.50 Hz), 7.32–7.14 (m, 4H), 6.99 (d, 1H, J = 8.4 Hz), 5.92 (s, 2H), 3.82 (s, 3H), 3.78 (s, 3H), 3.13 (s, 3H); ^{13}C NMR (DMSO-d_6) δ: 163.2, 148.9, 148.6, 139.0, 130.9, 130.2, 126.4, 125.6, 124.3, 122.3, 121.7, 121.3, 120.1, 118.7, 112.0, 111.7, 109.8, 74.4, 67.1, 55.5, 55.4. HRMS-ESI (m/z) for $C_{21}H_{21}NO_5Na$, (M+Na) found 390.1304, calcd 390.1317.

4.5.4. (*E*)-3-(2,5-Dimethoxystyryl)-1-methyl-1*H*-indole-2-carboxylic acid 20

Compound **20** was prepared according to the reaction conditions described above using ester **16** (0.66 g, 1.81 mmol) as a starting material. Yellow solid (0.50 g, 82%). Mp 172–174 °C; ^{1}H NMR (DMSO-d_6) δ: 8.03 (d, 1H, J = 8.2 Hz), 7.92 (d, 1H, J = 16.9 Hz), 7.62 (d, 1H, J = 8.4 Hz), 7.46–7.38 (m, 2H), 7.24 (t, 1H, J = 7.9 Hz), 7.14 (d, 1H, J = 3.0 Hz), 6.07 (d, 1H, J = 9.0 Hz), 6.97 (d, 1H, J = 9.0 Hz) 6.84 (dd, 1H, J = 8.9 Hz, 3.0 Hz), 3.99 (s, 3H), 3.81 (s, 3H), 3.75 (s, 3H); ^{13}C NMR (DMSO-d_6) δ: 164.0, 155.5, 154.1, 151.4, 139.4, 128.1, 125.8, 124.4, 124.2, 124.1, 122.3, 121.9, 120.3, 113.8, 113.3, 111.9, 111.7, 56.8, 56.1, 32.8. HRMS-ESI (m/z) for $C_{20}H_{19}NO_4Na$, (M+Na) found 360.1197, calcd 360.1212.

4.6. General procedure for amido alcohols 21–26[7]

The substituted indole-2-carboxylic acid **17**–**20** (3.60 mmol) was dissolved in a mixture of DCM (10 ml) and DMF (1.5 ml). Amino alcohol (4.00 mmol) was added, followed by BOP (benzotriazole-1-yl-oxy-tris(dimethylamino)-phosphonium hexafluorophosphate) (1.64 g, 3.90 mmol). The pH of the reaction mixtures was adjusted to between 9 and 10 with DIPEA. The product precipitated out during the reaction. When the reaction reached completion, according to TLC, the solvents were removed in vacuo and the reaction mixture was diluted with water. Pure product **21**–**26** was collected by filtration (1.4 g, 84%).

4.6.1. (*S,E*)-3-Styryl-*N*-(1-hydroxy-3-phenylpropan-2-yl)-1-methyl-1*H*-indole-carboxamide 21

Compound **21** was prepared according the reaction conditions described above using substituted indole-2-caboxylic acid **17** (1.0 g, 3.61 mmol), phenylalaninol (0.6 g, 3.97 mmol) and BOP (1.60 g, 3.79 mmol) as starting materials. Yellowish solid (1.41 g, 94%). Mp 198–200 °C; $[\alpha]_D^{20} = -65.7$ (c 1.0, $CHCl_3$); ^{1}H NMR (DMSO-d_6) δ: 8.59 (d, 1H, J = 8.9 Hz), 8.12 (d, 1H, J = 8.07 Hz), 7.53–7.49 (m, 3H), 7.40–7.51 (m, 12H), 5.04 (br s, 1H), 4.43–4.67 (m, 1H), 3.59 (d, 2H, J = 5.9 Hz), 3.49 (s, 3H), 3.00 (dd, 1H, J = 13.9 Hz, 4.7 Hz), 2.72 (dd, 1H, J = 13.3 Hz, 10.5 Hz); ^{13}C NMR (DMSO-d_6) δ: 162.1, 139.7, 139.0, 137.8, 126.3, 129.8, 128.3, 128.8, 127.3, 126.7, 126.4, 126.2, 124.7, 124.0, 122.2, 121.9, 121.5, 112.2, 111.3, 64.0, 53.5, 37.1, 31.3. HRMS-ESI (m/z) for $C_{27}H_{26}N_2O_2Na$, (M+Na) found 433.1879, calcd 433.1892.

4.6.2. (*S,E*)-3-(3,4-Dimethoxystyryl)-*N*-(1-hydroxy-3-phenylpropan-2-yl)-1-methyl-1*H*-indole-carboxamide 22

Compound **22** was prepared according the reaction conditions described above using substituted indole-2-carboxylic acid **18** (1.2 g, 3.60 mmol), phenylalaninol (0.65 g 4.00 mmol) and BOP (1.64 g, 3.90 mmol) as starting materials. Yellowish solid (1.4 g, 84%). Mp 176–178 °C; $[\alpha]_D^{20} = -77.6$ (c 0.5, $CHCl_3$); ^{1}H NMR (DMSO-d_6) δ: 8.55 (d, 1H, J = 8.9 Hz), 8.14 (d, 1H, J = 8.0 Hz), 7.49 (d, 1H, J = 8.2 Hz), 7.37–7.06 (m, 10H), 6.94 (d, 1H, J = 8.3 Hz), 5.02 (t, 1H, J = 6.1 Hz), 4.40 (m, 1H), 3.83 (s, 3H), 3.77 (s, 3H), 3.63–3.59 (m, 2H), 3.46 (s, 3H), 2.98 (dd, 1H, J = 12.9 Hz, 4.9 Hz), 2.73 (dd, 1H, J = 13.5 Hz, 9.7 Hz); ^{13}C NMR (DMSO-d_6) δ: 161.5, 148.9, 148.0, 139.1, 137.2, 135.0, 131.4, 129.2, 128.1, 126.0, 125.7, 124.0, 123.3, 121.3, 120.6, 119.5, 118.6, 111.9 (2C), 110.5, 108.8, 63.3, 55.4 (2C), 53.0, 36.6. 30.6. HRMS-ESI (m/z) for $C_{29}H_{30}N_2O_4Na$, (M+ Na) found 493.2089, calcd 493.2103.

4.6.3. (*S,E*)-3-(3,4-Dimethoxystyryl)-*N*-(1-hydroxy-3-phenylpropan-2-yl)-1-(methoxymethyl)-1*H*-indole-carboxamide 23

Compound **23** was prepared according the reaction conditions described above using substituted indole-2-carboxylic acid **19** (1.2 g, 3.27 mmol), phenylalaninol (0.524 g, 3.46 mmol) and BOP (1.40 g, 3.31 mmol) as starting materials. Pure product was obtained after recrystallization from *i*-PrOH. Yellowish solid (0.88 g, 54%). Mp 169–171 °C; $[\alpha]_D^{20} = -45.1$ (c 1.0, $CHCl_3$); ^{1}H NMR (DMSO-d_6) δ: 8.62 (d, 1H, J = 8.8 Hz), 8.16 (d, 1H, J = 8.0 Hz), 7.59 (d, 1H, J = 8.2 Hz), 7.38–7.19 (m, 9H), 7.09 (dd, 1H, J = 8.4 Hz, 1.4 Hz) 6.94 (d, 1H, J = 8.4 Hz), 5.45 (A, 1H, J_{AB} = 11.1 Hz), 5.37 (B, 1H, J_{AB} = 11.1 Hz), 5.00 (t, 1H, J = 5.8 Hz), 4.45–4.33 (m, 1H), 3.82 (s, 3H), 3.78 (s, 3H), 3.60–3.55 (m, 2H), 2.98–2.88 (m, 1H), 2.92 (s, 3H), 2.81–2.73 (m, 1H); ^{13}C NMR (DMSO-d_6) δ: 162.02, 149.6, 148.8, 139.7, 137.7, 135.0, 131.8, 129.7, 128.8, 127.8, 126.7, 125.3, 124.4, 122.2, 122.0, 120.0, 119.6, 114.3, 112.5, 112.0, 109.6, 75.0, 63.8, 56.2, 56.1, 56.0, 54.0, 37.1. HRMS-ESI (m/z) for $C_{30}H_{32}N_2O_5Na$, (M+Na) found 523.2212, calcd 523.2209.

4.6.4. (*S,E*)-3-(3,4-Dimethoxystyryl)-*N*-(1-hydroxy-3-methylbutan-2-yl)-1-methyl-1*H*-indole-carboxamide 24

Compound **24** was prepared according to the reaction conditions described above using substituted indole-2-carboxylic acid **18** (1.2 g, 3.6 mmol), valinol (0.419 g, 4.0 mmol) and BOP (1.64 g, 3.9 mmol). The product was recrystallized from *i*-PrOH. Yellowish solid (1.2 g, 81%). Mp 181–183 °C; $[\alpha]_D^{20} = -14.4$ (c 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ: 7.93 (d, 1H, J = 8.0 Hz), 7.35–7.00 (m, 6H), 6.84 (d, 1H, J = 8.3 Hz), 6.33 (d, 1H, J = 8.9 Hz), 4.04 (m, 1H), 3.93 (s, 3H), 3.90 (s, 3H), 3.87 (s, 3H), 3.86–3.82 (m, 1H), 3.72–3.67 (m, 1H), 1.93 (sep, 1H, J = 6.8 Hz), 1.00 (d, 3H, J = 6.8 Hz), 0.97 (d, 3H, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$) δ: 163.7, 149.4, 148.9, 138.5, 131.6, 131.2, 130.6, 125.1, 124.6, 121.7, 121.1, 119.8, 118.5, 115.3, 111.4, 110.4, 108.3, 64.1, 57.8, 56.2, 56.1, 31.6, 29.5, 19.9, 19.1. HRMS-ESI (m/z) for $C_{25}H_{30}N_2O_4Na$, (M+Na) found 445.2104, calcd 445.2103.

4.6.5. (*S,E*)-3-(3,4-Dimethoxystyryl)-*N*-(1-hydroxy-3-methylbutan-2-yl)-1-(methoxymethyl)-1*H*-indole-carboxamide 25

Compound **25** was prepared according to the reaction conditions described above using substituted indole-2-carboxylic acid **19** (1.2 g, 3.26 mmol), valinol (0.357 g, 3.46 mmol) and BOP (1.40 g, 3.31 mmol) as starting materials. Crude product was washed with *i*-PrOH (50 ml). Yellowish solid (1.1 g, 73%). Mp 181–183 °C; $[\alpha]_D^{20} = -10.5$ (c 1.0, $CHCl_3$); ^{1}H NMR (DMSO-d_6) δ:

8.48 (d, 1H, J = 9.1 Hz), 8.18 (d, 1H, 7.9 Hz), 7.65 (d, 1H, J = 8.2 Hz), 7.46 (d, 1H, J = 16.7 Hz), 7.37–7.22 (m, 4H), 7.14 (dd, 1H, J = 8.3 Hz, 1.6 Hz) 6.94 (d, 1H, J = 8.3 Hz), 5.64 (s, 2H, J = 5.63 Hz), 4.73 (t, 1H, J = 5.5 Hz), 3.97–3.95 (m, 1H), 3.82 (s, 3H), 3.77 (s, 3H), 3.67–3.50 (m, 2H), 3.16 (s, 3H), 1.92 (sep, 1H, J = 6.6 Hz), 0.99 (d, 3H, J = 6.75 Hz), 0.95 (d, 3H, J = 6.75 Hz); ^{13}C NMR (DMSO-d_6) δ: 167.4, 148.9, 148.2, 137.1, 134.8, 131.2, 127.0, 124.6, 123.7, 121.5, 121.3, 119.4, 119.2, 113.5, 111.8, 111.2, 108.6, 61.5, 56.9, 55.5 (2C), 55.4, 28.7, 18.8, 18.5. HRMS-ESI (m/z) for $C_{26}H_{32}N_2O_5Na$, (M+Na) found 475.2187, calcd 475.2209.

4.6.6. (*S,E*)-3-(2,5-Dimethoxystyryl)-*N*-(1-hydroxy-3-phenylpropan-2-yl)-1-methyl-1*H*-indole-carboxamide 26

Compound **26** was prepared according to the reaction conditions described above using substituted indole-2-carboxylic acid **20** (0.45 g, 1.33 mmol), phenylalaninol (0.22 g, 1.47 mmol) and BOP (0.590 g, 1.40 mmol) as starting materials. Yellowish product (0.48 g, 78%). Mp 221–223 °C; $[\alpha]_D^{20} = -124.6$ (c 0.5, DMF); ^{1}H NMR (DMSO-d_6) δ: 8.57 (d, 1H, J = 9.0 Hz), 7.97 (d, 1H, J = 7.9 Hz), 7.50 (d, 1H, 8.2 Hz), 7.38–7.17 (m, 10H), 6.95 (d, 1H, J = 9.0 Hz) 6.79 (dd, 1H, J = 8.9, 3.0 Hz), 5.00 (t, 1H, J = 5.7 Hz), 4.40–4.32 (m, 1H), 3.81 (s, 3H), 3.77 (s, 3H), 3.58–3.55 (m, 2H), 3.46 (s, 3H), 2.98 (dd, 1H, J = 13.7 Hz, 4.9 Hz), 2.70 (dd, 1H, J = 13.6 Hz, 9.7 Hz); ^{13}C NMR (DMSO-d_6) δ: 162.0, 154.1, 151.1, 139.8, 137.8, 136.1, 129.8, 128.7, 128.2, 126.7, 124.7, 124.0, 122.7, 121.5, 121.5, 121.4, 120.5, 113.9, 113.2, 112.7, 111.4, 110.4, 63.8, 56.9, 56.1, 53.8, 37.2, 31.3. HRMS-ESI (m/z) for $C_{29}H_{30}N_2O_4Na$, (M+ Na) found 493.2095, calcd 493.2103.

4.7. General procedure for ligands 1–6[7]

Mesylchloride (0.6 ml, 7.63 mmol) was carefully added to a stirred mixture of amino alcohol, Et_3N (3.40 ml, 24 mmol) and DMAP (75 mg, 20 mol %) in DCM (30 ml). The reactions were monitored by TLC (Hex/EtOAc 1:1), to observe the formation and disappearance of the mesylate intermediate. After 5 h, the oxazoline formed. The reaction was quenched with water and diluted with DCM. The product was extracted with DCM (2 × 50 ml). The combined DCM fractions were washed with water (50 ml) and brine (50 ml) and dried over Na_2SO_4. After filtration the solvents were removed in vacuo and product **1**–**6** was precipitated from methanol. Yellow solids **1**–**2** and **4**–**6** were filtered and **3** was obtained as a yellow oil.

4.7.1. (*S,E*)-4-Benzyl-2,3-styryl-1-methyl-1*H*-indol-2-yl)-4,5-dihyrdoxazole 1

Compound **1** was prepared according to the general procedure using amido alcohol **21** (0.60 g, 1.46 mmol), DCM (14 ml), Et_3N (1.6 ml, 11.7 mmol), DMAP (36 mg, 20 mol %) and MsCl (0.28 ml, 3.65 mmol) as starting materials. Yellow solid (0.380 g, 67%). Mp 109–111 °C; $[\alpha]_D^{20} = -47.3$ (c 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ: 8.11 (d, 1H, J = 8.1 Hz), 7.84 (d, 1H, J = 16.6 Hz), 7.54–7.51 (m, 2H), 7.40–7.20 (m, 12 H), 4.73–4.63 (m, 1H), 4.41 (dd, 1H, J = 9.3 Hz, 8.5 Hz)), 4.19 (dd, 1H, J = 8.4 Hz, 7.3 Hz), 4.01 (s, 3H), 3.23 (dd, 1H, J = 13.7 Hz, 5.7 Hz), 2.84 (dd, 1H, J = 13.7 Hz, 8.0 Hz); ^{13}C NMR ($CDCl_3$) δ: 158.9, 139.3, 138.8, 138.0, 129.5, 129.2, 128.7, 127.0 126.7, 126.3, 125.1, 124.6, 122.8, 122.0, 120.9, 118.9, 110.4, 71.2, 68.0, 42.0, 32.4. HRMS-ESI (m/z) for $C_{27}H_{25}N_2O$, (M+H) found 393.1947, calcd 393.1967.

4.7.2. (*S,E*)-4-Benzyl-2-(3-(3,4-dimethoxystyryl)-1-methyl-1*H*-indol-2-yl)-4,5-dihyrdoxazole 2

Compound **2** was prepared according to the general procedure using amido alcohol **22** (1.40 g, 2.98 mmol), DCM (30 ml), Et_3N (3.40 ml, 24 mmol), DMAP (75 mg, 20 mol %) and MsCl (0.60 ml, 7.63 mmol) as starting materials. Yellow solid (1.07 g, 80%). Mp 96–97 °C; $[\alpha]_D^{20} = -35.5$ (c 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ: 8.10 (d, 1H, J = 8.1 Hz), 7.72 (d, 1H, J = 16.6 Hz), 7.38–7.16 (m, 9H), 7.09–7.07 (m, 2H), 6.87 (d, 1H, J = 8.8 Hz), 4.70–4.63 (m, 1H), 4.40 (dd, 1H, J = 9.2, 8.5 Hz), 4.18 (dd, 1H, J = 7.3 Hz, 8.4 Hz), 4.01 (s, 3H), 3.93 (s, 3H), 3.91 (s, 3H), 3.24 (dd, 1H, J = 13.8, 5.6 Hz), 2.14 (dd, 2H, J = 13.8 Hz, 8.1 Hz); ^{13}C NMR ($CDCl_3$) δ: 159.0, 149.3, 148.7, 139.4, 138.1, 132.1, 129.5, 129.5, 129.1, 128.7, 126.8, 125.2, 124.7, 124.6, 122.0, 121.2, 120.8, 119.3, 119.1, 111.6, 110.3, 109.3, 71.2, 68.1, 56.2, 56.0, 42.0, 32.3. HRMS-ESI (m/z) for $C_{29}H_{29}N_2O_3$, (M+H) found 453.2173, calcd 453.2178.

4.7.3. (*S,E*)-4-Benzyl-2-(3-(3,4-dimethoxystyryl)-1-(methoxymethyl)-1*H*-indol-2-yl)-4,5-dihyrdoxazole 3

Compound **3** was prepared according to the general procedure using amido alcohol **23** (0.87 g, 1.74 mmol), DCM (20 ml), Et_3N (1.82 ml, 13 mmol), DMAP (39 mg, 20 mol %) and MsCl (0.30 ml, 4.10 mmol) as starting material. The reaction mixture was heated to 50 °C. The reaction was monitored by TLC using an eluent system of Hex/EtOAc 2:1. The crude product was filtered through a short pad of silica using Hex/EtOAc (1:1) as an eluent. Yellow oil (0.57 g, 67%). $[\alpha]_D^{20} = -26.0$ (c 1.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ: 8.10 (d, 1H, J = 8.1 Hz), 7.71 (d, 1H, J = 16.6 Hz), 7.55 (d, 1H, J = 8.3 Hz), 7.37–7.08 (m, 10H), 6.88 (d, 1H, J = 8.8 Hz), 5.98 (s, 2H), 4.68 (m, 1H, J = 7.6 Hz), 4.41 (t, 1H, J = 8.9 Hz), 4.17 (t, 1H, J = 7.9 Hz), 3.93 (s, 3H), 3.91 (s, 3H), 3.25–3.19 (m, 1H), 3.26 (s, 3H), 2.82 (dd, 1H, J = 13.7 Hz, 8.0 Hz); ^{13}C NMR ($CDCl_3$) δ: 158.6, 149.2, 148.8, 139.4, 138.0, 131.7, 130.3, 129.4, 129.2, 128.7, 128.3, 126.7, 125.7, 125.2, 124.1, 122.0, 121.6, 120.8, 120.7, 119.4, 111.4, 111.2, 109.2, 75.2, 71.2, 68.0, 56.1, 56.0, 41.9. HRMS-ESI for $C_{30}H_{30}N_2O_4Na$, (M+Na) found 505.2119, calcd 505.2103.

4.7.4. (*S,E*)-2-(3-(3,4-Dimethoxystyryl)-1-methyl-1*H*-indol-2-yl)-4-isopropyl-4,5-dihyrdoxazole 4

Compound **4** was prepared according to the general procedure using amido alcohol **24** (1.13 g, 2.67 mmol), DCM (30 ml), Et_3N (3.04 ml, 22 mmol), DMAP (67 mg, 20 mol %). and MsCl (0.53 ml, 6.86 mmol) as starting materials. Yellow solid (0.96 g, 89%). Mp 96–97 °C; $[\alpha]_D^{20} = -46.5$ (c 1.0, DMF); ^{1}H NMR ($CDCl_3$) δ: 8.11 (d, 1H, J = 8.1 Hz), 7.79 (d, 1H, J = 16.6 Hz), 7.38–7.36 (m, 2H), 7.26–7.18 (m, 2H), 7.12–7.07 (m, 2H), 6.88 (d, 1H, J = 8.2 Hz), 4.50–4.41 (m, 1H), 4.23–4.13 (m, 2H), 4.03 (s, 3H), 3.96 (s, 3H), 3.91 (s, 3H), 1.89 (sep, 1H, J = 6.6 Hz), 1.10 (d, 3H, J = 6.7 Hz), 1.01 (d, 3H, J = 6.7 Hz). ^{13}C NMR ($CDCl_3$) δ: 158.2, 149.2, 148.5, 139.3, 132.1, 128.8, 125.1, 125.0, 124.5, 122.0, 121.1, 120.8, 119.4, 118.8, 111.4, 110.3, 108.7, 72.9, 69.8, 56.1, 55.9, 33.2, 32.3 19.1, 18.7. HRMS-ESI (m/z) for $C_{25}H_{29}N_2O_3$, (M+H) found 405.2169, calcd 405.2178.

4.7.5. (*S,E*)-2-(3-(3,4-Dimethoxystyryl)-1-(methoxymethyl)-1*H*-indol-2-yl)-4-isopropyl-4,5-dihyrdoxazole 5

Compound **5** was prepared according to the general procedure using amido alcohol **25** (0.98 g, 2.15 mmol), DCM (20 ml), Et_3N (2.30 ml, 17 mmol), DMAP (51 mg, 20 mol %) and MsCl (0.40 ml, 5.25 mmol). The pure product was obtained after recrystallization from i-PrOH. Yellow solid (0.92 g, 99%). Mp 55– 57 °C; $[\alpha]_D^{20} = -43.1$ (c 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ: 8.10 (d, 1H, J = 8.0 Hz), 7.77 (d, 1H, J = 16.6 Hz), 7.55 (d, 1H, J = 8.3 Hz), 7.37 (td, 1H, J = 7.7, 1.2 Hz), 7.28–7.21 (m, 2H), 7.13–7.08 (m, 2H), 6.88 (d, 1H, J = 8.2 Hz), 6.03 (A, 1H, J_{AB} = 10.7 Hz), 5.94 (B, 1H, J_{AB} = 10.7 Hz), 4.50–4.42 (m, 1H), 4.22–4.12 (m, 2H), 3.95 (s, 3H), 3.91 (s, 3H), 3.24 (s, 2H), 1.87 (sep, 1H, J = 6.6 Hz), 1.10 (d, 3H, J = 6.7 Hz), 1.01 (d, 3H, J = 6.7 Hz); ^{13}C NMR ($CDCl_3$) δ: 157.9, 149.2, 148.7, 139.2, 131.8, 130.0, 125.7, 125.0, 124.4, 122.0, 121.5, 120.7, 120.5, 119.6, 111.4, 111.2, 108.8, 75.2, 72.9, 69.9, 56.1, 55.9, 33.2, 31.6, 19.1, 18.8. HRMS-ESI (m/z) for $C_{26}H_{30}N_2O_4Na$, (M+Na) found 457.2091, calcd 457.2103.

4.7.6. (*S*,*E*)-4-Benzyl-2-(3-(2,5-dimethoxystyryl)-1-methyl-1*H*-indol-2-yl)-4,5-dihyrdoxazole 6

Compound **6** was prepared according the general procedure using amido alcohol **26** (0.30 g, 0.64 mmol), DCM (6 ml), Et_3N (0.7 ml, 5.1 mmol), DMAP (16 mg, 20 mol %) and MsCl (0.12 ml, 1.60 mmol). Yellow solid (0.175 g, 61%). Mp 116–118 °C; $[\alpha]_D^{20} = -36.6$ (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ: 8.15 (d, 1H, *J* = 8.1 Hz), 7.80 (d, 1H, *J* = 16.7 Hz), 7.57 (d, 1H, *J* = 16.8 Hz), 7.38–7.21 (m, 9H), 6.85–6.75 (m, 2H), 4.71–4.62 (m, 1H), 4.40 (dd, 1H, *J* = 9.3 Hz, 8.5 Hz), 4.19 (dd, 1H, *J* = 8.4 Hz, 7.3 Hz), 4.02 (s, 3H), 3.85 (s, 3 H), 3.82 (s, 3H), 3.24 (dd, 1H, *J* = 13.7 Hz, 5.5 Hz), 2.83 (dd, 1H, *J* = 13.7 Hz, 8.2 Hz); ^{13}C NMR ($CDCl_3$) δ: 159.0, 153.9, 151.4, 139.4, 138.0, 129.5, 128.9, 128.7, 126.7, 125.1, 124.6, 123.8, 123.2, 122.2, 120.9, 119.5, 112.8, 112.3, 111.7, 110.3, 71.2, 68.0, 56.6, 55.9, 42.0, 32.3. HRMS-ESI (*m*/*z*) for $C_{29}H_{29}N_2O_3$, (M+H) found 453.2153, calcd 453.2178.[8]

4.8. Reduction of ligand 4

4.8.1. (*S*)-2-(3-(3,4-Dimethoxyphenethyl)-1-methyl-1*H*-indol-2-yl)-4-isopropyl-4,5-dihydrooxazole

Ligand **4** (0.1 g, 0.25 mmol) was dissolved in an MeOH/THF (2:1) (4,5 ml) solvent mixture and $NiCl_2{\cdot}6H_2O$ (45 mg, 0.19 mmol) was added. Next, $NaBH_4$ (93 mg, 2.5 mmol) was added slowly to the ice-cooled solution. After 30 min, the reaction was quenched with water and extracted to the EtOAc. The combined EtOAc fractions were washed with brine and dried over Na_2SO_4. Crude product **7** was filtered through a short pad of silica using EtOAc as an eluent. Yellow oil (44 mg, 44%). $[\alpha]_D^{20} = -37.7$ (*c* 0.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ: 7.61 (dt, 1H, *J* = 8.0, 0.8 Hz), 7.36–7.30 (m, 2H), 7.12 (ddd, 1H, *J* = 8.0, 6.3, 1.7 Hz), 6.83–6.76 (m, 2H), 6.71–6.70 (m, 1H), 4.39–4.30 (m, 1H), 4.15–4.05 (2H), 4.03 (s, 3H), 3.87 (s, 3H), 3.83 (s, 3H), 3.34–3.28 (m, 2H), 2.89–2.84 (m, 2H), 1.84 (sep, *J* = 6.6 Hz), 1.06 (d, 3H, *J* = 6.7 Hz), 0.97 (d, 3H, *J* = 6.7 Hz). ^{13}C NMR ($CDCl_3$) δ: 158.6, 148.8, 147.3, 138.7, 135.6, 127.0, 124.1, 123.8, 121.3, 120.4, 120.1, 119.6, 112.0, 111.3, 110.0, 72.3, 69.4, 56.1, 55.9, 37.5, 33.2, 32.1, 27.7, 19.1, 18.6. HRMS-ESI (*m*/*z*) for $C_{25}H_{31}N_2O_3$, (M+H) found 407.233, calcd 407.2335.

4.9. General procedure for the Rh-catalyzed 1,4-addition

The ligand (0.057 mmol) and $[Rh(ethylene)_2Cl]_2$ (10 mg, 0.026 mmol) were placed in a flask and flushed with argon. Dioxane (1.6 ml) was added and the reaction mixture was stirred at room temperature for 10 min. Phenylboronic acid (95 mg, 0.78 mmol) was added as a solid followed by 1 M KOH (aq) (0.16 ml) and neat 2-cyclohexenone (0.05 ml, 0.52 mmol). The reaction was monitored by TLC (Hex/DCM/acetone 10:10:1). When the enone was no longer detectable, aqueous satd $NaHCO_3$ solution was added and the product was extracted with Et_2O. The combined Et_2O fractions were washed with brine and dried over Na_2SO_4. After filtration and concentration in vacuo, the crude product was obtained as an orange oil. Purification by column chromatography (Hex/DCM/acetone 10:10:1) yielded the desired product as a colorless oil.

4.9.1. 3-Phenyl-cyclohexanone

TLC (Hex/DCM/acetone 10:10:1, Hanessian's stain): $R_f = 0.54$; $[\alpha]_D^{20} = -11.3$ (*c* 0.3, $CHCl_3$) (ee 89%); ^{1}H NMR ($CDCl_3$) δ: 7.35–7.29 (m, 2H), 7.25–7.20 (m, 3H), 3.04–2.96 (m, 1H), 2.61–2.33 (m, 4H), 2.18–2.05 (m, 2H), 1.90–1.74 (m, 2H); ^{13}C NMR ($CDCl_3$) δ: 211.1, 144.4, 128.7, 126.7, 126.6, 49.0, 44.7, 41.2, 32.8, 25.6. The enantiomeric excess was determined by HPLC using a Chiralpak IA column; Hex/*i*-PrOH 95:5; flow rate: 0.5 ml/min; UV at 220 nm; t_1 = 15.3 min (*S*) and t_2 = 16.8 (*R*).

4.9.2. 3-Phenyl-cyclopentanone

TLC (Hex/DCM/acetone 10:10:1, Hanessian's stain): $R_f = 0.51$; $[\alpha]_D^{20} = -79.2$ (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ: 7.36–7.22 (m, 5H), 3.46–3.35 (m, 1H), 2.65 (dd, 1H, *J* = 18.2 Hz, 7.7 Hz), 2.50–2.22 (m, 4H), 2.05–1.86 (m, 1H); ^{13}C NMR ($CDCl_3$) δ: 218.4, 143.0, 128.7, 126.8 (2C), 45.8, 42.2, 38.9, 31.2. The enantiomeric excess was also determined by comparing the specific rotation to the literature {$[\alpha]_D^{20} = +87.3$ (*c* 1.0, $CHCl_3$), ee 99%}.[13]

4.9.3. 3-Phenyl-cycloheptanone

TLC (Hex/DCM/acetone 10:10:1, Hanessian's stain): $R_f = 0.62$; $[\alpha]_D^{20} = -43.0$ (*c* 0.5, $CHCl_3$) (ee 75%); ^{1}H NMR ($CDCl_3$) δ: 7.32–7.27 (m, 2H), 7.22–7.16 (m, 2H), 2.91–2.89 (m, 2H), 2.66–2.57 (m, 3H), 2.08–1.97 (m, 3H), 2.10–1.43 (m, 3H). ^{13}C NMR ($CDCl_3$) δ: 213.6, 146.9, 128.6, 126.4, 126.3, 51.3, 43.9, 42.7, 39.2, 29.2, 24.2. The enantiomeric excess was determined by HPLC using a Chiralpak IC column; Hex/*i*-PrOH 95:5; flow rate: 1.0 ml/min; UV at 220 nm; t_1 = 16.4 min (*S*) and t_2 = 22.2 (*R*).

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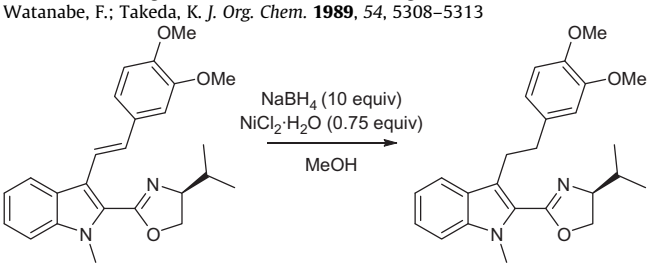

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