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The design and synthesis of a novel chiral 1,1′-disubsitituted ruthenocenyl phosphine–oxazoline ligand

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Abstract

Chiral ferrocene-based phosphine–oxazoline ligands have shown efficient asymmetric catalytic behaviors in asymmetric catalysis; however, the design and synthesis of the corresponding chiral ruthenocenes have not been widely explored. In this article, we report the synthesis of a chiral ruthenocene-based 1,1′-phosphine–oxazoline ligand, based on careful design and experimental exploration. The experimental results here reveal again that the synthetic preparation of 1,1′-disubstituted chiral ruthenocenyl ligands differs from the corresponding ferrocenes. The current method provides a feasible and practical strategy for the synthesis of 1,1′-disubstituted ruthenocene-based ligands.

Keywords 1,1′-disubstituted ruthenocene · Phosphine–oxazoline ligand · Chirality · Synthesis

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Introduction

The enantioselectivity and reactivity of asymmetric catalytic reactions mainly depend on the properties of the chiral catalyst. The performance of the chiral metal complex catalyst is largely determined by the chiral ligand [1–16]. Therefore, to some extent, the design, synthesis, and application of chiral ligands are pivotal to the research and development of asymmetric catalysis. Compared with ligands bearing central chirality and axial chirality, ligands with planar chirality have received less attention. However, planar chiral ligands have been shown to exhibit very efficient asymmetric catalytic effects in many asymmetric catalytic reactions and have attracted increasing attention [1, 17–24]. Some commonly encountered planar ligands include planar chiral arene chromium complexes [25–27], paracyclophane complexes (*PhanePhos*) [28], ferrocene complexes (*FcPHOX*) [29], and cyclopentadienone-ligated dimeric ruthenium complexes (Shvo catalysts) [30], among others. Ferrocene, which has greatly promoted the advancement of modern organometallic chemistry due its special structure, plays a very important role in the design and synthesis of planar chiral ligands. Many excellent ferrocene-based chiral ligands have been synthesized and applied to various asymmetric synthetic reactions. Some of them (such as *Josiphos*) have been successfully used in the industrial manufacture of optically pure compounds, including drugs and materials [31–33].

Compared with chiral ferrocene-based ligands, the synthesis and application of chiral ruthenocene-based ligands that also belong to the metallocene group have received little attention. It has been reported that the distance between the two cyclopentadienyl rings in ferrocene and ruthenocene is 0.332 and 0.368 Å, respectively [34, 35]. The approximately 10% longer distance between the two rings in ruthenocene is expected to present different electronic and steric effects compared with those exhibited by ferrocene ligands [36]. As a result, the development of chiral ruthenocene ligands will greatly expand the application of planar chiral metallocene ligands. Our group has a long-standing interest in the design and synthesis of chiral ferrocene and ruthenocene [37–51] ligands of which the 1,2′-disubstituted phosphine–oxazoline ligand RuPHOX exhibits highly efficient asymmetric catalytic behaviors in several types of reactions. During the synthesis of ruthenocene-based ligands, we have found that the methods and conditions needed for introducing groups onto the ruthenocene rings differ significantly from the corresponding ferrocenes [40].

In 1998, Zhang and Ikeda's group reported a 1,1′-disubstituted ferrocene-based phosphine–oxazoline ligand (**1**, Fig. 1), which gave the desired products in 91% ee for an enantioselective Pd-catalyzed asymmetric allyl alkylation reaction [52]. In particular, the ligand showed very high reactivity, and the reaction went to completion at room temperature within 30 min. In 2001, Hou and Dai developed a new type of 1,1′-disubstituted ferrocene phosphine–oxazoline ligand (**2**) by introducing an axial chiral BINOL molecule to the phosphorus atom of **1**. The ligands **2** showed excellent enantioselectivity and diastereoselectivity in a series of asymmetric catalytic reactions [53]. Encouraged by these results, we

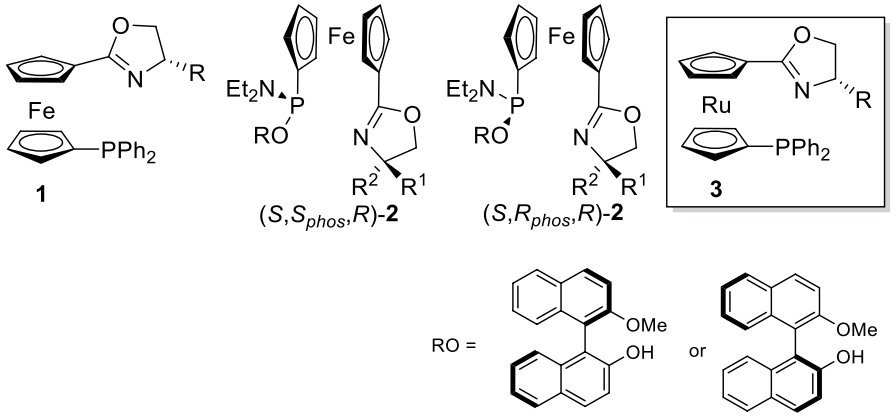

Fig. 1 Metallocene-based 1,1′-phosphine–oxazoline ligands

intended to explore the synthetic preparation of 1,1′-disubstituted ruthenocene phosphine–oxazoline ligand **3** with the aim of providing the synthetic method of such ligands and expanding to planar chiral ruthenocene ligands by further derivatization of **3**. Herein, we report a new and efficient method for the synthesis of 1,1′-disubstituted ruthenocene phosphine-oxazolines **3**, which is largely distinct from the synthesis of the corresponding ferrocene ligands.

Experiment

1,1′-dibromoruthencene (4) [54, 55]

The synthesis of **4** was accomplished following the previously published procedure with slight modifications. A mixture of *n*-butyllithium (2.5 M in *n*-hexane, 16 mL, 39.8 mmol) and PMDTA (*N,N,N′,N″,N″*-pentamethyldiethylenetriamine, 8.3 mL, 39.8 mmol) in *n*-hexane (50 mL) was added dropwise to the solution of ruthenocene (4 g, 17.3 mmol) in *n*-hexane (100 mL) at room temperature, and the mixture was then stirred for an additional 24 h to a slurry of dilithiated ruthenocene species. This *n*-hexane slurry was treated with 1,2-dibromotetrachloroethane (14 g, 43.3 mmol) at − 78 °C and then stirred at room temperature overnight. The reaction mixture was washed with water and brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by column chromatography using petroleum ether as the eluent to afford **4** as a yellow green solid (4.8 g, 72% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.88 (t, $J = 1.8$ Hz, 4H), 4.52 (t, $J = 1.8$ Hz, 4H).

1-bromo-1′-isopropylester ruthenocene (5)

To a solution of **4** (3 g, 7.7 mmol) in THF (60 mL) was added dropwise *n*-butyllithium (2.5 M in *n*-hexane, 3.1 mL, 7.7 mmol) at − 78 °C. After stirring for 0.5 h,

isopropyl chloroformate (1.3 mL, 11.6 mmol) was slowly added to the above solution at − 78 °C. The reaction mixture was warmed to room temperature and stirred overnight. After quenching with water, the solution was extracted with ethyl acetate (10 mL × 3). The organic phases were combined, washed with brine, dried over Na_2SO_4, and evaporated in vacuum. The residue was purified by column chromatography using petroleum ether/ethyl acetate (14:1, v/v) as the eluent to give **5** (1.5 g, 50% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.17 (t, J = 1.8 Hz, 2H), 5.13–5.06 (m, 1H), 4.86 (t, J = 1.7 Hz, 2H), 4.73 (t, J = 1.8 Hz, 2H), 4.48 (t, J = 1.7 Hz, 2H), 1.27 (d, J = 6.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.5, 79.1, 76.5, 75.0, 74.7, 74.0, 71.4, 67.7, 22.1; HRMS (ESI, *m/z*): Calcd. for $C_{14}H_{15}BrO_2Ru$ $[M+H]^+$ 396.9371 found, 396.9361.

1-bromo-1′-carboxy ruthenocene (6)

5 (1.5 g, 3.8 mmol) and NaOH (4.2 g, 76.7 mmol) were stirred at reflux temperature in mixed solvents of EtOH (140 mL) and H_2O (14 mL). After TLC indicated **5** had been consumed, the reaction was evaporated to dryness. The crude obtained was dissolved in H_2O (200 mL) and washed with Et_2O (15 mL × 3). The aqueous layer was acidified with aq. HCl solution (1 M) to pH = 2. After filtration and drying in vacuo, 1-bromo-1′-carboxy ruthenocene (**6**) was obtained (1.3 g, 97% yield).

^{1}H NMR (400 MHz, DMSO-d_6): δ 12.21 (brs, 1H), 5.08 (t, J = 1.8 Hz, 2H), 4.99 (t, J = 1.7 Hz, 2H), 4.81 (t, J = 1.8 Hz, 2H), 4.60 (t, J = 1.7 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.1, 79.1, 76.0, 74.8, 74.1, 73.7, 71.4; HRMS (ESI, *m/z*): Calcd. for $C_{11}H_9BrO_2Ru$ $[M\text{-}H]^-$ 352.8755 found, 352.8752.

1-bromo-1′-[*tert*-butyloxazolin-2-yl] ruthenocene (7)

To a solution of **6** (0.7 g, 2.0 mmol) in DCM (50 mL) was added oxalyl chloride (0.64 mL, 7.9 mmol) and pyridine (0.1 mL) at 0 °C. The mixture was heated at reflux for 5 h and then evaporated to dryness. The residue was washed with Et_2O (15 mL × 3), and the solvent was evaporated in vacuo. The resulting crude product was used directly in the next step without another further purification. To a solution of (*S*)-*tert*-leucinol (255.5 mg, 2.2 mmol) and DIPEA (*N*,*N*-diisopropylethylamine, 1.0 mL, 6.0 mmol) in DCM (dichloromethane, 20 mL) was added dropwise the solution of the above 1-bromo-1′-chlorocarbonyl ruthenocene in DCM (20 mL) at 0 °C. The reaction mixture was stirred at room temperature overnight. To this solution was added dropwise MsCl (methanesulfonyl chloride, 0.25 mL, 3.2 mmol) and DIPEA (1.3 mL, 8.0 mmol) at 0 °C, and then the solution was stirred at room temperature for another 4 h. The reaction mixture was washed with water and brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by column chromatography using petroleum ether/ethyl acetate (6:1, v/v) as the eluent to afford **7** as a yellow green solid (0.39 g, 58% yield for three steps).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.20–5.16 (m, 2H), 4.88–4.87 (m, 2H), 4.72–4.69 (m, 2H), 4.47 (t, J = 1.8 Hz, 2H), 4.21 (dd, J = 8.6, 10.0 Hz, 1H), 4.11 (dd, J = 7.2, 8.6 Hz, 1H), 3.88 (dd, J = 7.2, 10.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.5, 76.0, 74.6, 74.44, 74.41, 74.39, 73.3, 73.1, 71.29, 71.27, 68.6, 58.6, 34.0, 26.1, 18.6; HRMS (ESI, *m/z*): Calcd. for $C_{17}H_{20}BrNORu$ $[M+H]^+$ 435.9844 found, 435.9841.

1-[*tert*-butyloxazolin-2-yl]-2-diphenylphosphino ruthenocene (8) [40]

To a solution of **7** (0.5 g, 1.14 mmol) in THF (20 mL) was added dropwise *n*-butyllithium (2.5 M in *n*-hexane, 0.78 mL, 1.95 mmol) at − 78 °C. The reaction mixture was stirred for an additional 0.5 h and then trapped with $ClPPh_2$ (chlorodiphenylphosphine, 0.42 mL, 2.25 mmol) at this temperature. After stirring at room temperature overnight, TLC indicated that most of the raw material **7** was still present. After evaporation, the residue was purified by column chromatography using petroleum ether/ethyl acetate (8:1, v/v) as the eluent to afford unexpected product **8** (70 mg, 11% yield).

^{1}H NMR ($CDCl_3$, 400 Hz): δ 7.27–7.38 (m, 10H), 5.28 (brs, 1H), 4.66 (brs, 1H), 4.59 (s, 5H), 4.10 (dd, J = 8.4, 10 Hz, 1H), 3.95 (brs, 1H), 3.85 (dd, J = 7.6, 8.4 Hz, 1H), 3.69 (dd, J = 7.2, 10 Hz, 1H), 0.77 (s, 9H).

1-bromo-1′-diphenylphosphino ruthenocene

To a solution of **4** (0.25 g, 0.6 mmol) in THF (25 mL) was added dropwise *n*-butyllithium (2.5 M in *n*-hexane, 0.3 mL, 0.6 mmol) at − 78 °C. After stirring for 0.5 h, $ClPPh_2$ (0.13 mL, 0.7 mmol) was slowly added to the solution at − 78 °C. The reaction mixture was warmed to room temperature and stirred overnight. The solvent was removed under reduced pressure, and the residue was purified by column chromatography using petroleum ether/ethyl acetate (6:1, v/v) as the eluent to afford a yellow green solid (154 mg, 48.5% yield).

^{1}H NMR ($CDCl_3$, 400 Hz): δ 7.40–7.35 (m, 4H), 7.34–7.30 (m, 6H), 4.75 (dd, J = 1.5, 1.7 Hz, 4H), 4.54 (q, J = 1.7 Hz, 2H), 4.33 (t, J = 1.7 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 Hz): δ 133.8 (d, J_{pc} = 9.7 Hz), 133.2 (d, J_{pc} = 19.1 Hz), 128.3, 128.0 (d, J_{pc} = 6.7 Hz), 82.0 (d, J_{pc} = 10.9 Hz), 76.7 (d, J_{pc} = 31.8 Hz), 75.9, 75.3 (d, J_{pc} = 3.4 Hz), 74.1, 71.2; ^{31}P NMR ($CDCl_3$, 162 Hz): δ -17.43; HRMS (ESI, *m/z*): Calcd. for $C_{22}H_{18}BrPRu$ $[M+H]^+$ 494.9447 found, 494.9445.

Sodium carbomethoxycyclopentadienide (9) [56]

To a slurry of sodium (1.15 g, 50 mmol) in THF (60 mL) was added freshly cracked cyclopentadiene (10.3 mL, 125 mmol) at 0 °C. The mixture was magnetically stirred until the sodium was consumed. To the resulting pink solution of sodium cyclopentadienide was added dimethyl carbonate (13.1 mL, 155 mmol). The reaction mixture was stirred at room temperature for 10 min and subsequently heated at reflux for 4 h. The solvent was removed under reduced pressure, and the residue was washed with

Et_2O (20 mL × 3) until the filtrate was clear and dried to afford **9** as a cream-colored solid (6.83 g, 93% yield).

^{1}H NMR (400 MHz, acetone-d_6): δ 6.31 (t, J = 2.8 Hz, 2H), 5.69 (t, J = 2.8 Hz, 2H), 3.52 (s, 3H); ^{13}C NMR (100 MHz, CD_3COCD_3): δ 168.4, 112.3, 110.1, 109.0, 49.2.

[(η^5-C_5H_4COOMe)Ru(η^6-C_6H_6)]PF_6 (10) [57]

The synthesis of **10** was accomplished following the previously published procedure with slight modifications. To a solution of benzeneruthenium (II) chloride dimer (3 g, 6 mmol) in acetonitrile (300 mL) was added the solution of **9** (2.1 g, 14.4 mmol) in THF (20 mL) at room temperature. The reaction mixture was heated at reflux and stirred for 18 h. The resulting suspension was filtered through celite, and the solvent was evaporated in vacuo. The residue was dissolved in water followed by the addition of KPF_6. The resulting off-white precipitate was collected by filtration, washed with water, and dried under a high vacuum (12.3 g, 76% yield).

^{1}H NMR (400 MHz, CD_3CN): δ 6.16 (s, 6H), 5.79–5.78 (m, 2H), 5.46–5.45 (m, 2H), 3.81 (s, 3H); ^{13}C NMR (100 MHz, CD_3CN) δ: 166.1, 88.3, 86.3, 83.1, 81.7, 53.5.

[(η^5-C_5H_4COOMe)Ru(CH_3CN)$_3$]PF_6 (11)

A 250-mL flask was charged with **10** (2.32 g, 5.2 mmol), and degassed acetonitrile (150 mL) was added. The reaction mixture was irradiated with a medium-pressure mercury lamp for 12 h. Evaporation of the solvent yielded **11** (2.5 g, 98%, NMR yield) as a black green solid. The product was directly used in the next step without any further purification.

[boranatodiphenylphosphino]cyclopentadiene (13)

To a solution of freshly cracked cyclopentadiene (1.66 mL, 20 mmol) in Et_2O (20 mL) was added dropwise *n*-butyllithium (2.5 M in *n*-hexane, 8.8 mL, 22 mmol) at − 78 °C. After stirring for 3 h, $ClPPh_2$ (4.13 mL, 23 mmol) was added to the solution at − 78 °C. The reaction mixture was warmed to room temperature and stirred overnight. To the above solution was added slowly BH_3·THF (1 M, 24 mL, 24 mmol) at − 78 °C and stirred for 2 h at this temperature. The reaction mixture was quenched by 1 N HCl, diluted with ethyl acetate (30 mL), and washed with water and then with brine. The organic layer was dried over anhydrous Na_2SO_4 and removed under reduced pressure. The residue was purified by column chromatography using petroleum ether/ethyl acetate (10:1, v/v) as the eluent to afford **12** as a white solid (4.3 g, 81% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65–7.58 (m, 4H), 7.51–7.40 (m, 6H), 6.96–6.91 (m, 1H), 6.89–6.80 (m, 1H), 6.62–6.58 (m, 1H), 3.23 (s, 2H), 1.41–0.77 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.0 (d, J_{PC} = 8.8 Hz), 141.1 (d, J_{PC} = 6.3 Hz), 134.2 (d, J_{PC} = 64.4 Hz), 132.7 (d, J_{PC} = 9.8 Hz), 132.4 (d, J_{PC} = 13.2 Hz), 131.2

(d, J_{PC} = 2.4 Hz), 129.8 (d, J_{PC} = 59.0 Hz), 128.7 (d, J_{PC} = 10.2 Hz), 44.2 (d, J_{PC} = 11.4 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ 10.83 (d, J_{PB} = 75.9 Hz); HRMS (ESI, *m/z*): Calcd. for $C_{17}H_{18}BP$ $[M+Na]^+$ 287.1135 found, 287.1134.

1-methoxycarbonyl-1′-boranatodiphenylphosphino ruthenocene (14)

To a solution of **13** (2.83 g, 10.72 mmol) in THF (50 mL) was added dropwise *n*-butyllithium (2.5 M in *n*-hexane, 4.5 mL, 11.17 mmol) at 0 °C, and the solution was stirred for 3 h at this temperature. The above solution was slowly added to the solution of **11** in THF (200 mL) at 0 °C. After stirring overnight at this temperature, the reaction mixture was quenched by the addition of water. The organic solvent was evaporated in vacuo, and the residue was diluted with DCM. The organic layer was washed with brine and dried over anhydrous Na_2SO_4. The residue was purified by column chromatography using petroleum ether/dichloromethane (1:1, v/v) as the eluent to afford **14** as a slight orange solid (3.13 g, 72% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61–7.56 (m, 4H), 7.50–7.45 (m, 2H), 7.44–7.39 (m, 4H), 5.04 (t, J = 2.0 Hz, 2H), 4.84–4.83 (m, 2H), 4.78 (q, J = 1.7 Hz, 2H), 4.63 (t, J = 2.0 Hz, 2H), 3.65 (s, 3H), 1.24–0.67 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.0, 132.8 (d, J_{PC} = 9.7 Hz), 131.2 (d, J_{PC} = 2.6 Hz), 130.9 (d, J_{PC} = 59.1 Hz), 128.6 (d, J_{PC} = 10.0 Hz), 77.4, 76.2 (d, J_{PC} = 10.5 Hz), 75.8, 75.5 (d, J_{PC} = 6.9 Hz), 75.4 (d, J_{PC} = 64.7 Hz), 73.8, 51.8; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 15.90 (d, J_{PB} = 77.3 Hz); HRMS (ESI, *m/z*): Calcd. for $C_{24}H_{24}BO_2PRu$ $[M+Na]^+$ 511.0554 found, 511.0554.

1-carboxy-1′-boranatodiphenylphosphino ruthenocene (15)

A solution of **14** (2.2 g, 4.51 mmol) and NaOH (1.8 g, 45.1 mmol) in a mixed solvent system of THF, MeOH, and H_2O (30 mL, 30 mL and 30 mL, respectively) was stirred at room temperature. After TLC indicated **14** had been consumed, the reaction was evaporated to dryness. The obtained crude product was dissolved in H_2O (300 mL) and washed with Et_2O (30 mL × 3). The aqueous layer was acidified with aq. HCl solution (1 M) to pH = 2. After filtration and drying in vacuo, **15** was obtained as a slight yellow solid (2.07 g, 97% yield).

^{1}H NMR (400 MHz, DMSO-d_6): δ 12.24 (brs, 1H), 7.59–7.50 (m, 10H), 4.94–4.92 (m, 2H), 4.88 (t, J = 1.8 Hz, 2H), 4.82 (q, J = 1.7 Hz, 2H), 4.48 (t, J = 1.8 Hz, 2H), 1.28–0.65 (m, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.7, 132.2 (d, J_{PC} = 9.6 Hz), 131.3 (d, J_{PC} = 2.4 Hz), 130.4 (d, J_{PC} = 58.8 Hz), 128.7 (d, J_{PC} = 10.1 Hz), 78.1, 75.63 (d, J_{PC} = 22.4 Hz), 75.61 (d, J_{PC} = 4.8 Hz), 75.1, 74.3 (d, J_{PC} = 64.8 Hz), 73.4; ^{31}P NMR (162 MHz, DMSO-d_6): δ 14.60; HRMS (ESI, *m/z*): Calcd. for $C_{23}H_{22}BO_2PRu$ $[M-H]^-$ 473.0432 found, 473.0428.

Amide intermediate (16)

A mixture of **15** (1.5 g, 3.17 mmol), EDCI [1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, 1.34 g, 6.97 mmol], and HOBt (*N*-hydroxybenzotriazole,

0.64 g, 4.76 mmol) was dissolved in DMF (50 mL). DIPEA (1.1 mL, 6.66 mmol) was added to this mixture, and the reaction was stirred at room temperature for 0.5 h. To this solution was added (*S*)-*tert*-leucinol (0.46 g, 3.96 mmol) at room temperature. The reaction mixture was stirred overnight at room temperature. After the solvent was removed in vacuo, the residue was dissolved in DCM (150 mL), washed with water (150 mL) and brine (150 mL), and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by column chromatography using petroleum ether/ethyl acetate (4:1, v/v) as the eluent to afford **16** as a yellow green solid (1.6 g, 88% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63–7.54 (m, 4H), 7.51–7.39 (m, 6H), 6.23 (d, J = 9.4 Hz, 1H), 5.13–5.11 (m, 2H), 4.96–4.94 (m, 1H), 4.89–4.87 (m, 1H), 4.85–4.83 (m, 1H), 4.52–4.50 (m, 2H), 4.38–4.36 (m, 1H), 3.96–3.86 (m, 2H), 3.65 (dd, J = 11.1, 8.6 Hz, 1H), 1.68 (s, 1H), 1.58–1.03 (m, 3H), 0.98 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.7, 132.8 (dd, J_{PC} = 20.0, 9.6 Hz), 131.4 (d, J_{PC} = 2.4 Hz), 131.3 (d, J_{PC} = 2.4 Hz), 128.7 (t, J_{PC} = 10.3 Hz), 82.6, 77.7 (d, J_{PC} = 13.3 Hz), 75.6 (dd, J_{PC} = 9.4, 7.6 Hz), 75.2 (d, J_{PC} = 6.4 Hz), 74.4 (d, J_{PC} = 2.7 Hz), 73.7, 72.6, 63.2, 59.9, 33.9, 27.3; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 15.58; HRMS (ESI, *m/z*): Calcd. for $C_{29}H_{35}BNO_2PRu$ $[M+Na]^+$ 596.1447 found, 596.1456.

1-*tert*-butyloxazolinyl-1′-boranatodiphenylphosphino ruthenocene (17)

To a solution of **16** (1.35 g, 2.36 mmol) in DCM (50 mL) was added DIPEA (1.17 mL, 7.08 mmol) and MsCl (0.28 mL, 3.54 mmol) at 0 °C. The reaction mixture was warmed to room temperature and stirred until TLC indicated **16** had been consumed. After evaporation, the residue was purified by column chromatography using petroleum ether/ethyl acetate (8:1, v/v) as the eluent to afford **17** as a yellow green solid (1.18 g, 90% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62–7.57 (m, 4H), 7.49–7.44 (m, 2H), 7.43–7.38 (m, 2H), 5.05–5.04 (m, 1H), 4.99–4.98 (m, 1H), 4.81–4.79 (m, 2H), 4.78–4.74 (m, 2H), 4.59–4.56 (m, 2H), 4.09 (dd, J = 10.0, 8.6 Hz, 1H), 4.01 (dd, J = 8.6, 7.1 Hz, 1H), 3.78 (dd, J = 10.0, 7.1 Hz, 1H), 1.50–0.90 (m, 3H), 0.85 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.8, 132.8 (dd, J_{PC} = 9.5, 1.4 Hz), 131.12 (dd, J_{PC} = 8.4, 2.5 Hz), 131.09 (dd, J_{PC} = 58.7, 5.1 Hz), 128.6 (d, J_{PC} = 10.0 Hz), 77.4, 76.5, 76.1 (d, J_{PC} = 10.7 Hz), 75.9, 75.8 (d, J_{PC} = 10.4 Hz), 75.4 (t, J_{PC} = 6.7 Hz), 75.1 (d, J_{PC} = 1.9 Hz), 74.8 (d, J_{PC} = 65.1 Hz), 73.2, 72.9, 68.4, 34.0, 25.9; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 15.93 (d, J_{PB} = 58.3 Hz); HRMS (ESI, *m/z*): Calcd. for $C_{29}H_{33}BNOPRu$ $[M+H]^+$ 556.1522 found, 556.1522.

1-*tert*-butyloxazolinyl-1′-boranatodiphenylphosphino ruthenocene (3)

A mixture of **17** (600 mg, 1.1 mmol) and DABCO (triethylenediamine, 2.42 g, 22 mmol) was dissolved in degassed dioxane (30 mL) and stirred at reflux temperature overnight. After careful removal of the volatile solvent, the residue was purified by flash chromatography on silica gel using petroleum ether/ethyl acetate (10:1, v/v) as the eluent to afford **3** as a yellow green solid (572 mg, 97.7% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39–7.33 (m, 4H), 7.33–7.30 (m, 6H), 5.05–5.03 (m, 1H), 5.00–4.98 (m, 1H), 4.72–4.70 (m, 2H), 4.52–4.47 (m, 4H), 4.14 (dd, J = 10.0, 8.6 Hz, 1H), 4.06 (dd, J = 8.6, 7.1 Hz, 1H), 3.82 (dd, J = 10.0, 7.1 Hz, 1H), 0.87 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.1, 139.1 (dd, J_{PC} = 9.8, 7.8 Hz), 133.5 (dd, J_{PC} = 19.1, 10.5 Hz), 128.6 (d, J_{PC} = 10.7 Hz), 128.2 (d, J_{PC} = 6.6 Hz), 81.6 (d, J_{PC} = 10.8 Hz), 76.5 (dd, J_{PC} = 27.6, 15.9 Hz), 75.9, 75.8, 74.4 (d, J_{PC} = 7.8, 3.4 Hz), 73.7, 72.2 (d, J_{PC} = 7.1 Hz), 68.4, 34.0, 26.0; ^{31}P NMR (162 MHz, $CDCl_3$): δ -16.93; HRMS (ESI, *m/z*): Calcd. for $C_{29}H_{30}NOPRu$ $[M+H]^+$ 542.1189 found, 542.1187.

Results and discussion

Generally, the synthetic method for the preparation of 1,1′-disubstituted ferrocene is realized via the introduction of active groups, such as halogen or organotin compounds, to the two Cp rings (Fig. 2). Zhang and Ikeda's group synthesized 1,1′-disubstituted ferrocene phosphine–oxazoline ligand **1** via an organotin intermediate. First, the lithiation of ferrocene forms 1,1′-dilithiated ferrocene, which is trapped with tributyltin chloride to generate a 1,1′-ditributyltin ferrocene intermediate. The organotin intermediate is lithiated sequentially followed by phosphonylation with Ph_2PCl and the formation of the oxazoline ring, respectively, to provide **1** [52]. Using 1,2-dibromotetrafluoroethane instead of tributyltin chloride, Hou's group synthesized a halogen intermediate 1,1′-dibromoferrocene via a lithium–halogen exchange reaction. Ferrocene phosphine–oxazoline ligand **1** was then obtained using a similar process to that described above. Further derivation of **1** resulted in a series of planar chiral 1,1′-phosphine-oxazoline based ligands [58–60].

Similar to the synthetic strategy of ferrocene-based ligand **1**, we first intended to synthesize the target product **3** by introducing active groups to the two Cp rings in ruthenocene, followed by functionalization and formation of the oxazoline ring.

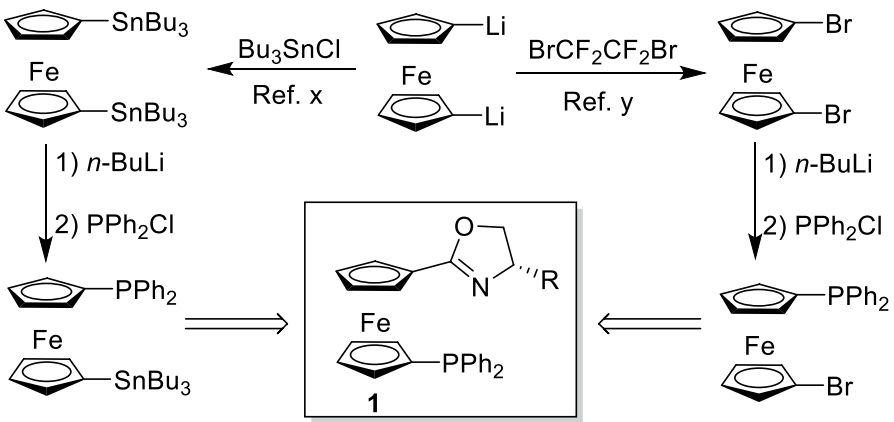

Fig. 2 The synthetic strategy for 1,1′-phosphine-oxazoline **1**

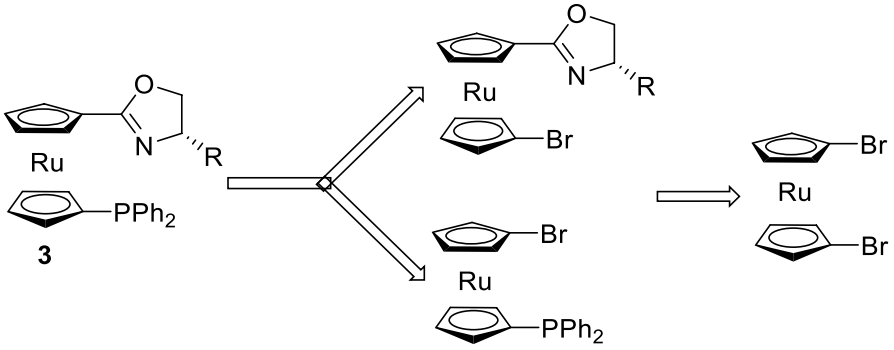

Fig. 3 The retrosynthesis of 1,1′-phosphine-oxazoline ruthenocene **3**

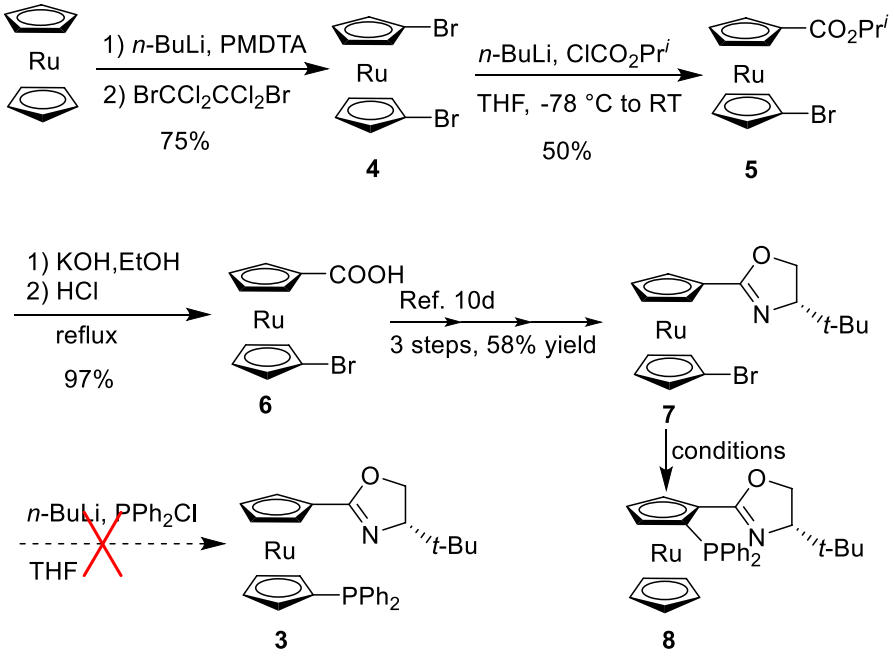

Fig. 4 The first synthetic route to **3**

Bromide was selected as the active group, and the retrosynthetic route is shown below: The target product **3** could be obtained via two types of intermediates, 1-bromo-1′-oxazolinyl ruthenocene or 1-bromo-1′-diphenylphosphino ruthenocene, which could be formed by functionalization of 1,1′-dibromoruthenocene (Fig. 3).

An attempt on the synthesis of **3** was first conducted via the 1-bromo-1′-oxazolinyl ruthenocene intermediate (Fig. 4). Using ruthenocene as the starting material, *n*-BuLi and PMDTA were added to *n*-hexane, and the brominated reagent 1,2-dibromotetetrachloroethane was added after stirring for 18 h at room

temperature. 1,1′-dibromoruthenocene (**4**) can be obtained in 75% yield. After lithium–halogen exchange, **4** was treated with isopropyl chloroformate to give **5** in 50% yield. Then, **6** was obtained conveniently in 93% yield after hydrolysis of **5** under alkaline conditions. According to our previous methods [52], the key intermediate 1-bromo-1′-oxazolinyl ruthenocene (**7**) was obtained easily. According to the synthesis of the corresponding ferrocene ligand **1**, target compound **3** could be obtained through lithium–bromide exchange of **7** followed by phosphonylation. However, the unexpected formation of 1,2-disubstituted ruthenocene phosphine–oxazoline ligand **8** instead of **3** was observed in this reaction.

We speculate that the formation of the unexpected product **8** may be due to the different distances between the two Cp rings of ruthenocene and ferrocene. The complexation and induction of the oxazoline group result in the stability of the negative ion in the 1′-position being far less stable than the anion formed in the 2-position after lithiation; this result in the negative charge is transferred to the ortho position of the oxazoline. Changing the solvent from THF to ether gave the same result.

In order to avoid the formation of the 1,2-substituted product due to the induction of the oxazoline group, the alternative route shown in Fig. 3 was chosen to introduce the diphenylphosphine group first to give the 1-bromo-1′-diphenylphosphino ruthenocene intermediate. This then undergoes lithium–bromide exchange and esterification to provide the target product **3** (Fig. 5). The first phosphonylation proceeded smoothly. However, the subsequent esterification was not successful with no reaction occurring. Extending the lithiation time, increasing the temperature and changing the solvent were tried but were also unsuccessful. It appears that the large steric hindrance and electron donating ability of the diphenylphosphine group make the lithium–halogen exchange difficult.

We also attempted to use *sec*-BuLi or add TMEDA (N,N,N’,N’-tetramethylethylenediamine) during lithiation with the aim of improving the lithiation step. However, debrominated products were formed with large amounts of starting materials remaining.

The negative results concerning the introduction of groups into the ruthenocene ring prompted us to explore a new synthetic strategy. We envisioned a more different pathway. First, derivatization of cyclopentadiene would afford two functionalized cyclopentadienes which could then react with the ruthenium species in a proper sequence to generate the key 1,1′-disubstituted ruthenocene backbone intermediate. Finally, the target product **3** could be obtained through further conventional derivatization.

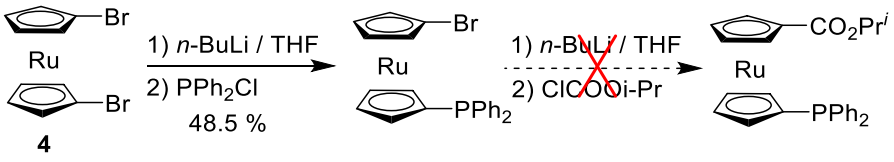

Fig. 5 The second synthetic route of **3**

Thus, the reaction between sodium and cyclopentadiene in THF was carried out followed by the addition of dimethyl carbonate. The reaction proceeded under reflux conditions, and compound **9** was obtained in more than 90% yield. Treating **9** with benzeneruthenium(II) chloride dimer in acetonitrile under reflux conditions for 18 h, followed by addition to a saturated aqueous solution of KPF_6, gave $[Cp(C_6H_6)Ru]PF_6$ (**10**) in 76% yield, which was used in the next step without further purification. The dissociation of the benzene ring from the Ru atom in **10** was conducted by irradiation using a medium-pressure mercury lamp (UV light with wavelength of 310 nm) in acetonitrile. Then, three acetonitrile molecules combine with the Ru atom to generate $[CpRu(CH_3CN)_3]PF_6$ (**11**). After the solvent was evaporated in vacuo, the brown-black powder **11** was obtained and used directly in the subsequent reaction without further purification (Fig. 6).

On the other hand, cyclopentadiene was reacted with *n*-BuLi to generate lithium cyclopentadiene, which was then reacted with $ClPPh_2$ to give compound **12**. Without additional workup, BH_3·THF was added to the reaction system at − 78 °C and a relatively stable compound **13** was obtained in 82% overall yield. Then, **13** was lithiated in THF and the reaction system was added to a solution of the above ruthenium complex **11** in THF. After reaction at 0 °C overnight, the key intermediate **14** was obtained in 72% yield (Fig. 6). The results reveal again that the method of introducing groups to the ruthenocene ring is quite different to that of the corresponding ferrocene. Although a total of 7 steps were used to obtain the key intermediate **14**, the current methodology provides a feasible and practical strategy for the synthesis of novel ruthenocene-based ligands.

The hydrolysis of **14** was carried out using a mixed solvent system of THF-MeOH-H_2O at room temperature, providing the carboxylic acid **15**. This was then condensed with amino alcohol in the presence of EDCI and HOBt to generate the

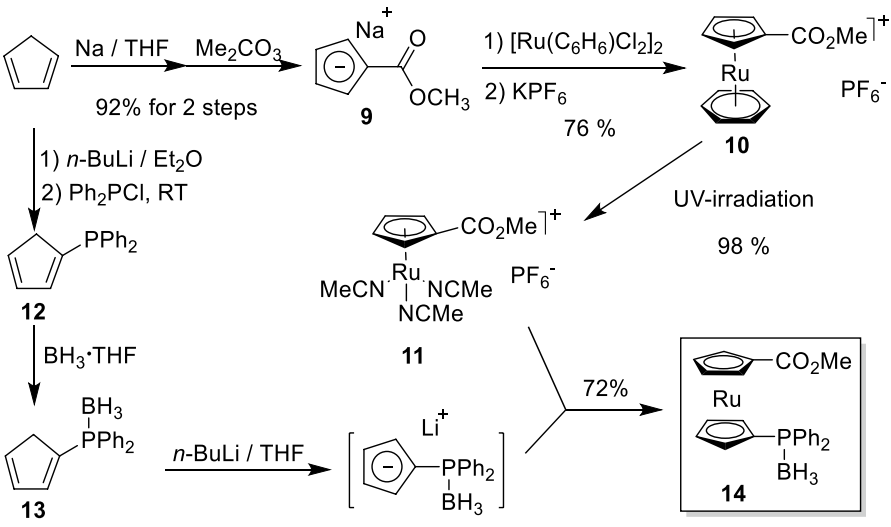

Fig. 6 The synthetic strategy for the key intermediate **14**

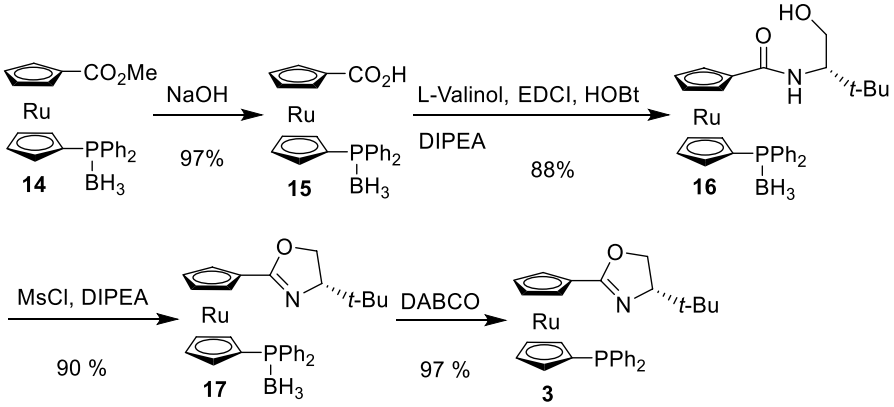

Fig. 7 The synthetic strategy for 1,1′-phosphine-oxazoline **3**

amide intermediate **16**. The formation of the oxazoline ring was realized by treating **16** with MsCl to give the ligand precursor **17** in 90% yield. Finally, the target product **3** was obtained via the removal of borane using DABCO in near quantitative yield (Fig. 7).

Conclusion

In conclusion, we have developed a novel chiral ruthenocene-based 1,1′-phosphine–oxazoline ligand **3** based on careful design and experimental exploration. First, a key intermediate 1-ester-1′-boranediphenylphosphine ruthenocene was obtained by using cyclopentadiene as a starting material, followed by functionalization and metallocene-forming steps. Next, the formation of the oxazoline ring was realized according to our previous method. Finally, 1,1′-disubstituted ruthenocene phosphine–oxazoline ligand **3** was obtained conveniently after the removal of borane. The experimental results indicate that the synthesis of 1,1′-disubstituted ruthenocene phosphine–oxazoline ligands is, to a great extent, different from the corresponding ferrocene ligands. The work provides crucial guidance and assistance for the synthesis of novel chiral ruthenocene-based ligands, especially for further derivatization to synthesize a broader array of planar chiral ruthenocene-based ligands.

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