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Ru(II)-catalyzed asymmetric cyclopropanation using chiral diphenylphosphino(oxazolinyl)quinoline ligands

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Abstract

Several chiral 8-diphenylphosphino-2-oxazolinylquinolines were synthesized starting from 2-cyano-8-hydroxyquinoline. These *N,N,P*-chelates were successfully employed in the Ru(II)-catalyzed asymmetric cyclopropanation reactions of diazo-alkenes. The catalytic system exhibited good reactivity and high thermal stability and provided high yields in the intramolecular cyclopropanation, albeit somewhat decreased enantioselectivities compared to known catalytic systems. A dramatic dependency of the enantioselectivity on the substituents of the oxazoline ring was observed.

1. Introduction

The development of chiral ligands for transition metal catalyzed asymmetric reactions has been intensively pursued with the aim of obtaining efficient catalytic systems. As an ongoing project in this area, we have been involved in the synthesis of chiral oxazoline-containing chelates such as biferrocene-based bis(oxazolines) **1** for Cu(I)-catalyzed asymmetric cyclopropanation reactions between diazoacetates and alkenes.[1] Although our catalytic system provided high enantioselectivities for certain substrates, it exhibited a decreased reactivity compared to the Cu(I) catalysts of malonate-based bis(oxazolines) **2**.[2] When the catalytic reaction is slow, dimerization of the diazoacetates is problematic and thus low yields result. This is particularly true in the case of less reactive substrates. Recently, Nishiyama and co-workers have reported an efficient catalytic system, a Ru(II)–pybox complex **3**.[3] The ruthenium catalyst exhibited improved *trans*/*cis*-selectivity in addition to excellent enantioselectivity in the cyclopropanation. Moreover, the corresponding Ru–carbene complex, a presumed reaction intermediate, exhibited significant chemical stability as characterized by NMR spectroscopy.[4]

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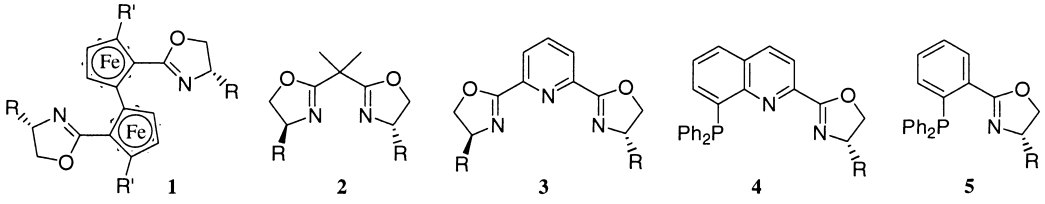
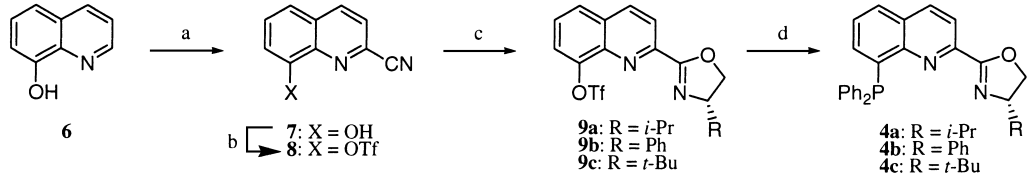
Considering the apparent stability of the ruthenium complex, we were interested in a hybrid ligand system such as *N*,*N*,*P*-chelates **4**. These heterochelates are reminiscent of the *N*,*P*-chelates **5**, which have been proven to be excellent ligands in several transition metal catalyzed asymmetric reactions.[5] However, chelates **4** would exhibit totally different behavior in the catalytic reactions, owing to the presence of the central nitrogen donor. Here we wish to report an efficient synthesis of these *N*,*N*,*P*-chelates, starting from readily available 8-hydroxyquinoline, and their application to the Ru(II)-catalyzed asymmetric cyclopropanation.



2. Synthesis of 8-diphenylphosphino-2-oxazolinylquinolines DPOQ 4

2-Cyano-8-hydroxyquinoline **7**, prepared from 8-hydroxyquinoline **6** by the literature procedure,[6] is an adequate starting material for the synthesis of the target molecules. The oxazoline moiety could be introduced by $ZnCl_2$-catalyzed condensation between the nitrile group and the corresponding aminoalcohols,[7] and the diphenylphosphino group could be introduced by the Ni(0)-catalyzed coupling reaction between the triflate of the hydroxyl group and diphenylphosphine.[8a] This synthetic plan was realized and the results are summarized in Scheme 1. We found that the $ZnCl_2$-catalyzed oxazoline formation gave better yields when the 8-hydroxyl group was converted to the corresponding triflate; otherwise, in the presence of the free hydroxyl group, lower yields were obtained.[8b] In the presence of 10 mol% of $ZnCl_2$, the condensation of L-valinol and nitrile **8** in refluxing chlorobenzene provided the corresponding oxazoline **9a** in 77% yield. Oxazoline **9a** could be purified further by recrystallization from ethyl acetate–hexanes if necessary. Similarly, oxazolines **9b** and **9c** were synthesized in good yields. Introduction of the phosphino group was successfully done by the Ni(0)-catalyzed coupling reaction between oxazoline **9** and diphenylphosphine.[8a] Thus, treatment of the oxazoline **9a** with diphenylphosphine in the presence of 10 mol% of $NiCl_2$(dppe) and two molar equivalents of DABCO in DMF at 80°C for 8 h gave the corresponding DPOQ **4a** in 43% isolated yield. If the reaction was carried out at 100°C as in the literature, the coupling yield decreased. It could be purified further by recrystallization. Other DPOQs **4b** and **4c** were synthesized under the same reaction conditions in similar yields.

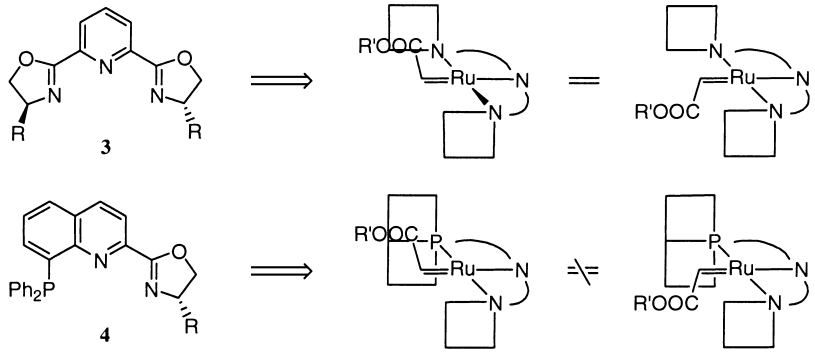


[a] Reagents and conditions: (a) reference 6; (b)Tf_2O, pyridine, CH_2Cl_2, 0 °C; (c) amino alcohol, 10 mol% $ZnCl_2$, PhCl, reflux; (d) Ph_2PH, 10 mol% $NiCl_2$(dppe), DABCO, DMF, 80 °C.

Scheme 1.

3. Cyclopropanation catalyzed by Ru(II)–DPOQ complexes

Nishiyama explained the *trans*/*cis*- and enantioselectivities observed in the cyclopropanation reaction by a face-selective approach of an olefin to the Ru–carbene complex.[3] The pybox ligand has C_2 symmetry and thus only a single isomeric metal–carbene complex would be generated. In contrast, the Ru–DPOQ system can have two diastereomeric metal–carbene complexes. Therefore, both the diastereomeric complexes should be taken into consideration in the explanation of the selectivities (Scheme 2). The diphenyl groups at the phosphorus atom would shield one side of the π-face of the metal–carbene complex, providing one open quadrant for the approach of a diazo group. With those ligands optimized for this scenario, we may expect high selectivity for the cyclopropanation. Recently, Nishiyama and co-workers reported unsymmetrical ligands that shield only one quadrant. The catalytic system provided up to 94% ee for the intermolecular cyclopropanation of olefins.[9]

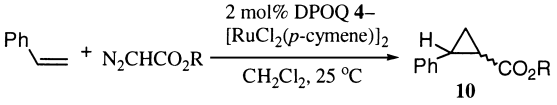


Scheme 2.

We studied the Ru(II)-catalyzed asymmetric cyclopropanation of diazo-enes using DPOQ as the ligands. Both inter- and intramolecular cyclopropanations were studied, following the experimental procedure of Nishiyama and co-workers.[3] The reaction between ethyl diazoacetate and styrene was carried out in the presence of 2 mol% of Ru(II)–DPOQ complex, maintaining a low concentration of styrene during the reaction (by syringe-pump addition).† Although yields were good, disappointingly low enantioselectivities were observed (Table 1). Also, somewhat decreased *trans*/*cis*-selectivity was observed compared to that observed with the Nishiyama catalyst. At this point, we focused our attention on the intramolecular cyclopropanation of diazo-enes. Compared to the intermolecular cyclopropanation reaction, relatively few catalytic systems for the corresponding intramolecular reaction have been reported.[10] Also, the enantioselectivities of the catalytic cyclopropanation reactions are known to be greatly dependent on the substrates used. The intramolecular reaction was carried out using 5 mol% of the catalyst. Optimal reaction conditions were determined for the reaction of diazo-ene **11**.[3] It was found that the reaction proceeded well at 0°C, indicating that our catalytic system has much improved reactivity compared to the bis(oxazoline) **1**–Cu(I) complexes. The catalytic reaction proceeded at normal concentrations (0.2 M solution), which removed the need for the syringe-pump addition of diazo compounds. Under these conditions, side products were not observed. The enantioselectivity was greatly dependent on the solvent used: 75% ee was observed in chloroform while 25% ee was obtained in 1,2-dichloroethane. The results are summarized in Table 2.

† The *trans/cis*-selectivity was determined by NMR analysis of the products and the enantioselectivity of each isomer was determined by GC analysis after converting the ester products into the corresponding diastereomeric amides using (*S*)-α-phenethylamine.

Table 1
Intermolecular cyclopropanations



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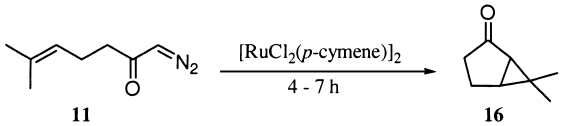
Ligand	R	Yield, %	*trans:cis*	%ee	
				trans	*cis*
4a	Et	59	62 : 38	4	7
4c	*l*-menthyl	81	89 : 11	28	65

Table 2
Intramolecular cyclopropanations



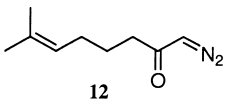
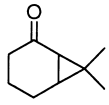
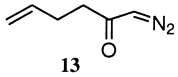
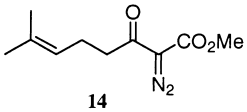
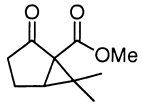
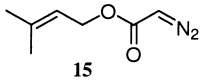
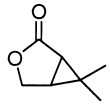
11 16

Ligand	Temp	Solvent	Yield (%)	% Ee
4a	25 °C	CH_2Cl_2	76	23 (1*S*, 5*R*)
4a	0 °C	$CHCl_3$	87	9 (1*S*, 5*R*)
4b	0 °C	$CHCl_3$	65	0
4c	0 °C	CH_2Cl_2	87	68 (1*R*, 5*S*)
4c	0 °C	$ClCH_2CH_2Cl$	84	25 (1*R*, 5*S*)
4c	0 °C	$CHCl_3$	91	75 (1*R*, 5*S*)
4c	-20 °C	$CHCl_3$	no rxn	

A particularly interesting result is that, depending on the ligands used, a dramatic change in the sense and extent of the enantioselectivity was observed. Under the same reaction conditions, the ruthenium complex of **4c** gave the (1*R*,5*S*)-isomer in 75% ee while that of **4a** gave the (1*S*,5*R*)-isomer in 9% ee. The catalytic system of **4b** produced an almost racemic mixture. This is quite surprising, considering that these ligands are structurally similar. A simple molecular modeling study for the two diastereomeric metal–carbene complexes in Scheme 2 indicated that the sterically demanding ligand **4c** causes a significant difference in the minimized energy between the two, while **4b** does not.[‡] However, because we do not know whether the stability of the metal–carbene complexes leads to the enantioselectivity or not, a further study is necessary to provide a more convincing explanation for the observation. Several other substrates **12**–**15**[11] were studied, but poor to moderate selectivities were observed, showing once again a large fluctuation in the enantioselectivity depending on the substrates used (Table 3). It is notable that the cyclopropanation of less reactive substrate **14** gave the corresponding keto-ester **19** in 60% ee

[‡] MacSpartan plus® from Wavefunction, Inc. (http://www.wavefun.com) was used as the modeling program.

Table 3
Intramolecular cyclopropanations[a]

Substrates	Products		Conditions	Yield(%)	%ee[b]
 **12**		**17**	25 °C / 8 h	71	18
 **13**		**18**	0 °C / 7 h	84	5 (1*R*,5*S*)
 **14**		**19**	reflux / 24 h	68	60
 **15**		**20**	25 °C / 4 h	82	36 (1*R*,5*S*)

[a]catalyst 5 mol% $[RuCl_2(p\text{-cymene})]_2$-DPOQ **4c**, solvent: $CHCl_3$. [b]Those of major enantiomers otherwise unspecified.

and 68% yield.[§] The reaction required the refluxing temperature of chloroform. This result indicates that the catalytic system is thermally robust. A further modification including fine-tuning of the substituents of the donor atoms in DPOQ would provide more efficient ligand systems.

In summary, we have synthesized several chiral phosphino(oxazolinyl)quinolines, starting from 8-hydroxyquinoline. The new *N*,*N*,*P*-chelates are found to be potentially useful ligands in the ruthenium-catalyzed asymmetric intramolecular cyclopropanation. A dramatic dependency of the enantioselectivity on the substituents of the oxazoline ring was observed. A further structural modification to enhance the enantioselectivity is under study.

4. Experimental

4.1. General

All reactions were carried out under an argon atmosphere. Solvents were dried and purified prior to use. All the reagents were commercial products otherwise unspecified and used without further purification. Purification by chromatography means flash column chromatography performed on silica gel (230–400 mesh). Melting points determined are uncorrected.

§ For this substrate, the Cu(I)–bis(oxazoline) **1** system did not give the reaction product.

4.2. 2-Cyano-8-(trifluoromethanesulfonyloxy)quinoline **8**

To a solution of 2-cyano-8-hydroxyquinoline (2.0 g, 1.8 mmol) and pyridine (1.1 mL, 13 mmol) in dry dichloromethane (7 mL) at 0°C was added dropwise triflic anhydride (2.5 mL, 15 mmol), and the resulting solution was allowed to warm to room temperature and stirred for 1 h. The mixture was treated with a saturated aqueous NH_4Cl solution and extracted with dichloromethane. The organic phase was washed with brine, dried, and concentrated. The resulting solid was purified by chromatography (eluent: 50% dichloromethane in hexanes) to give the product (3.6 g, 11.3 mmol) in 95% yield. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.45 (d, 1H, *J*=8.5 Hz), 7.94–7.99 (m, 1H), 7.83 (d, 1H, *J*=8.5 Hz), 7.78–7.75 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 145.9, 141.3, 138.2, 135.1, 130.3, 129.5, 128.6, 125.4, 123.7, 121.4, 117.2; ^{19}F NMR ($CDCl_3$, 300 MHz) δ 3.84 (reference: CF_3CO_2H in D_2O); MS (EI) *m*/*z* 302.00 (M^+, 20%).

4.3. (S)-2-(4-Isopropyl-2-oxazolin-2-yl)-8-(trifluoromethanesulfonyloxy)quinoline **9a**

To a solution of nitrile **8** (2.50 g, 8.3 mmol) and zinc chloride (113 mg, 0.83 mmol) in chlorobenzene (15 mL) at 25°C, was added dropwise a solution of L-valinol (1.28 g, 12.4 mmol) in chlorobenzene (5 mL). The reaction mixture was refluxed for 24 h. Most of the solvent was evaporated at reduced pressure, and the residue was dissolved in dichloromethane. The organic phase was washed with a saturated aqueous ammonium chloride solution, dried, and filtered. The filtered solution was concentrated and the residue was purified by chromatography (20% ethyl acetate in hexanes) to give the oxazoline in 77% yield (2.46 g, 6.3 mmol). Mp 89.5°C; $[\alpha]_D^{24}$ −75.3 (*c* 0.17, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.35 (d, 1H, *J*=8.6 Hz), 8.27 (d, 1H, *J*=8.6 Hz), 7.87 (dd, 1H, *J*=5.8, 1.9 Hz), 7.67–7.58 (m, 2H), 4.61 (dd, 1H, *J*=8.5, 1.0 Hz), 4.29 (t, 1H, *J*=8.5 Hz), 4.22–4.14 (m, 1H), 1.93–1.86 (m, 1H), 1.07 (d, 3H, *J*=6.7 Hz), 0.97 (d, 3H, *J*=6.7 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 163.2, 148.7, 146.6, 140.7, 136.8, 130.4, 128.3, 127.7, 123.1, 122.2, 121.4, 73.5, 71.7, 33.4, 19.4, 18.9; ^{19}F NMR ($CDCl_3$, 300 MHz) δ 2.74 (reference: CF_3CO_2H in D_2O). Anal. calcd for $C_{16}H_{15}F_3O_4N_2S$: C, 49.48; H, 3.89; N, 7.21. Found: C, 49.20; H, 3.93; N, 7.14.

4.4. (S)-2-(4-Phenyl-2-oxazolin-2-yl)-8-(trifluoromethanesulfonyloxy)quinoline **9b**

Using a similar procedure, oxazoline **9b** was prepared in 82% yield (2.3 g, 5.4 mmol), starting from nitrile **8** (2.0 g, 6.62 mmol) and (*S*)-phenylglycinol (1.0 g, 7.28 mmol). $[\alpha]_D^{24}$ −109.8 (*c* 1.05, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.45–8.40 (m, 1H), 8.29 (d, 1H, *J*=8.7 Hz), 7.88 (t, 1H, *J*=6.4 Hz), 7.67–7.63 (m, 2H), 7.40–7.34 (m, 5H), 5.56–5.48 (m, 1H), 5.00 (dd, 1H, *J*=8.7, 1.7 Hz), 4.47 (t, 1H, *J*=8.7 Hz); ^{19}F NMR ($CDCl_3$, 300 MHz) δ 3.30 (reference: CF_3CO_2H in D_2O); MS (EI) *m*/*z* 422.1.

4.5. (S)-2-(4-tert-Butyl-2-oxazolin-2-yl)-8-(trifluoromethanesulfonyloxy)quinoline **9c**

Using a similar procedure, oxazoline **9c** was prepared in 83% yield (2.2 g, 5.5 mmol), starting from nitrile **8** (2.0 g, 6.62 mmol) and (*S*)-*tert*-leucinol (0.985 g, 7.28 mmol). Mp 110–111°C; $[\alpha]_D^{24}$ −28.6 (*c* 0.14, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.34 (d, 1H, *J*=8.6 Hz), 8.24 (d, 1H, *J*=8.6 Hz), 7.84 (dd, 1H, *J*=7.9, 1.6 Hz), 7.63–7.58 (m, 2H), 4.53 (dd, 1H, *J*=10.3, 8.8 Hz), 4.36 (t, 1H, *J*=8.7 Hz), 4.15 (dd, 1H, *J*=10.3, 8.7 Hz), 0.98 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 163.1, 148.7, 146.5, 140.6, 136.7, 130.4, 128.3, 127.6, 123.1, 122.2, 121.4, 76.9, 70.1, 34.5, 2.64; ^{19}F NMR ($CDCl_3$, 300 MHz) δ 3.25 (reference: CF_3CO_2H in D_2O). Anal. calcd for $C_{17}H_{17}F_3O_4N_2S$: C, 50.74; H, 4.26; N, 6.96. Found: C, 50.69; H, 4.16; N, 6.74.

4.6. (S)-8-Diphenylphosphino-2-(4-isopropyl-2-oxazolin-2-yl)quinoline **4a**

A mixture of $NiCl_2$(dppe) (410 mg, 0.77 mmol) and diphenylphosphine (0.40 mL, 2.3 mmol) in DMF was heated at 100°C for 30 min, and then it was cooled to 80°C. To this mixture was added a solution of oxazoline **9a** (3.0 g, 7.72 mmol) and 1,4-diazabicyclo[2.2.2]octane (1.73 g, 15.4 mmol) in DMF (10 mL) through a cannula. Additional diphenylphosphine (1.2 mL, 6.7 mmol) was added, and the resulting mixture was stirred for 8 h at 80°C. After cooling the reaction mixture to room temperature, most of the DMF was removed by vacuum distillation. The residue was diluted with dichloromethane and washed successively with 5% aqueous $Na_2S_2O_3$, 10% aqueous citric acid solution, and brine. The organic phase was dried and concentrated. The residue was purified by chromatography (50% ethyl ether in hexanes) to give the product in 43% yield (1.49 g, 3.51 mmol). Mp 161.1°C; $[\alpha]_D^{24}$ −94.4 (*c* 0.23, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.16 (s, 2H), 7.79 (d, 1H, *J*=8.1 Hz), 7.74 (t, 1H, *J*=7.4 Hz), 7.39–7.29 (m, 10H), 7.28–7.22 (m, 1H), 4.45 (dd, 1H, *J*=8.5, 1.2 Hz), 4.15 (t, 1H, *J*=8.5 Hz), 4.10–4.06 (m, 1H), 1.86–1.80 (m, 1H), 1.02 (d, 3H, *J*=6.7 Hz), 0.90 (d, 3H, *J*=6.7 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 163.8, 146.5, 141.0, 140.8, 137.84, 137.81, 137.69, 137.67, 136.89, 136.87, 134.9, 134.8, 134.7, 134.6, 134.5, 128.9, 128.7, 128.6, 128.1, 121.6, 73.3, 71.2, 33.4, 19.5, 18.8; ^{31}P NMR ($CDCl_3$, 121 MHz) δ −12.59 (reference: H_3PO_4 in D_2O). Anal. calcd for $C_{27}H_{25}ON_2P$: C, 76.40; H, 5.94; N, 6.60. Found: C, 76.30; H, 5.85; N, 6.54.

4.7. (S)-8-Diphenylphosphino-2-(4-phenyl-2-oxazolin-2-yl)quinoline **4b**

Using a similar procedure, ligand **4b** was prepared in 46% yield (830 mg, 1.85 mmol), starting from oxazoline **9b** (1.7 g, 4.02 mmol). Mp 84°C; $[\alpha]_D^{24}$ −95.4 (*c* 2.49, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.54 (d, 1H, *J*=8.3 Hz), 8.33–8.23 (m, 2H), 7.86 (d, 1H, *J*=2.1 Hz), 7.52–7.13 (m, 16H), 5.43–5.36 (m, 1H), 3.83–3.68 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 164.2, 148.3, 147.6, 139.7, 139.0, 138.5, 135.2, 134.8, 134.7, 134.6, 134.4, 129.6, 129.4, 129.2, 129.12, 129.06, 129.01, 128.8, 128.7, 128.4, 127.2, 119.5, 54.4, 48.2; ^{31}P NMR ($CDCl_3$): δ −10.13 (reference: H_3PO_4 in D_2O). Anal. calcd for $C_{30}H_{23}ON_2P$: C, 78.59; H, 5.06; N, 6.11. Found: C, 78.21; H, 4.72; N, 6.18.

4.8. (S)-8-Diphenylphosphino-2-(4-tert-butyl-2-oxazolin-2-yl)quinoline **4c**

Using a similar procedure, ligand **4c** was prepared in 47% yield (710 mg, 1.64 mmol), starting from oxazoline **9c** (1.4 g, 3.48 mmol). Mp 74–76°C; $[\alpha]_D^{24}$ −93.5 (*c* 0.23, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.16 (s, 2H), 7.79 (d, 1H, *J*=8.0 Hz), 7.45 (t, 1H, *J*=7.6 Hz), 7.39–7.26 (m, 10H), 7.23–7.19 (m, 1H), 4.39 (dd, 1H, *J*=10.3, 1.5 Hz), 4.24 (t, 1H, *J*=8.5 Hz), 4.05 (dd, 1H, *J*=10.3, 1.5 Hz), 0.93 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 163.7, 146.5, 140.9, 140.8, 137.8, 137.7, 136.8, 134.9, 134.8, 134.7, 134.6, 134.5, 128.9, 128.8, 128.7, 128.6, 128.1, 121.7, 76.7, 69.7, 34.4, 26.4; ^{31}P NMR ($CDCl_3$, 121 MHz) δ −12.86 (reference: H_3PO_4 in D_2O). Anal. calcd for $C_{28}H_{27}ON_2P$: C, 76.69; H, 6.21; N, 6.39. Found: C, 76.39; H, 6.19; N, 6.50.

4.9. Representative procedure of the intermolecular cyclopropanation

A mixture of $[RuCl_2(p\text{-cymene})]_2$ (24 mg, 0.04 mmol) and DPOQ **4a** (34 mg, 0.08 mmol) in dry dichloromethane (15 mL) was stirred for 1.5 h at 25°C. To this ruthenium complex was added styrene (2.3 mL, 20 mmol) using a syringe, followed by a solution of ethyl diazoacetate (456 mg, 4.0 mmol) in dichloromethane (5 mL) for 8 h using a syringe pump. The resulting mixture was stirred for a further 8

h. The reaction mixture was concentrated and subjected to chromatography (10% ethyl ether in hexanes) to afford *trans*/*cis*-cyclopropanecarboxylates in 59% yield (450 mg). The *trans*/*cis*-ratio was determined by ^{1}H NMR analysis (diagnostic peaks: 4.19 ppm (*trans*-isomer); 3.89 ppm (*cis*-isomer)). Enantiopurity of each isomer was determined by GC analysis (column HP-1; oven temp 180°C; flow rate 1.0 mL/min): t_R: *trans*-isomer, 57.8 min (minor), 62.7 min (major); *cis*-isomer, 43.4 min (minor), 47.9 min (major) for the corresponding amides that were prepared in 93% yield by transamidation of the products with (*S*)-1-phenylethylamine in the presence of trimethylaluminum in refluxing 1,2-dichloroethane for 3 h. *l*-Menthyl 2-phenylcyclopropanecarboxylates: the *trans/cis*-ratio was similarly determined: *trans*-isomer, 4.7 ppm; *cis*-isomer, 4.4 ppm. The enantioselectivity was determined by GC analysis (column HP-1; oven temp 180°C, flow rate 1.0 mL/min): t_R: *cis*-(1*S*,2*R*)-isomer, 36.3 min; *cis*-(1*R*,2*S*)-isomer, 37.9 min; *trans*-(1*R*,2*R*)-isomer, 44.1 min, *trans*-(1*S*,2*S*)-isomer, 46.7 min.

4.10. Representative procedure for the intramolecular cyclopropanation

A solution of $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 0.025 mmol) and ligand **4c** (21.9 mg, 0.05 mmol) in dry chloroform was stirred for 1.5 h at 25°C. The ruthenium complex was cooled to 0°C and treated with a solution of 1-diazo-6-methyl-5-hepten-2-one (**11**) (152 mg, 1.0 mmol) in chloroform (2 mL) by a cannula. The reaction mixture was stirred for 8 h at 0°C. The mixture was concentrated and subjected to chromatography (10% ethyl ether in hexanes) to afford 6,6-dimethyl[3.1.0]bicyclohexan-2-one (**16**) in 90% yield (112 mg). The enatiopurity of the product was determined by GC analysis (chiral column G-TA, oven temp 110°C, flow rate 1 mL/min): t_R: (1*R*,5*S*)-isomer, 8.7 min; (1*S*,5*R*)-isomer, 10.7 min. Under similar reaction conditions other substrates were subjected to the cyclopropanation and isolated similarly. The enantiopurity of the cyclopropanation products were similarly determined by GC analysis using the same chiral column except for compound **19**. The conditions and retention times are given as follows: product **17** (oven temp 110°C, flow rate 1 mL/min): t_R: major isomer, 17.1 min; minor isomer, 16.3 min; product **18** (oven temp 110°C, flow rate 1 mL/min): t_R: major (1*R*,5*S*)-isomer, 4.4 min; minor (1*S*,5*R*)-isomer, 5.0 min; product **20** (oven temp 140°C, flow rate 1 mL/min): t_R: major (1*R*,5*S*)-isomer, 7.8 min; minor (1*S*,5*R*)-isomer, 11.5 min. The enantiopurity of compound **19** was determined by ^{1}H NMR analysis using a chiral shift reagent, Eu(hfc)$_3$: one of the diagnostic peaks was the methyl carboxylate group: δ 4.02 (minor), 4.00 (major).

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