

# Design and Synthesis of [2.2]Paracyclophane-based Oxazole-Pyrimidine Ligands and Application in Nickel-Catalyzed 1,2-Reduction of $\alpha,\beta$ -Unsaturated Ketones

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## Abstract

The [2.2]paracyclophane-derived oxazole-pyrimidine ligands with planar chirality (PYMCOX) were designed, synthesized and successfully applied in nickel-catalyzed asymmetric 1,2-reduction of  $\alpha,\beta$ -unsaturated ketones, affording the chiral allylic alcohols with up to 99% yield and 99% ee. Meanwhile, this reduction reaction could be conducted on gram-scale without loss of activity and enantioselectivity, and the chiral ligand could be conveniently recovered with high yield.

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Synthesis of Planar-Chiral [2.2]Paracyclophane-based Oxazole-Pyrimidine Ligands and Application in Nickel-Catalyzed 1,2-Reduction of  $\alpha,\beta$ -Unsaturated Ketones

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## Keywords

Oxazole-Pyrimidine Ligands | Planar Chirality | Nickel-Catalyzed Hydroboration |  $\alpha,\beta$ -Unsaturated Ketones

## Comprehensive Summary

The [2.2]paracyclophane-derived oxazole-pyrimidine ligands with planar chirality (PYMCOX) were designed, synthesized and

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## Background and Originality Content

The remarkable modification ability of  $\alpha$ -chiral allylic alcohols has attracted extensive attentions of researchers, and has demonstrated fascinating functionalities in the field of natural product synthesis as well as polymer and material science.<sup>[1]</sup> As one of the most direct and efficient strategies, asymmetric 1,2-reduction of readily available  $\alpha,\beta$ -unsaturated ketones was adopted by many researchers to synthesize  $\alpha$ -chiral allylic alcohols with various chiral catalyst systems, such as Ru,<sup>[2]</sup> Ir,<sup>[3]</sup> Cu,<sup>[4]</sup> etc.<sup>[5]</sup> However, there were relatively few reports involving fertile metallic nickel. In 2017, Zhu's group reported the first nickel-catalyzed chemoselec-

tive 1,2-reduction of  $\alpha,\beta$ -unsaturated ketones with oxazoline-pyrimidine ligand with central chirality, affording the allylic alcohols with excellent reactivity and enantioselectivity.<sup>[6]</sup> Until now, there were no other type ligands applied in this catalytic system. Therefore, it is extremely attractive to exploit a novel type of chiral ligands to achieve nickel-catalyzed enantioselective 1,2-reduction of  $\alpha,\beta$ -unsaturated ketones with high enantioselectivity.

In recent years, planar-chiral ligands have been widely applied as a class of unique and significant ligands in asymmetric catalysis. Planar-chiral ligands mainly include ferrocenes, metal carbonyl- complexes, paracyclophane units, etc.<sup>[7]</sup> Among them, the skeleton of [2.2]paracyclophane has the advantages of stable properties, rigid structure and large steric hindrance.<sup>[8]</sup> Considering the characteristics of this skeleton, our group has been committed to design and synthesis of various kinds of [2.2]paracyclophane-derived ligands with planar chirality, such as chiral oxazole-pyridine ligands and tridentate PNO ligands.<sup>[9]</sup> Inspired by the excellent performance of the [2.2]paracyclophane skeleton, a series of [2.2] paracyclophane-derived oxazole-pyrimidine ligands containing planar chirality (abbreviated as PYMCOX) were designed, synthesized, and successfully applied in nickel-catalyzed asymmetric 1,2-reduction of  $\alpha,\beta$ -unsaturated ketones with up to 99% yield and 99% ee. Furthermore, the reduction could be conducted at gram-scale without loss of activity, and the oxazole-pyrimidine ligand could be also recovered by flash column chromatography.

**Scheme 1** Metal-catalyzed asymmetric 1,2-reduction of  $\alpha,\beta$ -unsaturated ketones

## Results and Discussion

At the beginning, the paracyclophane-derived chiral *N,N*-ligands PYMCOX (*R<sub>p</sub>*)-**L1-10** were synthesized from the known [2,2]paracyclophane-derived chiral aminophenol (*R<sub>p</sub>*)-**1** through two approaches according to the known similar procedures (see Supporting Information). Method A: 2-cyanopyrimidines **2** underwent the nucleophilic addition with methanol to give the intermediates methyl ester of imino-pyrimidine acid derivatives.<sup>[10]</sup> Then, the intermediates underwent the condensation reaction with paracyclophane-derived aminophenol (*R<sub>p</sub>*)-**1** to afford the chiral PYMCOX ligands (*R<sub>p</sub>*)-**L1-9**. Method B: 2-cyanopyrimidine **2** underwent the hydrolysis to give the carboxylic acid **3**.<sup>[11]</sup> Then, two step condensation/cyclization reactions between chiral aminophenol (*R<sub>p</sub>*)-**1** and carboxylic acid **3** were conducted to provide the chiral PYMCOX ligand (*R<sub>p</sub>*)-**L10**.<sup>[12]</sup>

**Scheme 2** The synthesis of chiral PYMCOX ligands

With the chiral PYMCOX ligands in hand, we began our investigation with (*E*)-4-phenylbut-3-en-2-one (**4a**) as model substrate. Ni(COD)<sub>2</sub> (2.0 mol %) and PYMCOX **L1** (2.4 mol %) were employed in the presence of 1.2 equivalent of pinacolborane (HBpin), 1.5 equivalent of 1,4-diazobicyclo[2.2.2]octane (DABCO) and toluene at -25 °C for 1 hour. To our delight, the chemoselective reduction underwent smoothly to afford the desired allylic alcohol **5a** (entry 1, 92% yield, 97% ee), and the product of 1,4-reduction was not detected. The other parameters were summarized as follows: (a) Ni precursors such as nickel triflate and nickel acetate were completely inefficient (entries 2, 3). (b) The base is of utmost importance, in which DABCO was optimum. Others like DBU and DIPEA, the target product was obtained with lower yield or enantioselectivity (entries 4, 5). (c) While the reductant HBpin was a competent hydrogen source, both catcholborane (CB) and Ph<sub>2</sub>SiH<sub>2</sub> were ineffective (entries 6, 7). (d) The activity and enantioselectivity were also affected by the changes in solvents. It was found that the solvents like dichloromethane (DCM), ethyl acetate (EA) and diethyl ether were superior to polar aprotic and protic alternatives (entries 8-11). Encouraged by these results, compared with different chiral ligands ((*R<sub>p</sub>*)-**L1** to (*R<sub>p</sub>*)-**L10**), the oxazole-pyrimidine ligand **L2** bearing 4-methylpyrimidine motif provided the highest 99% of yield and 98% of enantioselectivity.

**Table 1** Optimization of reaction parameters.<sup>a</sup>

Entry	[Ni]	Base	[H] source	Solvent	<b>L</b>	Yield of <b>5a</b> (%) <sup>b</sup>	ee of <b>5a</b> (%) <sup>c</sup>
1	Ni(COD) <sub>2</sub>	DABCO	HBpin	Toluene	( <i>R<sub>p</sub></i> )- <b>L1</b>	92	97
2	Ni(OTf) <sub>2</sub>	DABCO	HBpin	Toluene	( <i>R<sub>p</sub></i> )- <b>L1</b>	<5	-

Entry	[Ni]	Base	[H] source	Solvent	<b>L</b>	Yield of <b>5a</b> (%) <sup>b</sup>	ee of <b>5a</b> (%) <sup>c</sup>
3	Ni(OAc) <sub>2</sub>	DABCO	HBpin	Toluene	( <i>R<sub>P</sub></i> )- <b>L1</b>	<5	-
4	Ni(COD) <sub>2</sub>	DBU	HBpin	Toluene	( <i>R<sub>P</sub></i> )- <b>L1</b>	40	15
5	Ni(COD) <sub>2</sub>	DIPEA	HBpin	Toluene	( <i>R<sub>P</sub></i> )- <b>L1</b>	93	92
6	Ni(COD) <sub>2</sub>	DABCO	CB	Toluene	( <i>R<sub>P</sub></i> )- <b>L1</b>	<5	-
7	Ni(COD) <sub>2</sub>	DABCO	Ph <sub>2</sub> SiH <sub>2</sub>	Toluene	( <i>R<sub>P</sub></i> )- <b>L1</b>	<5	-
8	Ni(COD) <sub>2</sub>	DABCO	HBpin	Et <sub>2</sub> O	( <i>R<sub>P</sub></i> )- <b>L1</b>	99	95
9	Ni(COD) <sub>2</sub>	DABCO	HBpin	DCM	( <i>R<sub>P</sub></i> )- <b>L1</b>	97	94
10	Ni(COD) <sub>2</sub>	DABCO	HBpin	EA	( <i>R<sub>P</sub></i> )- <b>L1</b>	92	97
11	Ni(COD) <sub>2</sub>	DABCO	HBpin	<sup>i</sup> PrOH	( <i>R<sub>P</sub></i> )- <b>L1</b>	<5	-
12	Ni(COD) <sub>2</sub>	DABCO	HBpin	Toluene	( <i>R<sub>P</sub></i> )- <b>L2</b>	99	98
13	Ni(COD) <sub>2</sub>	DABCO	HBpin	Toluene	( <i>R<sub>P</sub></i> )- <b>L3</b>	99	96
14	Ni(COD) <sub>2</sub>	DABCO	HBpin	Toluene	( <i>R<sub>P</sub></i> )- <b>L4</b>	99	97
15	Ni(COD) <sub>2</sub>	DABCO	HBpin	Toluene	( <i>R<sub>P</sub></i> )- <b>L5</b>	96	96
16	Ni(COD) <sub>2</sub>	DABCO	HBpin	Toluene	( <i>R<sub>P</sub></i> )- <b>L6</b>	91	7
17	Ni(COD) <sub>2</sub>	DABCO	HBpin	Toluene	( <i>R<sub>P</sub></i> )- <b>L7</b>	89	82
18	Ni(COD) <sub>2</sub>	DABCO	HBpin	Toluene	( <i>R<sub>P</sub></i> )- <b>L8</b>	98	98
19	Ni(COD) <sub>2</sub>	DABCO	HBpin	Toluene	( <i>R<sub>P</sub></i> )- <b>L9</b>	<5	-
20	Ni(COD) <sub>2</sub>	DABCO	HBpin	Toluene	( <i>R<sub>P</sub></i> )- <b>L10</b>	87	95

<sup>a</sup> Reaction conditions: **4a** (0.2 mmol), [Ni] (2.0 mol%), **L** (2.4 mol%), [H] source (1.2 equiv.), base (1.5 equiv.), solvent (2.0 mL), -25 °C, 0.8 - 4.0 h. <sup>b</sup> Isolated yield. <sup>c</sup> Determined by HPLC with chiral column. Et<sub>2</sub>O: ethyl ether, DCM: dichloromethane, EA: ethyl acetate, <sup>i</sup> PrOH: isopropanol, CB: catecholborane, DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene, DIPEA: *N,N*-diisopropylethylamine.

With the optimum conditions in hand, the substrate scope of this methodology was examined. Firstly, the aryl ring in  $\alpha,\beta$ -unsaturated ketones with different functional groups including *ortho*-, *meta*- and *para*-substitutions could be reacted well to afford the target products in high yields and excellent enantiomeric excesses (**5a-5l**). The *ortho*-substituents were methyl (**5b** : 99% yield, 99% ee), methoxyl (**5c** : 96% yield, 99% ee) and cyano (**5d** : 99% yield, 96% ee). The *meta*-substituents were methyl (**5e** : 99% yield, 98% ee) and halogen (**5f** , **5g** , **5h** : 91-99% yield, 97-98% ee). The *para*-substituents were methyl (**5i** : 97% yield, 97% ee), halogen (**5j** : 96% yield, 98% ee and **5k** : 99% yield, 98% ee) and phenyl (**5l** : 99% yield, 98% ee). When the naphthyl was employed as substituent group, excellent yield and enantiomeric excess (**5m** : 99% yield, 98% ee) were observed. Secondly,  $\alpha'$ -substituents, such as ethyl (**5n** : 99% yield, 98% ee) and *n*-propyl (**5o** : 99% yield, 94% ee), were also suitable for this reductive reaction in high yields and enantiomeric excesses under the standard conditions. But when  $\alpha'$ -substituent was changed to isopropyl (**5p**), the enantiomeric excess decreased to moderate 65% ee.

Moreover, the heteroaromatic substrate, like furan, could also work smoothly to deliver the desired product in excellent enantiomeric excess (**5q** : 76% yield, 94% ee).  $\beta,\beta$ -Disubstituted enones (**4r** and **4s**) were successfully participated to afford the reductive products (**5r** : 88% yield, 74% ee and **5s** : 85% yield, 58% ee), respectively. Subsequently, we attempted to use the (*E*)-2-benzylidenecyclohexanone (**4t**) as the substrate to explore the substrate scope. Unfortunately, the enantiomeric excess was unsatisfied (**5t** : 93% yield, 26% ee). In addition, chalcone substrate (**4u**) underwent 1,2-reduction to afford the chiral alcohol in moderate yield and enantiomeric excess after a series of ligands screening (**5u** : 76% yield, 68% ee, **L9**), and a small amount of sideproduct of 1,4-reduction (24% yield) was also observed. For the substrate **5v** with strong electron-withdrawing trifluoromethyl group, 91% yield and moderate 74% of enantiomeric excess were obtained. Finally, the substrates with  $\alpha'$ -substituent such as methoxycarbonyl group and benzyl were investigated, and the results were also unsatisfactory.

**Scheme 3** Substrate scope for  $\alpha,\beta$ -unsaturated ketones

## Scheme 4 Scale-up experiment

To demonstrate the practicality of this methodology, the asymmetric reduction at the 6.84 mmol scale of **4a** was proceeded under the standard conditions, and the reductive product **5a** was isolated in 99% yield and 96% ee without loss of activity. Notably, the chiral ligand PYMCOX ( $R_p$ )-**L2** could be recovered with 97% isolated yield by flash silica gel column chromatography. These results showed the potential application of [2,2]paracyclophane-derived oxazole-pyrimidine ligands.

## Conclusions

In conclusion, we have successfully designed and synthesized a series of [2,2]paracyclophane-derived oxazole-pyrimidine ligands from the chiral [2,2]paracyclophane-derived aminophenol, and successfully applied them in nickel-catalyzed asymmetric 1,2-reduction of  $\alpha,\beta$ -unsaturated ketones, affording the chiral allylic alcohols with up to 99% yield and 99% ee. Meanwhile, the chiral ligand could be conveniently recovered at gram-scale with high yield through flash column chromatography. Highlights of this work involve a series of easily accessible chiral ligands, inhibition of asymmetric 1,4-reduction, wide substrate scope and mild reaction condition. Further efforts to expand other fertile metal-catalyzed asymmetric reactions are currently under investigation in our laboratories.

## Experimental

### Procedures for synthesis of chiral PYMCOX ligands( $R_p$ )-L1-10

**Method A : typical procedure for synthesis of PYMCOX ( $R_p$ )-L1:** A stirred solution of sodium (18.4 mg, 0.8 mmol) in methanol (16.0 mL) was cooled to 0 °C. After sodium was fully consumed, 2-cyanopyrimidines **2** (8.0 mmol) were added. The resulting mixture was warmed to room temperature and stirred for 24 hours. Then, the chiral [2,2]paracyclophane-derived aminophenol ( $R_p$ )-**L1** (1.920 g, 8.0 mmol) was added. The mixture was stirred at 50 °C for 24 hours. Then, the volatiles were evaporated under the reduced pressure. The crude residue was dissolved in dichloromethane, and water (10 mL) was added. The aqueous phase was extracted three times with dichloromethane. The combined organic phases were dried over anhydrous sodium sulfate, filtered and concentrated under the reduced pressure. The crude residue was purified by flash column chromatography on silica gel using hexanes/ethyl acetate as eluent (20/1 - 5/1) to give the desirable chiral PYMCOX ligand ( $R_p$ )-**L1** 1.460 g with 56% yield.

The same method was used for the synthesis of ( $R_p$ )-**L2 -9** . These chiral PYMCOX ligands are solid, and could be further purified by recrystallization with acetone and hexanes.

**Method B: the synthesis of PYMCOX ( $R_p$ )-L10:** The 4-trifluoromethyl-pyrimidine-2-carbonitrile (0.350 g, 2.0 mmol) was dissolved in a solution of hydrogen chloride in water (6 M, 10 mL) and heated at reflux temperature overnight. The reaction mixture was cooled to room temperature, and concentrated under the reduced pressure. Toluene (10 mL) was then added and the mixture was concentrated under the reduced pressure. This process was repeated with 1,4-dioxane and ethyl ether. Then the solids were filtered off. The filtrate was concentrated under the reduced pressure to afford 0.410 g of 4-trifluoromethyl-pyridine-2-carboxylic acid as white solid, which was directly used in the next step without the further purification.

The chiral aminophenol ( $R_p$ )-**1** (0.240 g, 1.0 mmol) and 4-trifluoromethyl-pyridine-2-carboxylic acid (0.288 g, 1.5 mmol) were dissolved in dichloromethane (5.0 mL). Then, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC-HCl, 0.383 g, 2.0 mmol) and 1-hydroxybenzotriazole (HOBT, 0.304 g, 2.0 mmol) were added at 0 °C under nitrogen gas. The mixture was stirred at room temperature for 18 hours. Water (10 mL) was added to quench the reaction. The aqueous phase was extracted three times with dichloromethane. The combined organic phases were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under the reduced pressure to give amide intermediate.

A solution of the above amide intermediate (0.487 g, 1.0 mmol) and *p*-toluenesulfonic acid monohydrate (0.285 g, 1.5 mmol) in *np*-xylene (10 mL) was stirred at 120 °C (oil bath temperature) for 24 h. After cooled to room temperature, saturated sodium carbonate solution (10 mL) was added. The aqueous phase

was extracted three times with ethyl acetate. The combined organic phases were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under the reduced pressure. The crude residue was purified by flash column chromatography on silica gel using hexanes/dichloromethane/ethyl acetate (15/1/1) as eluent to give the chiral PYMCOX ligand (*R*<sub>p</sub>)-**L10**.

**Γενεράλ προσεδуре φορνιςκελ-ςαταλψζεδ 1,2-ρεδυστιον οφ α,β-υνσατυρατεδ κετονες:**  
 In a nitrogen-filled glovebox, Ni(COD)<sub>2</sub> (2.2 mg, 0.008 mmol, 2.0 mol%), (*R*<sub>p</sub>)-2-(4-methylpyrimidin-2-yl)[2.2] paracyclophano[4,5-*d*]oxazole (PYMCOX **L2**) (3.3 mg, 0.0096 mmol, 2.4 mol%), and 1,4-diazobicyclo[2.2.2]octane (DABCO, 67.8 mg, 0.6 mmol) were added to a 10 mL Schlenk tube, equipped with a magnetic stirring bar. Then, toluene (1.6 mL) was added and the mixture was stirred for 10 min before addition of pinacolborane (HBpin) (70 μL, 0.48 mmol). The reaction tube was sealed with a Teflon screw cap, removed from glovebox and stirred for 10 min in a cooling bath at -25°C before the α,β-unsaturated ketones **4** (0.4 mmol in 0.4 mL toluene) solution was added by syringe. Then the reaction mixture was stirred at this temperature for 1-8 h. A saturated solution of ammonium fluoride in methanol (1.0 mL) was added, and the mixture was removed from the cooling bath, then stirred at room temperature for 30 min and followed by addition of water (2.0 mL) and ethyl acetate (3.0 mL). The aqueous phase was extracted three times with ethyl acetate. The combined organic phases were dried over anhydrous sodium sulfate, filtered and concentrated under the reduced pressure. The residue was purified by chromatography on silica gel using hexanes/ethyl acetate as eluent (20/1 - 5/1) to afford the desirable chiral product allylic alcohols **5**.

The enantiomeric excesses were determined by HPLC analysis using the chiral column. The racemates could be prepared by the Luche or sodium borohydride reduction at 0 °C.

#### Supporting Information

The supporting information for this article is available on the WWW under <https://doi.org/10.1002/cjoc.2023xxxxx>.

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## Entry for the Table of Contents

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Σψντησεις οφ Πλαναρ-ήιραλ [2.2]Παραςψςλοπηανε-βασεδ Οξαζολε-Πψριμιδινε Λιγανδς ανδ Αππλιςα  
The [2.2]paracyclophane-derived oxazole-pyrimidine ligands with planar chirality (PYMCOX) were designed, synthesized and

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