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Enantioselective transfer hydrogenation of ketones with planar chiral ruthenocene-based phosphinooxazoline ligands

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Abstract

1,2-Disubstituted planar chiral ruthenocene-based phosphinooxazoline ligands (Rc-PHOX, **3** and **4**) were synthesized easily and applied in the transfer hydrogenation of ketones to chiral alcohols using 2-propanol as a source of hydrogen with excellent enantioselectivity and high catalytic activity.

Keywords: Ruthenocene-based phosphinooxazoline ligands; Transfer hydrogenation; Planar chiral; Ketones

1. Introduction

Ferrocene-based chiral ligands designed for asymmetric synthesis have attracted tremendous scientific interest over the past decades.[1] However, the ruthenocene-based chiral ligands have received much less attention and only few papers appeared so far.[2] Recently, we have developed the air-stable C_2-symmetric tetrasubstituted ruthenocene compounds **1** (Fig. 1) and applied them to palladium-catalyzed asymmetric allylic substitution.[3] Comparing with the corresponding ferrocene ligands,[4] much higher catalytic activity and comparable excellent enantioselectivity were observed. Then, the central chirality was removed by the transformation of the oxazoline moieties in the molecule to give ligands **2** (Fig. 1) with only planar chirality, which also showed excellent effectiveness for palladium-catalyzed asymmetric allylic substitution,[5] comparable with or better than their corresponding ferrocene analogs.[6]

In the course of developing new ruthenocene-based chiral ligands, we want to examine whether the monometallic systems would provide different reactivity patterns with bimetallic systems. So C_1-symmetric ruthenocene-based phosphinooxazoline ligands (Rc-PHOX, **3** and **4**, Fig. 1) were designed for asymmetric catalysis, by comparing with their corresponding C_2-symmetric tetrasubstituted ruthenocene compounds **1**.[3a] To the best of our knowledge, only one precedent concerning 1,2-disubstituted ruthenocene-based chiral ligand was reported by Bolm.[2c] Here, we report the synthesis of 1,2-disubstituted ruthenocene-based phosphinooxazoline ligands **3** and **4** and their application in the transfer hydrogenation of ketones to chiral alcohols.

2. Results and discussion

The compounds **3** can be easily prepared from ruthenocene via six steps (Scheme 1). First, the Friedel–Crafts acylation of ruthenocene was studied. Details are shown in Table 1.

The procedure according to literature[7] did not give the satisfactory result (Table 1, entry 1). Then, the molar ratios of the aluminum trichloride and *o*-chlorobenzoyl chloride (OCBC) for the acylation were studied carefully (Table 1, entries 2–8), and the optimal ratio was ascertained (Table 1, entry 8). Thus, ruthenocene treated with 1.5 equiv aluminum trichloride and 10 equiv OCBC in dichloromethane overnight, followed by hydrolysis to give 1-carboxylic ruthenocene **5** in 66% overall yield.

Then, this acid **5** reacted with 4 equiv oxalyl chloride in dichloromethane to give 1-chlorocarbonyl ruthenocene **6**. Without any purification, **6** was used directly to react with

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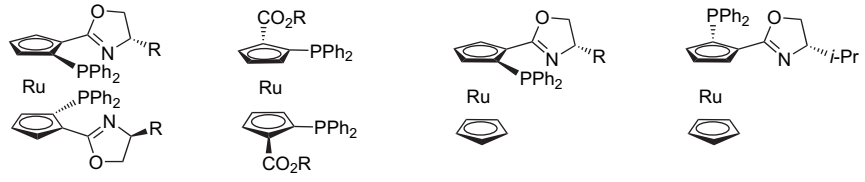
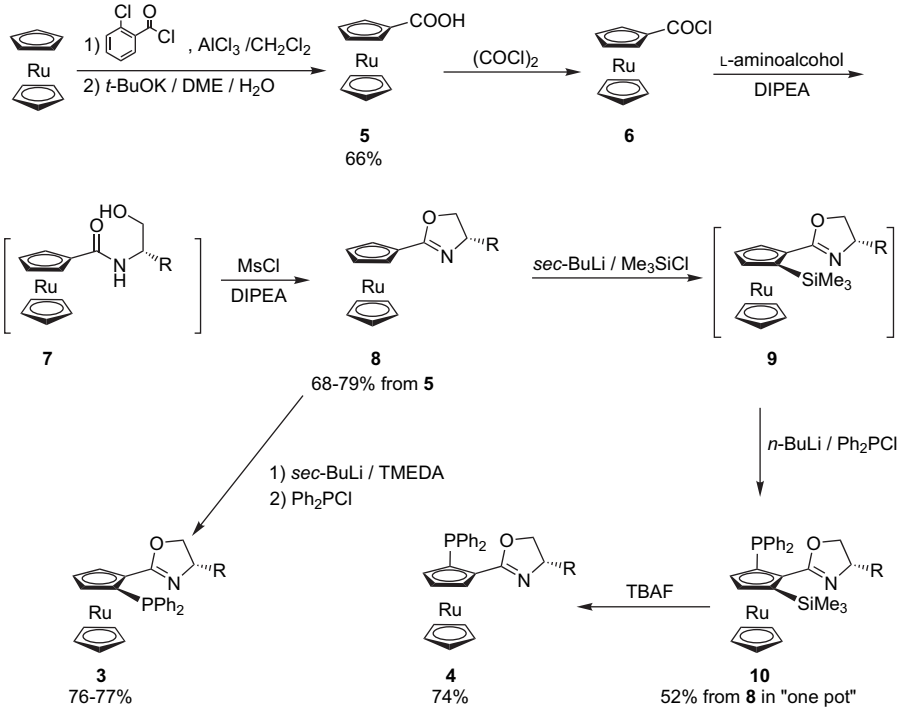


Figure 1.



Scheme 1.

1.1 equiv L-aminoalcohol and then treated with 1.5 equiv methyl sulfonyl chloride in 'one-pot' to afford the 1-[(*S*)-4-substituted-oxazolin-yl]-ruthenocene **8** in 68–79% overall yield from **5**.

Lithiation of **8** was initially investigated using *n*-BuLi in THF followed by addition of chlorodiphenylphosphine (Ph_2PCl),[8] but the reaction did not occur and only trace amount of **3** was produced upon addition of TMEDA. This reaction did not occur in Et_2O under the above-mentioned conditions. Finally, this reaction proceeded smoothly with *sec*-BuLi and TMEDA in Et_2O. Thus, **8** in Et_2O was treated with 1.3 equiv of *sec*-BuLi and 1.3 equiv of TMEDA for a period of 2 h at −78 °C and then 20 min at 0 °C to ensure complete dilithiation. The lithiated species of **8** was then quenched with 1.3 equiv of Ph_2PCl at 0 °C. After stirred at 0 °C for 3 h, **3** was obtained in 76–77% yield. To our delight, compounds **3** were obtained as the sole product and no **4** was observed.

Table 1
Effect of the amount of $AlCl_3$ and OCBC on Friedel–Crafts acylation

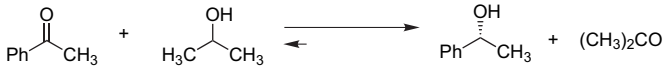
Entry	$AlCl_3$ (equiv)	OCBC (equiv)	Conversion[a] (%)
1[b]	1	1	13.9
2	1	3	21.5
3	1	10	66.3
4	1	15	65.4
5	1.5	1	29.2
6	3	1	28.4
7	1.5	5	77.5
8	1.5	10	85.5

[a] Determined by ^1H NMR.
[b] According to Ref. 7.

In order to obtain **4**, intermediate **10** should be prepared first.[8b,f,g] Thus, the above lithiated species of **8** was quenched with 1.3 equiv of trimethylchlorosilane at 0 °C to give (*S*,*R*p)-**9** with the yield of 68%. Compound **10** was then obtained in 44% yield by treating **9** with 1.3 equiv of *sec*-BuLi in Et_2O at −78 °C for a period of 2 h and then 20 min at 0 °C, followed by addition of Ph_2PCl. The overall yield was 30% from **8**. Furthermore, without isolation, **9** could be directly treated with Ph_2PCl in 'one-pot' to give **10** with the overall yield of 52% from **8**. Compound **4** was then obtained in

74% yield by treating **10** with TBAF (1 M in THF) under reflux for 20 h.

Transfer hydrogenation using 2-propanol (IPA) as a source of hydrogen is an attractive method for the reduction of ketones to alcohols.[9] The reaction utilizes inexpensive reagents, is simple to perform, and does not require the use of reactive metal hydrides or hydrogen. With the novel planar chiral ligands in hand, we tried to apply them in H-transfer hydrogenation of ketones (Scheme 2). The complexes of novel ligands with Ru(II) showed excellent turnover and catalytic activity in the reduction of acetophenone. Details are shown in Table 2.



Scheme 2.

Compound **3a** was used as a chiral ligand in this hydrogenation, and high catalytic activity and good enantioselectivity were obtained within 5 min (Table 2, entry 1). But the ee value decreased with longer reaction time since this reaction is an equilibration. The substituent R on the oxazolinyl ring had much effect on the enantioselectivity and a bulkier group gave a better ee value. When **3b** with a *tert*-butyl group was used as a chiral ligand, up to 96.8% ee was obtained (Table 2, entry 2). Temperature affected the enantioselectivity obviously, and the ee value was enhanced to 99.9% if the temperature was lowered from reflux to 40 °C (Table 2, entry 3).

Table 2
H-transfer reduction with IPA as hydrogen donor[a]

Entry	Ligand	Temp (°C)	Time (min)	Conversion[b] (%)	ee[c,d] (%)
1	**3a**	Reflux	5	98	88.5
			10	99	81.2
			20	99	76.2
			30	99	74.8
			45	99	67.7
			60	99	66.8
2	**3b**	Reflux	5	93	96.8
			10	99	95.8
			30	99	94.8
			60	98	93.8
			180	98	93.5
3	**3b**	40	24 h	38	99.9
4	**4**	Reflux	5	99	65.7
			10	99	58.5
			30	99	33.5
			60	99	30.2
5	**1a**	Reflux	1	98	83.3
			5	99	80.6
			10	99	77.4
			30	99	70.3
			60	99	68.7

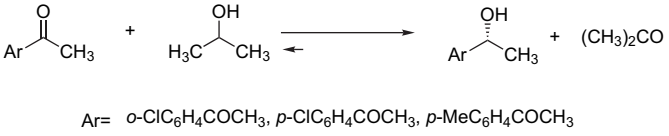
[a] Preparation of the catalyst: $Ru(II)Cl_2(PPh_3)_3$ (1.0 mol %) and chiral ligand (1.3 mol %) were dissolved in 2-propanol (5 mL) and the mixture was refluxed under nitrogen atmosphere for 0.5 h before use.
[b] Determined by ^1H NMR.
[c] Determined by GC with Varian Chiralsil-L-Val column.
[d] Absolute configuration of product was assigned through comparison of the sign of specific rotations with the literature data.[11]

The effect of planar chirality was examined also.[10] When **3a** was replaced by **4**, only 65.7% ee was obtained with the same configuration of product (Table 2, entry 4). However, high catalytic activity was also obtained since the reaction almost completed within 5 min. This demonstrates that the enantioselectivity in the reactions discussed above is mainly determined by the central chirality of 1,2-disubstituted ruthenocene-based ligands. To match planar and central chiralities is essential for obtaining excellent asymmetric induction.

Meanwhile, the C_2-symmetric tetrasubstituted P,N-chelate **1** was used in this H-transfer hydrogenation. High catalytic activity and good enantioselectivity were also obtained (Table 2, entry 5). But **1** gave somewhat lower enantioselectivity than **3a** did.

From aforementioned results, it was known that the ruthenocene-based ligands also showed high catalytic activity and much higher enantioselectivity for the H-transfer hydrogenation of acetophenone, comparing with their corresponding ferrocene-based phosphinooxzoline ligands.[12]

In order to examine the steric and/or electric effect of the substituent in the phenyl group of the substrate, several substituted substrates were examined (Scheme 3). All reactions showed high catalytic activity and the reactions completed within 5 min (Table 3).



Scheme 3.

It was shown that the steric hindrance played an important role in determining the degree of the enantioselectivity of the reaction: *ortho*-substituted acetophenone gave higher enantiomeric excess than their *para*-substituted analogs (Table 3, entries 1 and 2). On the other hand, electronic effects of the aromatic ring substituents also seemed to have influence in this case in the same way. When the substituent on the benzene

Table 3
H-transfer reduction with IPA as hydrogen donor using **3a**[a]

Entry	Substrate	Temp (°C)	Time (min)	Conversion[b] (%)	ee[c,d] (%)
1	*o*-$ClC_6H_4COCH_3$	Reflux	5	100	82.2
			15	100	76.4
2	*p*-$ClC_6H_4COCH_3$	Reflux	5	100	61.1
			15	100	59.4
3	*p*-$MeC_6H_4COCH_3$	Reflux	5	100	66.2
			15	100	61.1
4	*p*-$MeOC_6H_4COCH_3$	Reflux	5	100	81.1
			15	100	69.2

[a] Preparation of the catalyst: $Ru(II)Cl_2(PPh_3)_3$ (1 mol %) and chiral ligand (1.3 mol %) were dissolved in 2-propanol (5 mL) and the mixture was refluxed under nitrogen atmosphere for 0.5 h before use.
[b] Determined by ^1H NMR.
[c] Determined by GC with Varian Chiralsil-L-Val column.
[d] Absolute configuration of product was assigned through comparison of the sign of specific rotations with the literature data.[12]

ring was changed to electron withdrawing group such as chloro, the value of enantiomeric excess was decreased to 61.1% (Table 3, entry 2). However, better enantioselectivity were obtained when strong electron donating substituted groups such as methyl and methoxyl were located in the *para*-position of the benzene ring (66.2 and 81.1% ee, respectively, Table 3, entries 3 and 4).

3. Conclusion

In summary, we have developed the novel 1,2-disubstituted ruthenocene-based phosphinooxazoline ligands **3** and **4** and applied them in asymmetric H-transfer hydrogenation of ketones. High catalytic activity and excellent enantioselectivity have been observed. Based on the experimental results, the enantioselectivity of this reaction is mainly determined by the central chirality in the oxazoline ring. It is essential to match planar and central chiralities to obtain excellent asymmetric induction. Studies on the steric and/or electric effects of the aromatic ring substituents show that they have nonneglectable effects on the enantioselectivity in this reaction.

4. Experimental

4.1. General comments

All reactions were performed under a nitrogen atmosphere and the workup was carried out in air. The reaction solvents were distilled prior to use (tetrahydrofuran was distilled from sodium-benzophenone ketyl, methanol and ethanol were dried with magnesium, and dichloromethane was distilled from CaH_2). The commercially available reagents were used without further purification. Melting points were measured on a XT-5 microscopic melting point apparatus and are uncorrected. ^{1}H NMR (400 MHz) spectra, ^{13}C NMR (100 MHz) spectra, and ^{31}P NMR (162 MHz) spectra were recorded on a Varian MERCURY plus-400 spectrometer. The ee values were determined by GC using Varian Chiralsil-L-Val column.

4.2. Procedure for the preparation of ligands *3* and *4*

4.2.1. 1-Carboxylic ruthenocene (*5*)

Ruthenocene (11.6 g, 50 mmol), 2-chlorobenzoyl chloride (63 mL, 0.5 mol), and dichloromethane (100 mL) were added to a 250 mL flask. The mixture was then cooled to 0–2 °C, followed by the addition of anhydrous aluminum trichloride (8.7 g, 65 mmol) in three portions. The reaction mixture was stirred at room temperature overnight. Water (20 mL) was then added carefully and the mixture was stirred for another 2 h. Toluene (200 mL) was added to the flask and the mixture was washed with 10% NaOH solution, water, and brine. The organic phase was dried with anhydrous Na_2SO_4 and then the solvent was evaporated in vacuum. The residue was purified on silica gel column chromatography with petrol ether–ethyl acetate (20:1) to afford pure product 2-chlorobenzoyl ruthenocene (13.5 g, 73%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.64 (s, 5H), 4.83 (t, J=2 Hz, 2H), 5.01 (t, J=2 Hz, 2H), 7.28–7.55 (m, 3H), 7.99–8.05 (m, 1H).

To a 500 mL flask was added 2-chlorobenzoyl ruthenocene (8.2 g, 22 mmol) and *t*-BuOK (9.9 g, 88 mmol) under N_2 atmosphere. Dimethoxy ethane (DME, 220 mL) and water (0.44 mL, 23 mmol) were added and the reaction mixture was refluxed for 18 h. The mixture was diluted by water (220 mL) and extracted with dichloromethane (200 mL) and ethyl ether (200 mL). The aqueous phase was adjusted to pH=2 with hydrochloric acid followed by filtration to afford gray solid **5** (4.65 g, 90%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.63 (s, 5H), 4.76 (t, J=2 Hz, 2H), 5.17 (t, J=2 Hz, 2H).

4.2.2. 1-[(S)-4-Isopropyloxazolin-2-yl]-ruthenocene (*8a*)

1-Carboxylic ruthenocene (2.53 g, 10 mmol) was suspended in dichloromethane (60 mL) followed by the addition of oxalyl chloride (4.0 mL, 40 mmol) and pyridine (0.1 mL). This mixture was refluxed for 2 h and then evaporated to dryness. The residue was washed with ethyl ether and the organic phase was evaporated to offer 1-chlorocarbonyl ruthenocene as a yellow-green solid. The product was directly used in the next step without any purification.

To a solution of (*S*)-(+)-valinol (1.13 g, 11 mmol) and diisopropylethylamine (3.9 mL, 22 mmol) in 20 mL of dichloromethane was added dropwise the above 1-chlorocarbonyl ruthenocence in 40 mL of dichloromethane under nitrogen atmosphere in ice-water bath. The reaction mixture was stirred at room temperature overnight. To this solution was added dropwise diisopropylethylamine (5.3 mL, 30 mmol) and methane sulfonyl chloride (1.2 mL, 15 mmol) for a period of 30 min at 0 °C, and then the solution was stirred at room temperature for 2 h. The resulting solution was washed with chilled water (5 °C) and then brine. The organic layer was dried over Na_2SO_4 and then the solvent was evaporated in vacuum. The residue was purified on silica gel column chromatography with ethyl acetate to afford pure product **8a** (2.7 g, 79%) as a light yellow solid. $[\alpha]_D^{27}$ −79.26 (*c* 1.46, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (d, J=6.4 Hz, 3H), 0.95 (d, J=6.4 Hz, 3H), 1.79–1.91 (m, 1H), 3.92–4.02 (m, 2H), 4.20 (dd, J=8.4, 9.2 Hz, 1H), 4.58 (s, 5H), 4.67 (br s, 2H), 5.09 (br s, 1H), 5.14 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.17, 18.96, 32.39, 69.34, 71.04, 71.74 (5C), 72.08, 72.16, 74.79, 164.88; MS (MALDI): *m/z* 344 [M+1$^+$] (100); HRMS calcd for $C_{16}H_{20}NORu$ 344.0587, found 344.0583.

4.2.3. 1-[(S)-4-tert-Butyloxazolin-2-yl]-ruthenocene (*8b*)

Following a procedure identical to what was described for the preparation of **8a**, compound **8b** (68%) was afforded as a light yellow solid. $[\alpha]_D^{27}$ −106.94 (*c* 1.02, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.90 (s, 9H), 3.83 (dd, J=6.8, 10 Hz, 1H), 4.08–4.18 (m, 2H), 4.57 (s, 5H), 4.65 (br s, 2H), 5.05 (br s, 1H), 5.17 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.03, 34.10, 68.48, 71.04, 71.08, 71.68, 72.03, 72.08, 74.86, 75.93, 164.81; MS (MALDI): *m/z* 358 [M+1$^+$] (100); HRMS calcd for $C_{17}H_{22}NORu$ 358.0736, found 358.0739.

*4.2.4. 2-[(S)-4-Isopropyloxazolin-2-yl]-(S)-1-diphenylphosphino ruthenocene (**3a**)*

To a solution of **8a** (138 mg, 0.4 mmol) in ethyl ether (7 mL) was added dropwise TMEDA (42 μL, 0.52 mmol) and a solution of *sec*-BuLi (0.6 mL, 0.98 M in cyclohexane, 0.52 mmol) at −78 °C under nitrogen atmosphere. The reaction solution was stirred at the temperature for 3 h and then at 0 °C for 40 min. Ph_2PCl (0.10 mL, 0.52 mmol) was added dropwise at 0 °C to the solution containing dilithiated species generated from **8a**, and then the solution was stirred at room temperature for 3 h. The reaction mixture was diluted with ethyl ether (20 mL) and washed with saturated $NaHCO_3$ solution, water, and brine. The organic layer was dried over Na_2SO_4 and then the solvent was evaporated in vacuum. The residue was purified on silica gel column chromatography with ethyl acetate–petrol ether (10:1) to afford pure product **3a** (0.162 g, 77%) as a light yellow solid. Mp 136–138 °C; $[\alpha]_D^{27}$ −97.51 (*c* 0.46, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 Hz): δ 0.67 (d, *J*=6.8 Hz, 3H), 0.79 (d, *J*=6.8 Hz, 3H), 1.64–1.68 (m, 1H), 3.67 (t, *J*=7.6 Hz, 1H), 3.79–3.84 (m, 1H), 3.94 (br s, 1H), 4.16–4.20 (dd, *J*=8, 10 Hz, 1H), 4.59 (s, 5H), 4.67 (br s, 1H), 5.31 (br s, 1H), 7.27–7.40 (m, 10H); ^{13}C NMR ($CDCl_3$, 100 Hz): δ 17.7, 18.7, 32.2, 69.7, 72.1, 72.8, 74.3, 73.1 (5C), 76.5, 76.6, 79.5 (d, *J*=18 Hz), 81.7 (d, *J*=17.6 Hz), 128.0, 128.1, 128.2, 128.3, 128.4, 128.9, 132.6, 132.8, 134.6, 134.8, 138.3 (d, *J*=13.6 Hz), 139.8 (d, *J*=14.5 Hz); ^{31}P NMR ($CDCl_3$, 162 Hz, 85% H_3PO_4): δ −14.94; MS (MALDI): *m/z* 528 [M+1$^+$] (100); HRMS calcd for $C_{28}H_{29}NOPRu$ 528.1025, found 528.1041.

*4.2.5. 1-[(S)-4-tert-Butyloxazolin-2-yl]-(S)-1-diphenylphosphino ruthenocene (**3b**)*

Following a procedure identical to that described for the preparation of **3a**, compound **3b** (76%) was afforded as a light yellow solid. Mp 176–178 °C; $[\alpha]_D^{27}$ −142.98 (*c* 0.13, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 Hz): δ 0.77 (s, 9H), 3.69 (dd, *J*=7.2, 10 Hz, 1H), 3.85 (dd, *J*=7.6, 8.4 Hz, 1H), 3.95 (br s, 1H), 4.10 (dd, *J*=8.4, 10 Hz, 1H), 4.59 (s, 5H), 4.66 (br s, 1H), 5.28 (br s, 1H), 7.27–7.38 (m, 10H); ^{13}C NMR ($CDCl_3$, 100 Hz): δ 25.86, 34.00, 68.55, 72.75, 73.15 (5C), 74.24, 74.25, 76.11, 76.61, 76.65, 128.06, 128.13, 128.22, 128.28, 128.80, 138.51, 138.63, 139.96, 140.08, 163.71, 163.72; ^{31}P NMR ($CDCl_3$, 162 Hz, 85% H_3PO_4): δ −15.42. MS (MALDI): *m/z* 542 [M+1$^+$] (100); HRMS calcd for $C_{29}H_{31}NOPRu$ 542.1181, found 542.1165.

*4.2.6. 1-[(S)-4-Isopropyloxazolin-2-yl]-2-(S)-(trimethylsilyl)-ruthenocene (**9**)*

To a solution of **8a** (276 mg, 0.8 mmol) in ethyl ether (10 mL) was added dropwise TMEDA (0.17 mL, 1.04 mmol) and a solution of *sec*-BuLi (1.06 mL, 0.98 M in cyclohexane, 1.04 mmol) at −78 °C under nitrogen atmosphere. The reaction solution was stirred at the temperature for 3 h and then at 0 °C for 20 min. Chlorotrimethylsilane (0.13 mL, 1.04 mmol) was added dropwise at 0 °C to the solution containing dilithiated species generated from **8a**, and then the solution was stirred at room temperature overnight. The reaction mixture was diluted with ethyl ether (20 mL) and washed with saturated $NaHCO_3$ solution, water, and brine. The organic layer was dried over Na_2SO_4 and then the solvent was evaporated in vacuum. The residue was purified on silica gel column chromatography with ethyl acetate–petrol ether (15:1) to afford pure product **9** (0.21 g, 68%) as a light yellow oil. $[\alpha]_D^{27}$ +7.07 (*c* 0.36, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 Hz): δ 0.22 (s, 9H), 0.86 (d, *J*=6.4 Hz, 3H), 0.96 (d, *J*=6.4 Hz, 3H), 1.72–1.81 (m, 1H), 3.85–3.95 (m, 2H), 4.17 (dd, *J*=7.6, 8.8 Hz, 1H), 4.54–4.56 (m, 1H), 4.54 (s, 5H), 4.70 (t, *J*=2.4 Hz, 1H), 5.17–5.18 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 Hz): δ 0.8, 18.1, 19.2, 32.7, 69.4, 71.8 (5C), 72.8, 73.2, 74.7, 77.1, 78.6, 79.4, 165.1; MS (MALDI): *m/z* 416 [M+1$^+$] (100); HRMS calcd for $C_{31}H_{37}NOSiPRu$ 600.1415, found 600.1420.

*4.2.7. 1-[(S)-4-Isopropyloxazolin-2-yl]-2-(R)-diphenylphosphino)-5(S)-(trimethylsilyl)ruthenocene (**10**)*

To a solution of **9** (87 mg, 0.23 mmol) in Et_2O (10 mL) was added *sec*-BuLi (0.3 mL, 0.98 M in cyclohexane, 0.3 mmol) at −78 °C under nitrogen atmosphere. The reaction solution was stirred at the temperature for 2 h and then at 0 °C for 30 min. Ph_2PCl (54 μL, 0.3 mmol) was added dropwise at 0 °C to the solution and then the solution was stirred at room temperature overnight. The reaction mixture was diluted with ethyl ether (10 mL) and washed with saturated $NaHCO_3$ solution, water, and brine. The organic layer was dried over Na_2SO_4 and then the solvent was evaporated in vacuum. The residue was purified on silica gel column chromatography with ethyl acetate–petrol ether (15:1) to afford pure product **10** (60 mg, 44%) as a light yellow solid. $[\alpha]_D^{27}$ +51.77 (*c* 0.20, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 Hz): δ 0.22 (s, 9H), 0.58 (d, *J*=6.4 Hz, 3H), 0.65 (d, *J*=6.4 Hz, 3H), 1.42–1.50 (m, 1H), 3.79–3.89 (m, 2H), 3.96 (dd, *J*=8.4, 10 Hz, 1H), 4.01 (d, *J*=2.4 Hz), 4.54 (d, *J*=2.4 Hz), 4.56 (s, 5H), 7.23–7.47 (m, 10H); ^{13}C NMR ($CDCl_3$, 100 Hz): δ 1.1, 18.2, 18.4, 32.8, 69.5, 72.0, 72.6, 73.2 (5C), 74.0, 78.3, 78.4, 79.0, 81.0, 127.9, 128.0, 128.14, 128.15, 128.2, 128.3, 128.8, 132.5, 132.6, 135.0, 135.2, 139.0, 139.2, 140.0, 140.1, 164.3, 164.4; ^{31}P NMR ($CDCl_3$, 162 Hz, 85% H_3PO_4): δ −15.26; MS (MALDI): *m/z* 528 [M+1$^+$] (100); HRMS calcd for $C_{28}H_{29}NOPRu$ 528.1025, found 528.1036.

*4.2.8. 1-[(S)-4-Isopropyloxazolin-2-yl]-2-(R)-diphenylphosphino)-5(S)-(trimethylsilyl)ruthenocene (**10**), preparation in 'one-pot' from **8***

To a solution of **8a** (276 mg, 0.8 mmol) in ethyl ether (10 mL) was added dropwise TMEDA (0.17 mL, 1.04 mmol) and a solution of *sec*-BuLi (1.06 mL, 0.98 M in cyclohexane, 1.04 mmol) at −78 °C under nitrogen atmosphere. The reaction solution was stirred at the temperature for 3 h and then at 0 °C for 20 min. Chlorotrimethylsilane (0.13 mL, 1.04 mmol) was added dropwise at 0 °C to the solution containing dilithiated species generated from **8a**, and then the solution was stirred at room temperature for 3 h.

To the above reaction mixture was added THF (10 mL) and then cooled to −78 °C again. *n*-BuLi (0.4 mL, 2.89 M in cyclohexane, 1.04 mmol) was added carefully and the mixture was stirred at the temperature for 2 h and then at 0 °C for 2 h. Ph_2PCl (0.19 mL, 1.04 mmol) was added dropwise at 0 °C to the solution

and then the solution was stirred at room temperature overnight. The reaction mixture was diluted with ethyl ether (20 mL) and washed with saturated $NaHCO_3$ solution, water, and brine. The organic layer was dried over Na_2SO_4 and then the solvent was evaporated in vacuum. The residue was purified on silica gel column chromatography with ethyl acetate–petrol ether (15:1) to afford pure product **10** (0.22 g, 52%) as a light yellow solid.

*4.2.9. 2-[(S)-4-Isopropyloxazolin-2-yl]-(R)-1-diphenylphosphino ruthenocene (**4**)*

To the silyl compound **10** (0.25 g, 0.42 mmol) in THF (5 mL) was added tetrabutylammonium fluoride (1 M, 5 mL). Then the resulting reaction mixture was heated to reflux for 20 h. The mixture was extracted with ethyl ether (10 mL×2) and washed with water and brine. The organic layer was dried over Na_2SO_4 and then the solvent was evaporated in vacuum. The residue was purified on silica gel column chromatography with ethyl acetate–petrol ether (15:1) to afford pure product **4** (0.22 g, 74%) as a light yellow solid, mp 169–171 °C. $[\alpha]_D^{27}$ +130.47 (*c* 0.46, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 Hz): δ 0.62 (d, J=6.8 Hz, 3H), 0.64 (d, J=6.8 Hz, 3H), 1.51–1.57 (m, 1H), 3.86–4.00 (m, 3H), 4.60 (s, 5H), 4.67 (br s, 1H), 5.30 (br s, 1H), 7.26–7.42 (m, 10H); ^{13}C NMR ($CDCl_3$, 100 Hz): δ 18.0, 18.1, 32.6, 69.7, 72.1, 72.5, 73.1 (5C), 74.4, 76.8, 76.9, 79.2 (d, J=18.3 Hz), 81.5 (d, J=16 Hz), 128.0, 128.1, 128.2, 128.3, 128.4, 128.8, 132.6, 132.9, 134.8, 135.0, 138.4 (d, J=12 Hz), 139.6 (d, J=11.5 Hz); ^{31}P NMR ($CDCl_3$, 162 Hz, 85% H_3PO_4): δ −15.74: MS (MALDI): *m/z* 528 [M+1$^+$] (100); HRMS calcd for $C_{28}H_{29}NOPRu$ 528.1025, found 528.1036.

4.3. General procedure for asymmetric transfer hydrogenation

Under an atmosphere of argon, 1 mol % of $[RuCl_2(PPh_3)_3]$ and 1.3 mol % of chiral ligand were dissolved by heating to reflux in degassed dry 2-propanol (5 mL) for 30 min. Then a solution of the ketone (4 mmol) in degassed dry 2-propanol (3 mL) was added and the mixture was refluxed for 15 min. The reaction was started by addition of a solution of *t*-BuOK in 2-propanol (0.2 M, 0.2 mL) and refluxed. The above reaction mixture was concentrated under reduced pressure. The residue was determined by ^{1}H NMR directly to give the percent conversion and purified on silica gel column chromatography with EtOAc to afford pure product for the determination of ee value by HPLC.

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References and notes

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