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

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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 oxazolinones 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,[1] for example serving as Evans' chiral auxiliaries.[2] The chiral 2-oxazolidinones also played a unique and significant role in many fields of pharmaceuticals, antibiotics, cosmetics, food additives, and others.[3] A lot of research groups paid more attention to the synthesis of chiral 2-oxazolidinones.[3a,b] 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[4] or using the mixture of CO/O_2 via oxidative carbonylation (Scheme 1).[3i,5] 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.[6] 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),[7] 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[8] and azydki[9] 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.[10] 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 α-hydroxylation reaction and condensation reaction, and the products were obtained with moderate to good yields (Scheme 2).

Results and discussion

4-Phenyloxazol-2(3*H*)-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

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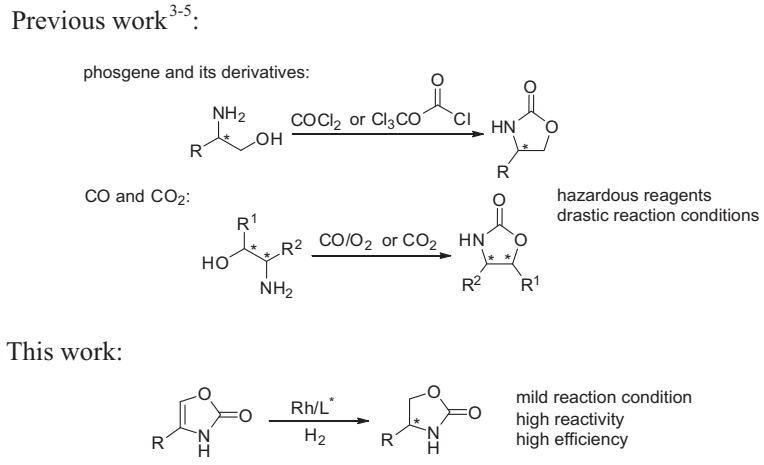
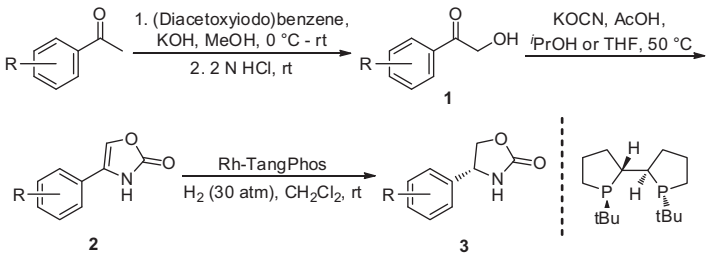
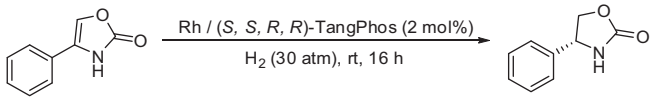


Scheme 1. Synthesis of chiral 4-substituted oxazolinones.



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**[a]



2a **3a**

Entry	Cat.	Solvent	Conversion[b] (%)	ee[c] (%)
1	[Rh(COD)(*S*,*S*,*R*,*R*)-TangPhos]BF_4	MeOH	82	9.6
2	[Rh(COD)(*S*,*S*,*R*,*R*)-TangPhos]BF_4	CH_2Cl_2	>99	78
3	[Rh(COD)(*S*,*S*,*R*,*R*)-TangPhos]BF_4	IPA	46.3	9.9
4	[Rh(COD)(*S*,*S*,*R*,*R*)-TangPhos]BF_4	EtOH	13.5	5
5	[Rh(COD)(*S*,*S*,*R*,*R*)-TangPhos]BF_4	TFE	32	31
6	[Rh(COD)(*S*,*S*,*R*,*R*)-TangPhos]BF_4	THF	36	6.5
7	[Rh(COD)(*S*,*S*,*R*,*R*)-TangPhos]BF_4	Dioxane	12.3	25.5
8	[Rh(COD)(*S*,*S*,*R*,*R*)-TangPhos]BF_4	DME	Trace	—
9	[Rh(COD)(*S*,*S*,*R*,*R*)-TangPhos]BF_4	Toluene	94	51
10	[Rh(NBD)(*S*,*S*,*R*,*R*)-TangPhos]BF_4	CH_2Cl_2	>99	77

[a] 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.
[b] Determined by ^1H NMR spectroscopy.
[c] 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_2 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_2Cl_2 was the best choice with 78% ee (Table 1, entry 2). And we found metal precursor [Rh(NBD)$_2$]BF_4 obtained similar results with [Rh(COD)$_2$]BF_4 (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_c,S_p)-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_3-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_4 as the catalyst and CH_2Cl_2 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_4 as the best catalyst for asymmetric hydrogenation of 4-substituted cyclic enamido esters in CH_2Cl_2 under 30 atm of H_2 at 25 °C.

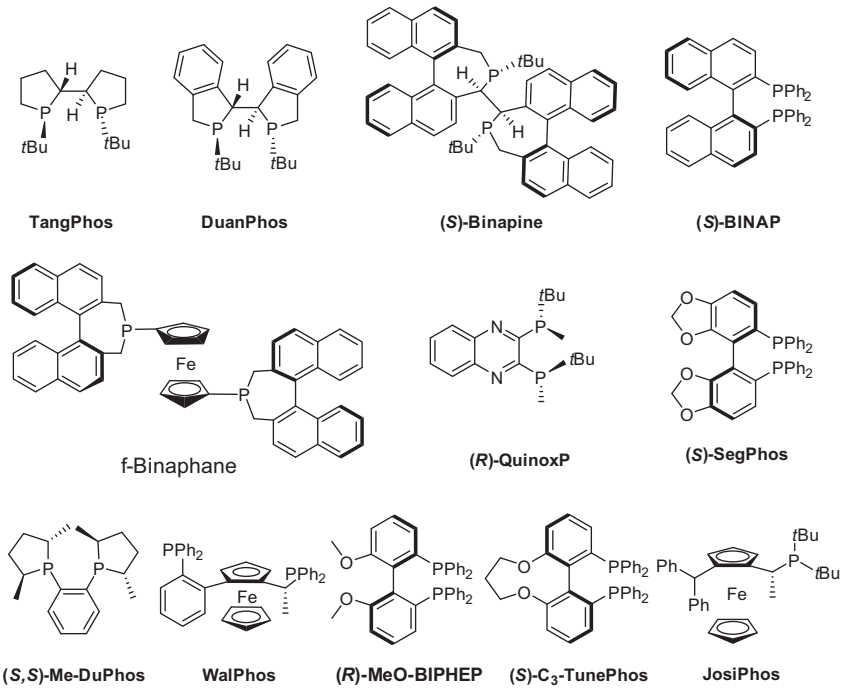
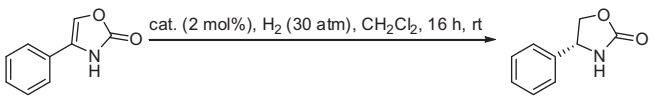


Figure 1. Structures of the phosphine ligands for hydrogenation of 4-phenyloxazol-2(3*H*)-one **2a**.

Table 2
Ligands screening for Rh-catalyzed asymmetric hydrogenation of 4-phenyloxazol-2(3*H*)-one **2a**[a]

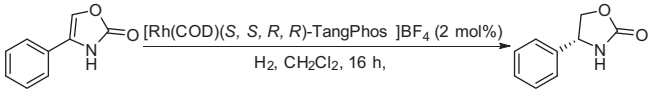


2a **3a**

Entry	Cat.	Conversion[b] (%)	ee[c] (%)
1	(*S*,*S*,*R*,*R*)-TangPhos	>99	78
2	(*S*)-Binaphine	>99	17
3	(*S*)-Binap	70	9
4	f-Binaphane	>99	55
5	(*R*,*R*)-Quinoxp	>99	52
6	(*S*)-SegPhos	98	15
7	(*S*,*S*)-Me-DuPhos	42	33
8	(R_c,S_p)-DuanPhos	92	58
9	(*R*)-WalPhos	>99	5
10	(*R*)-MeO-Biphep	98	14
11	(*S*)-C_3-TunaPhos	97	20

[a] Unless otherwise mentioned, all reactions were carried out with a [Rh]/L*/substrate ratio of 1:1.1:50 in 1 mL CH_2Cl_2, at room temperature under hydrogen (30 atm) for 16 h.
[b] Determined by ^{1}H NMR spectroscopy.
[c] Determined by HPLC analysis using a chiral stationary phase. COD = 1,5-cyclooctadiene.

Table 3
Pressure and temperature screening for Rh-catalyzed asymmetric hydrogenation of 4-phenyloxazol-2(3*H*)-one **2a**[a]



2a **3a**

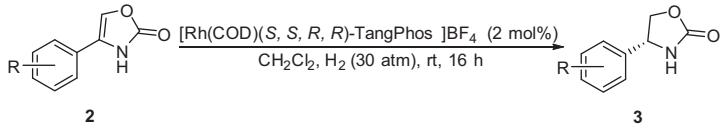
Entry	H_2 (atm)	*T* (°C)	Conversion[b] (%)	ee[c] (%)
1	30	25	>99	78
2	10	25	96	78
3	5	25	91	79
4	30	0	95	78
5	30	50	>99	65

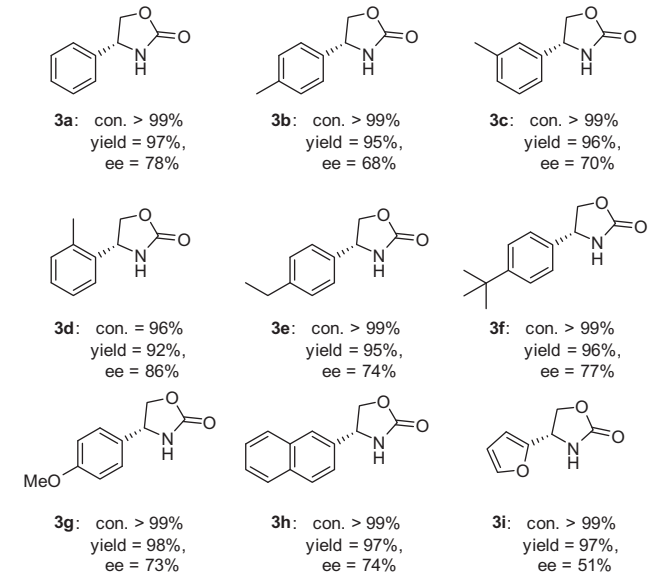
[a] Unless otherwise mentioned, all reactions were carried out with a [Rh]/(*R*,*R*,*S*,*S*)-TangPhos/substrate ratio of 1:1.1:50 in 1 mL CH_2Cl_2 for 16 h.
[b] Determined by ^{1}H NMR spectroscopy.
[c] Determined by HPLC analysis using a chiral stationary phase.

With the optimized reaction conditions in hand, we turned our attention to the scope of the asymmetric hydrogenation. As shown in Table 4, all the 4-aryl substituted substrates with electron-rich group were converted to the corresponding chiral 4-substituted oxazolinones **3** with good ee (Table 4, entries **3b**–**3g**). Interestingly, we found that *o*-substituted enamide moiety **2d** showed high enantioselectivity (86% ee) (Table 4, entry **3d**). Additionally replacement of the phenyl group by a more sterically hindered 2-naphthyl moiety resulted in complete conversion and 74% ee (Table 4, entry **3h**). Importantly, furan group substituted cyclic enamido ester **2i** also performed well in the hydrogenation (Table 4, entry **3i**).

In summary, we have reported the first asymmetric hydrogenation of 4-substituted cyclic enamido esters for the preparation of 4-substituted oxazolinones catalyzed by Rh/TangPhos complex with good enantioselectivities and high yields. Further exploration on expanding the challenging and interesting substrate scope and improving the enantioselectivities and reactivities are underway in our laboratory.

Table 4
Rh-catalyzed asymmetric hydrogenation of 4-substituted cyclic enamido esters **2**[a,b,c]





[a] 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 CH_2Cl_2, at room temperature under hydrogen (30 atm) for 16 h.
[b] The conversion and the yield of the isolated product was determined by ^1H NMR spectroscopy.
[c] The ee value was determined by HPLC analysis using a chiral stationary phase. Upon comparison of ^1H NMR, ^{13}C NMR and the optical rotation of **3a** with the literature,[7h] the absolute config **3a** was determined as (*R*).

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.12.105.

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