



## New synthetic strategy for chiral 2-oxazolidinones derivatives via rhodium-catalyzed asymmetric hydrogenation



Qingli Wang<sup>†</sup>, Xuefeng Tan<sup>†</sup>, Ziyue Zhu, Xiu-Qin Dong<sup>\*</sup>, Xumu Zhang<sup>\*</sup>

College of Chemistry and Molecular Sciences, Wuhan University, Wuhan City, Hubei Province 430072, China

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### ABSTRACT

Asymmetric hydrogenation of 4-substituted cyclic enamido esters catalyzed by a rhodium–TangPhos complex provides an efficient method for the synthesis of chiral 4-substituted oxazolidinones with excellent yields and good enantioselectivities. The products are valuable chiral building blocks and the applications as chiral auxiliaries and pharmaceuticals are well-known.

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### Introduction

In last decades, chiral 2-oxazolidinone compounds and their derivatives owned considerable attraction due to the wide application in asymmetric synthesis,<sup>1</sup> for example serving as Evans' chiral auxiliaries.<sup>2</sup> The chiral 2-oxazolidinones also played a unique and significant role in many fields of pharmaceuticals, antibiotics, cosmetics, food additives, and others.<sup>3</sup> A lot of research groups paid more attention to the synthesis of chiral 2-oxazolidinones.<sup>3a,b</sup> The conventional synthetic approaches to access optical 2-oxazolidinone compounds were the reactions of chiral amino alcohols as the chiral source with phosgene and its derivatives<sup>4</sup> or using the mixture of CO/O<sub>2</sub> via oxidative carbonylation (Scheme 1).<sup>3i,5</sup> It was well known that phosgene and CO are extremely dangerous and toxic reagents. With the decreasing use of phosgene and its derivatives, dialkyl carbonates were used to synthesize oxazolidinones with high yields.<sup>6</sup> In addition, many research groups were dedicated to developing much more greener ways to obtain 2-oxazolidinones through chiral amino alcohols reacting with carbon dioxide (Scheme 1),<sup>7</sup> but the reaction conditions were very drastic, such as high temperature, high pressure, and strong base, leading to their severely limited applications. Other

common transformations made use of aziridines<sup>8</sup> and azydkis<sup>9</sup> as starting materials, but they were expensive and inconveniently available. Therefore, the development of efficient strategy for the construction of chiral 2-oxazolidinone compounds was not only a necessity for biochemists and medicinal chemists, but also a challenge for synthetic chemists. Consequently, it is urgent to explore more practical and greener synthetic methodology for the preparation of chiral 2-oxazolidinones. The asymmetric hydrogenation of functionalized olefins was a powerful and environmentally friendly route to obtain chiral compounds.<sup>10</sup> Herein, we successfully developed rhodium catalyzed asymmetric hydrogenation of cyclic enamido esters to obtain chiral 2-oxazolidinones with high yields and good stereoselectivities under mild conditions for the first time.

A series of new substrates, 4-substituted cyclic enamido esters **2** were synthesized from their corresponding aromatic ketones, which were commercially available starting materials, through  $\alpha$ -hydroxylation reaction and condensation reaction, and the products were obtained with moderate to good yields (Scheme 2).

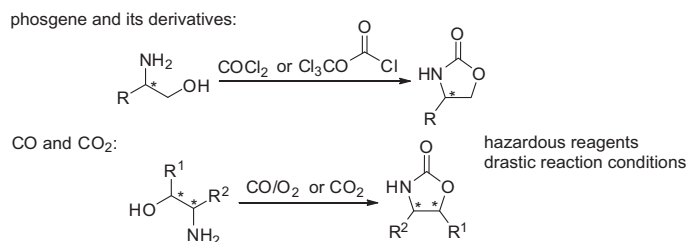
### Results and discussion

4-Phenyloxazol-2(3H)-one (**2a**) was selected as the model substrate to investigate the hydrogenation conditions. Rh/TangPhos complex was initially tested as the catalyst, which was efficient for the asymmetric hydrogenation. The reaction was performed

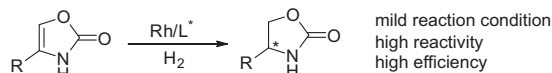
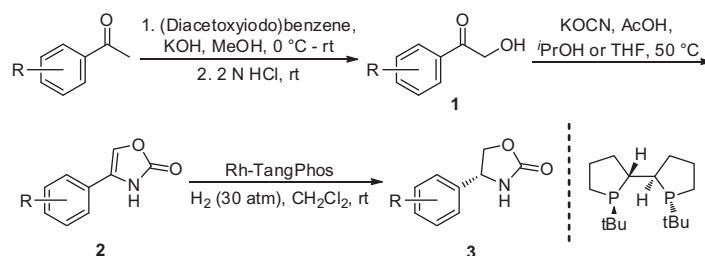
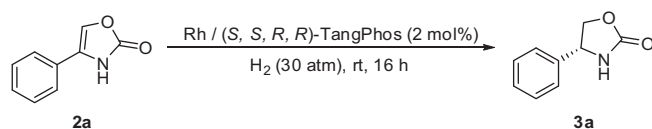
\* Corresponding authors.

E-mail addresses: [xuqindong@whu.edu.cn](mailto:xuqindong@whu.edu.cn) (X.-Q. Dong), [xumu@whu.edu.cn](mailto:xumu@whu.edu.cn) (X. Zhang).

<sup>†</sup> Qingli Wang and Xuefeng Tan contributed equally to this work.

Previous work<sup>3-5</sup>:

## This work:

**Scheme 1.** Synthesis of chiral 4-substituted oxazolinones.**Scheme 2.** Design and synthesis of chiral 4-substituted oxazolinones.**Table 1**  
Solvent screening for Rh-catalyzed asymmetric hydrogenation of 4-phenyloxazol-2 (3*H*)-one **2a**<sup>a</sup>

Entry	Cat.	Solvent	Conversion <sup>b</sup> (%)	ee <sup>c</sup> (%)
1	[Rh(COD)( <i>S,S,R,R</i> )-TangPhos]BF <sub>4</sub>	MeOH	82	9.6
2	[Rh(COD)( <i>S,S,R,R</i> )-TangPhos]BF <sub>4</sub>	CH <sub>2</sub> Cl <sub>2</sub>	>99	78
3	[Rh(COD)( <i>S,S,R,R</i> )-TangPhos]BF <sub>4</sub>	IPA	46.3	9.9
4	[Rh(COD)( <i>S,S,R,R</i> )-TangPhos]BF <sub>4</sub>	EtOH	13.5	5
5	[Rh(COD)( <i>S,S,R,R</i> )-TangPhos]BF <sub>4</sub>	TFE	32	31
6	[Rh(COD)( <i>S,S,R,R</i> )-TangPhos]BF <sub>4</sub>	THF	36	6.5
7	[Rh(COD)( <i>S,S,R,R</i> )-TangPhos]BF <sub>4</sub>	Dioxane	12.3	25.5
8	[Rh(COD)( <i>S,S,R,R</i> )-TangPhos]BF <sub>4</sub>	DME	Trace	—
9	[Rh(COD)( <i>S,S,R,R</i> )-TangPhos]BF <sub>4</sub>	Toluene	94	51
10	[Rh(NBD)( <i>S,S,R,R</i> )-TangPhos]BF <sub>4</sub>	CH <sub>2</sub> Cl <sub>2</sub>	>99	77

<sup>a</sup> Unless otherwise mentioned, all reactions were carried out with a [Rh]/(*S,S,R,R*)-TangPhos/substrate ratio of 1:1.1:50 in 1 mL solvent, at room temperature under hydrogen (30 atm) for 16 h.

<sup>b</sup> Determined by <sup>1</sup>H NMR spectroscopy.

<sup>c</sup> Determined by HPLC analysis using a chiral stationary phase. NBD = 2,5-norbornadiene, COD = 1,5-cyclooctadiene, IPA = isopropanol, TFE = trifluoroethanol, THF = tetrahydrofuran, DCE = 1,2-dichloroethane.

in MeOH under 30 atm of H<sub>2</sub> for 16 h. Under this condition, **2a** was hydrogenated to **3a** with 82% conversion and low ee (10% ee, Table 1, entry 1). Then, solvent screening showed that CH<sub>2</sub>Cl<sub>2</sub> was the best choice with 78% ee (Table 1, entry 2). And we found

metal precursor [Rh(NBD)<sub>2</sub>]BF<sub>4</sub> obtained similar results with [Rh(COD)<sub>2</sub>]BF<sub>4</sub> (Table 1, entry 10).

In our next experiments, a wide range of diphosphine ligands were also tested (Fig. 1). As shown in Table 2, TangPhos developed by our group gave the best enantioselectivity (Table 2, entry 1). Electron-donating P-chiral diphosphine ligands (*R,R*)-QuinoxP and (*R<sub>c</sub>,S<sub>p</sub>*)-DuanPhos afforded high activities but moderate enantioselectivities (Table 2, entries 5 and 8). When some chiral bisphosphorus ligands such as (*S*)-Binapine, (*S*)-SegPhos, (*R*)-MeO-Biphep, and (*S*)-C<sub>3</sub>-TunePhos were employed, the expected product was obtained with excellent yields but lower enantioselectivities (97–>99% con., 5–20% ee) (Table 2, entries 2, 6, 10, and 11). While chiral biaryl bisphosphorus ligand (*S*)-BINAP and electron-donating P-chiral diphosphine ligand (*S,S*)-Me-DuPhos provided neither high yields nor good enantioselectivities (Table 2, entries 3 and 7). Chiral ferrocenyl ligands f-Binapohane and (*R*)-WalPhos were also investigated with low to moderate enantioselectivities and high activities (Table 2, entries 4 and 9).

Encouraged by these results, the hydrogen pressure and reaction temperature were also evaluated with [Rh(COD)(*S,S,R,R*)-TangPhos]BF<sub>4</sub> as the catalyst and CH<sub>2</sub>Cl<sub>2</sub> as the solvent. When the hydrogen pressure reduced, the similar ee values were obtained but with a slightly lower conversion (Table 3, entries 2 and 3). Under a lower reaction temperature, the enantioselectivity was maintained but resulted in decreasing reactivity, while increasing the temperature to 50 °C led to the decrease of enantioselectivity (Table 3, entries 4 and 5). At last, we obtained the best reaction condition was that [Rh(COD)(*S,S,R,R*)-TangPhos]BF<sub>4</sub> as the best catalyst for asymmetric hydrogenation of 4-substituted cyclic enamido esters in CH<sub>2</sub>Cl<sub>2</sub> under 30 atm of H<sub>2</sub> at 25 °C.

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