Letter

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Efficient Access to Chiral 2-Oxazolidinones via Ni-Catalyzed Asymmetric Hydrogenation: Scope Study, Mechanistic Explanation, and Origin of Enantioselectivity

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ABSTRACT: Cheap transition metal Ni-catalyzed asymmetric hydrogenation of 2-oxazolones was successfully developed, which provided an efficient synthetic strategy to prepare various chiral 2-oxazolidinones with 95%-99% yields and 97%->99% ee. The gram-scale hydrogenation could be proceeded well with >99% ee in the presence of low catalyst loading (up to 3 350 TON). This Ni-catalyzed hydrogenation protocol demonstrated great synthetic utility, and the chiral 2-oxazolidinone product was easily converted to a variety of other important molecules in good yields and without loss of ee values, such as chiral dihydrothiophene-2(3H)-thione, amino alcohol, oxazoline ligand and allenamide. Moreover, a series of deuterium labelling experiments, control experiments and DFT calculations were conducted to illustrate a reasonable catalytic mechanism for this Ni-catalyzed asymmetric hydrogenation, which involved a tautomerization between the enamine and its isomer imine, and then went through asymmetric 1,2-addition of Ni(II)-H to the preferred imine.

KEYWORDS: Asymmetric hydrogenation, Nickel catalytic system, Chiral 2-oxazolidinones, Enantioselectivity, Chiral phosphine ligand.

Chiral 2-oxazolidinones have been occupied a prominent and unique position in the field of asymmetric synthesis, which not only worked as the Evans' chiral auxiliaries as a reliable strategy for the stereoselective construction of enantioenriched compounds,[1] but also emerged as an important class of heterocyclic motifs of many nature products, pharmaceuticals and biologically active molecules.[2-5] As shown in Figure 1, the IDH889 was identified with 2-HG inhibitory activity in a mutant IDH1 xenograft mouse model.[3] The (-)-Cytoxazone was isolated from Streptomyces sp., which is a selective modulator of Th2 cytokine secretion.[4] The Zolmitriptan (311C90) is a selective agonist of serotonin (5-hydroxytryptamine, 5-HT) type 1B and 1D receptors.[5]

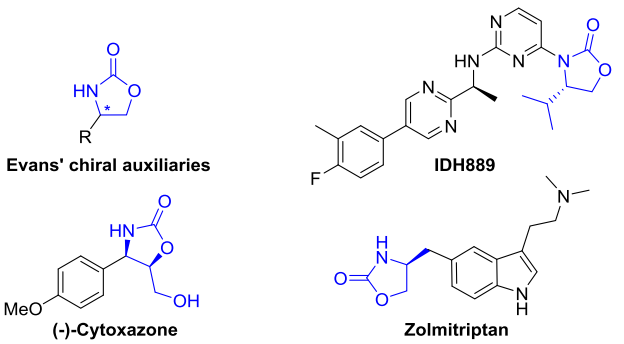
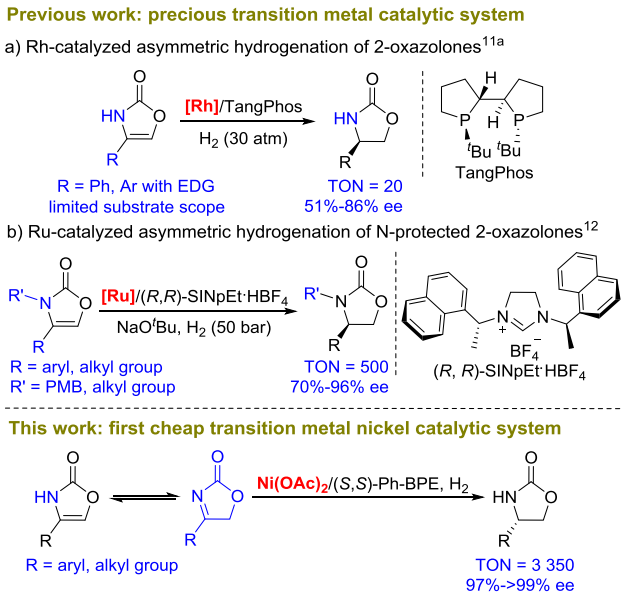


Figure 1. Some chiral auxiliaries and biologically active molecules containing chiral 2-oxazolidinone motifs.

Owing to their great important applications in many fields, tremendous efforts have been devoted to developing synthetic methodologies for the preparation of chiral 2-oxazolidinones and derivatives in the past decades.[1e, 1g, 2a, 6-9, 11-12] Among them, carbonylation of chiral β-amino alcohols substrates with electrophilic "C=O" reagents is the most widely used method to produce chiral 2-oxazolidinones, however, which always needs the use of extremely dangerous and toxic reagents (phosgene, CO) or with CO_2 in drastic reaction conditions.[7] Another conventional method to access chiral 2-oxazolidinones is through the transformations of highly toxic isocyanates with glycidols and derivatives.[8] Transition-metal-catalyzed intramolecular C-H amination of carbamates to obtain chiral 2-oxazolidinones have been developed in recent years, but generally poor to good enantioselectivities were achieved.[9] Therefore, it is in high demand to develop an efficient approach to access chiral 2-oxazolidinone derivatives. Asymmetric hydrogenation of unsaturated heterocyclic compounds has been regarded as a direct and efficient method to synthesize chiral heterocyclic compounds.[10] Therefore, it is an attractive and powerful way to access chiral 2-oxazolidinone derivatives through asymmetric hydrogenation of 2-oxazolones. However, there are only two examples involving asymmetric hydrogenation of 2-oxazolones through precious transition metal catalytic systems. In 2016, our group reported the Rh-catalyzed asymmetric hydrogenation of 2-oxazolones to provide chiral 2-oxazolidinones with moderate to good enantioselectivities (51%-86% ee), which was mainly restricted to the substrates with electron-donating groups on the aryl ring

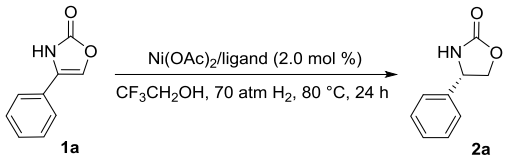
(Scheme 1a).[11a] Most recently, Glorius and co-workers described an efficient and important hydrogenation of 2-oxazolones catalyzed by chiral Ru/NHC system with excellent results (70%-96% ee, Scheme 1b).[12] It was very critical to introduce a protecting group on the N atom of the substrates and no reaction was observed for the free NH substrate, which required an additional deprotection operation to liberate versatile NH products. Currently, most asymmetric hydrogenation catalytic systems heavily relied on the scarce and precious transition metals,[10] which always related to the problems of environmental contamination and high costs. Therefore, great attention would be paid to developing the first-row transition metal catalytic systems depending on earth-abundant metals, such as Fe, Co and Ni, which exhibited the cheap and less/nontoxic advantages, and greatly contributed to the sustainable development.[13-14] Herein, we successfully developed the first cheap transition metal Ni-catalyzed highly efficient asymmetric hydrogenation of 2-oxazolones to afford chiral 2-oxazolidinones with excellent results, and it well tolerated free NH group with a broad range of substrate scope (scheme 1, downside).

Scheme 1. Synthesis of chiral 2-oxazolidinones *via* asymmetric catalytic hydrogenation.



We initially studied $Ni(OAc)_2$-catalyzed asymmetric hydrogenation of model substrate 4-phenyloxazol-2(3H)-one **1a** to investigate various chiral diphosphine ligands (Figure 2) under 70 atm H_2 in CF_3CH_2OH at 80 °C for 24 h. The hydrogenation product **2a** can be obtained with full conversions and excellent enantioselectivities using (*S*)-Binapine, (*R*,*S*)-^{t}Bu-Josiphos, (*S*,*S*)-Ph-BPE as the ligand (>99% conversion, 95%->99% ee, Table 1, entries 1, 4-5). The (*Rc*,*Sp*)-Duanphos and (*S*,*S*)-Me-Duphos provided poor enantioselectivities (Table 1, entries 2-3). In addition, this asymmetric hydrogenation was not finished in the presence of (*S*)-Binap, and very poor enantioselectivity was afforded (Table 1, entry 6). The (*S*,*S*)-Ph-BPE was proven to be the preferred ligand; this transformation was still proceeded smoothly when the catalyst loading was decreased to 1.0 mol% (>99% conversion, >99% ee, Table 1, entry 7).

Table 1. Screening chiral diphosphine ligands for the $Ni(OAc)_2$-catalyzed asymmetric hydrogenation of 4-phenyloxazol-2(3H)-one **1a**.[a]



entry	ligand	conv. (%)[b]	ee (%)[c]
1	(*S*)-Binapine	>99	95
2	(*Rc*,*Sp*)-DuanPhos	>99	48
3	(*S*,*S*)-Me-DuPhos	>99	-40
4	(*R*,*S*)-^{t}Bu-Josiphos	>99	97
5	(*S*,*S*)-Ph-BPE	>99	>99
6	(*S*)-Binap	24	-35
7[d]	(*S*,*S*)-Ph-BPE	>99	>99

[a] Unless otherwise noted, all reactions were carried out with a $Ni(OAc)_2$/ligand/substrate **1a** (0.1 mmol) ratio of 1:1.1:50 in 1.0 mL CF_3CH_2OH under 70 atm H_2 at 80 °C for 24 h. The configuration of **2a** was determined by comparing the optical rotation data with those reported in the literature.[11a] [b] Determined by ^{1}H NMR analysis. [c] Determined by chiral HPLC analysis. [d] 1.0 mol% catalyst loading.

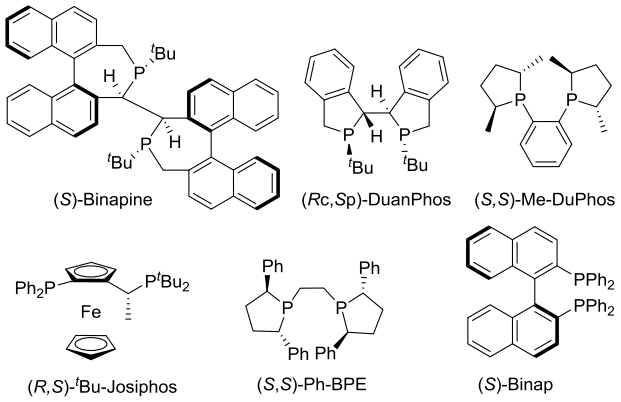
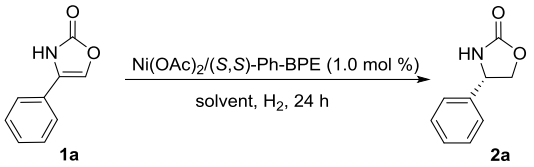


Figure 2. The structure of chiral diphosphine ligands.

The optimization of reaction conditions was continued to examine solvent effect using (*S*,*S*)-Ph-BPE as the ligand. As shown in Table 2, although >99% ee was detected in MeOH and EtOH, very poor conversions were provided (4%-13% conversions, >99% ee, Table 2, entries 1-2). And trace conversion was afforded in ^{i}PrOH (Table 2, entry 3). We found that high conversions and excellent enantioselectivities were obtained in CF_3CH_2OH, $(CF_3)_2CHOH$ (>99% conversions, >99% ee, Table 2, entries 4-5). No reaction was observed in nonprotic solvents, such as CH_2Cl_2, THF and 1,4-dioxane (Table 2, entries 6-8). In order to obtain the best reaction solvent, this reduction was conducted with a lower catalyst loading (0.3 mol %) in CF_3CH_2OH and $(CF_3)_2CHOH$, and $(CF_3)_2CHOH$ provided higher conversion (73% conversion *vs* >99% conversion, Table 2, entries 9-10). Full conversion can be achieved when the reaction temperature was decreased from 80 °C to 50 °C (Table 2, entry 11). To our delight, >99% conversion and >99% ee was still realized when H_2 pressure was gradually decreased from 70 atm to 1 atm (Table 2, entries 13-16). Moreover, this Ni-catalyzed asymmetric hydrogenation still can be finished within 12 h (>99% conversion, >99% ee, Table 2, entry 17).

Table 2. Optimization reaction condition for the Ni-catalyzed asymmetric hydrogenation of 4-phenyloxazol-2(3H)-one **1a**.[a]

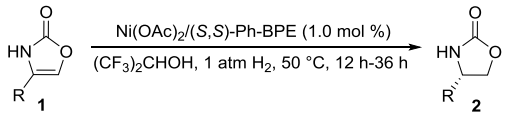


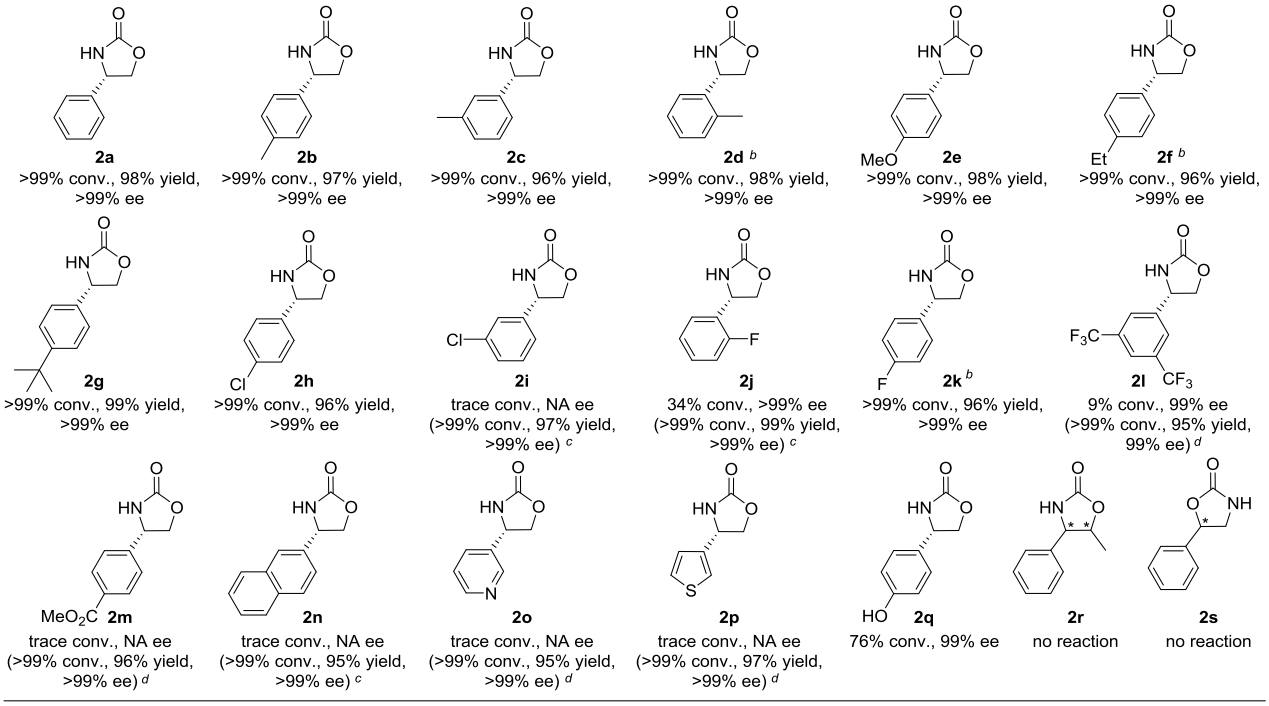
entry	solvent	H_2 (atm)	T (°C)	conv. (%)[b]	ee (%)[c]
1	MeOH	70	80	13	>99
2	EtOH	70	80	4	>99
3	^{i}PrOH	70	80	trace	NA
4	CF_3CH_2OH	70	80	>99	>99
5	$(CF_3)_2CHOH$	70	80	>99	>99
6	CH_2Cl_2	70	80	NR	NA
7	THF	70	80	NR	NA
8	1,4-dioxane	70	80	NR	NA
9[d]	CF_3CH_2OH	70	80	73	>99
10[d]	$(CF_3)_2CHOH$	70	80	>99	>99
11	$(CF_3)_2CHOH$	70	50	>99	>99
12	$(CF_3)_2CHOH$	70	25	62	>99
13	$(CF_3)_2CHOH$	40	50	>99	>99
14	$(CF_3)_2CHOH$	10	50	>99	>99
15	$(CF_3)_2CHOH$	5	50	>99	>99
16	$(CF_3)_2CHOH$	1	50	>99	>99
17[e]	$(CF_3)_2CHOH$	1	50	>99	>99

[a] Unless otherwise noted, all reactions were carried out with a $Ni(OAc)_2$/(*S*,*S*)-Ph-BPE/substrate **1a** (0.1 mmol) ratio of 1:1.1:100 in 1.0 mL solvent for 24 h. [b] Determined by ^1H NMR analysis. [c] Determined by chiral HPLC analysis. [d] 0.3 mol% catalyst loading. [e] 12 h. NR = No Reaction, NA = Not Available.

With the optimized reaction conditions in hands, we made effort to investigating the substrate scope generality of the Ni-catalyzed asymmetric hydrogenation of 2-oxazolones. These results were summarized in Scheme 2. This protocol exhibited well tolerance towards both electronic properties and substituent positions when a range of aryl substituted 2-oxazolones were used, the corresponding chiral 2-oxazolidinones were obtained with high yields and excellent enantioselectivities (>99% conversion, 95%-99% yields, 99%->99% ee). The substrates 2-oxazolones with electron-rich groups (**1b**-**1g**) were hydrogenated efficiently to provide the desired hydrogenation products (**2b**-**2g**) with full conversions, 96%-99% yields and >99% ee. The asymmetric hydrogenation of the substrates with electron-deficient substituents, 2-napthyl fused motif (**1n**), heteroaryl groups including pyridine (**1o**) and thiophene (**1p**) moieties displayed relatively low reactivity, which could be hydrogenated under high H_2 pressure and temperature to afford the corresponding products with excellent results (full conversions, 95%-99% yields and 99%->99% ee). Moreover, the 2-oxazolone with phenol hydroxyl group (**1q**) was tolerated with 76% conversion and 99% ee. We found that the challenging 4,5-disubstituted-2-oxazolone (**1r**) was difficult to be hydrogenated under the standard conditions. In addition, 3-oxazolone 5-phenyloxazol-2(3H)-one (**1s**) also did not work in this catalytic system.

Scheme 2. Scope study for the $Ni(OAc)_2$-catalyzed asymmetric hydrogenation of 2-oxazolones.[a]

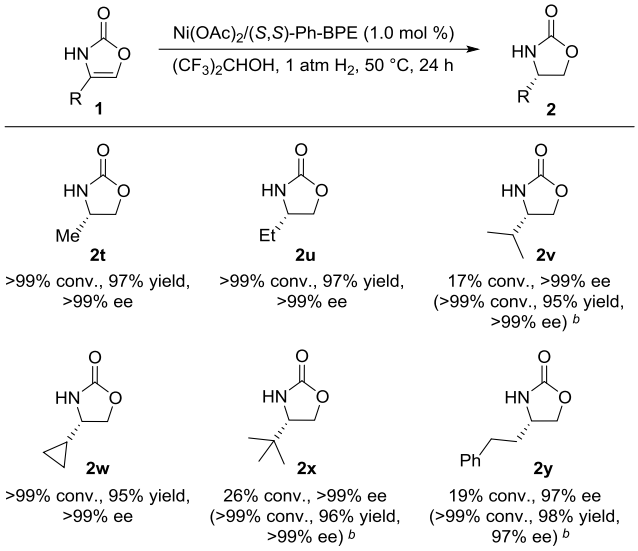




[a] Unless otherwise noted, all reactions were carried out with a Ni(OAc)$_2$/(*S*,*S*)-Ph-BPE/substrate **1** (0.1 mmol) ratio of 1:1.1:100 in 1.0 mL $(CF_3)_2CHOH$ under 1 atm H_2 at 50 °C for 12 h. Conversion was determined by ^{1}H NMR analysis. Yield is isolated yield. Ee value was determined by chiral HPLC analysis. [b] 36 h. [c] 70 atm H_2, 80 °C, 24 h. [d] S/C = 20, 70 atm H_2, 80 °C, 24 h.

Encouraged by the success in the Ni/(*S*,*S*)-Ph-BPE-catalyzed enantioselective hydrogenation of a variety of aryl substituted 2-oxazolones, we further explored the substrate scope with a series of alkyl substituted 2-oxazolones substrates. As shown in Scheme 3, a wide range of alkyl substituted substrates with different steric hindrances were hydrogenated well in our catalytic system, which led to the desired products with excellent results. The methyl (**1t**), ethyl (**1u**), cyclopropyl (**1w**) substituted 2-oxazolones proceeded smoothly to obtain desired products (**2t-2u**, **2w**) with 95%-97% yields and >99% ee. In addition, other alkyl substituted substrates, such as *iso*-propyl (**1v**), *tert*-butyl (**1x**) and phenylethyl (**1y**) substituents displayed a little low reactivity, which could be hydrogenated well under high H_2 pressure and temperature with excellent results (95%-98% yields, 97%->99% ee).

Scheme 3. Substrate scope study for the Ni-catalyzed asymmetric hydrogenation of 2-oxazolones.[a]



[a] Unless otherwise noted, all reactions were carried out with a Ni(OAc)$_2$/(*S*,*S*)-Ph-BPE/substrate **1** (0.1 mmol) ratio of 1:1.1:100 in 1.0 mL $(CF_3)_2CHOH$ under 1 atm H_2 at 50 °C for 24 h. Conversion was determined by ^{1}H NMR analysis. Yield is isolated yield. The ee value was determined by chiral HPLC analysis. [b] 70 atm H_2, 80 °C, 24 h.

A series of Ni-catalyzed asymmetric hydrogenation of 2-oxazolone with model substrate 4-phenyloxazol-2(3H)-one **1a** were conducted in the presence of the (*S*,*S*)-Ph-BPE ligand with different enantiopurities under the standard reaction conditions. As shown in Figure 3, linear effect was observed in this asymmetric reduction, which disclosed that there should be no catalyst self-aggregation or ligand-substrate agglomeration in this reaction system.[15]

In order to investigate the possible hydrogenation mechanism for this Ni-catalyzed asymmetric hydrogenation, a series of deuterium labelling studies were conducted (Scheme 4). The model substrate 4-phenyloxazol-2(3H)-one **1a** was hydrogenated with 1 atm D_2 in $(CF_3)_2CHOH$, the deuterium atom was completely added at the benzylic position and partly

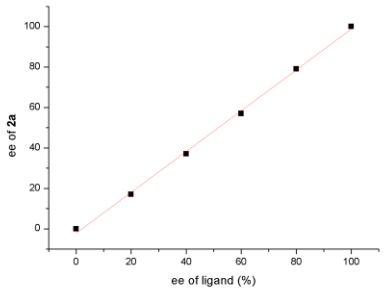
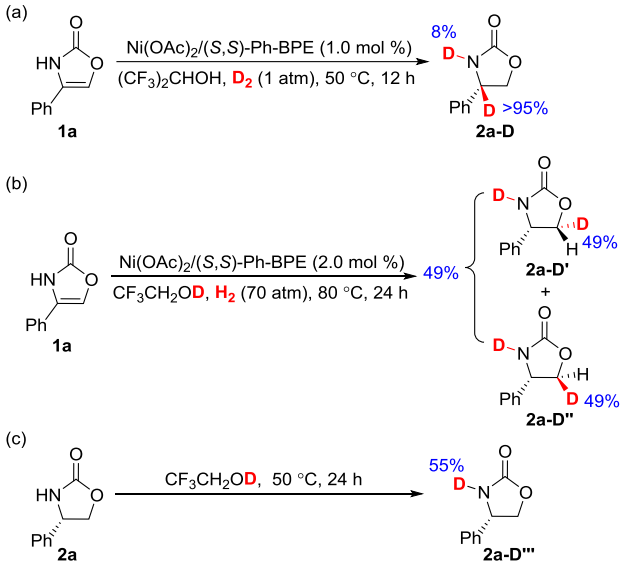


Figure 3. Investigation for the nonlinear effect of hydrogenation of substrate **1a** using (*S*,*S*)-Ph-BPE with different ee values.

at the nitrogen atom of the product (Scheme 4a). In addition, this Ni-catalyzed asymmetric reduction was repeated in the presence of H_2 and CF_3CH_2OD, we found that the deuterium atom was partly located at the nitrogen atom and the two H atoms of methylene neighboring the oxygen atom were deuterated almost half-and-half, which indicated that the fast deuterium/proton exchange between N-H of substrate and CF_3CH_2OD should exist, and the tautomerization of enamine to imine also should exist in the hydrogenation process (Scheme 4b). Moreover, hydrogenation product **2a** was dissolved and stirred in CF_3CH_2OD, the deuterium atom was detected to be partly incorporated at the N-H position, which showed that deuterium/proton exchange should exist in this process (Scheme 4c). These results suggested that the H atom at the benzylic position of the product **2a** was solely from H_2.

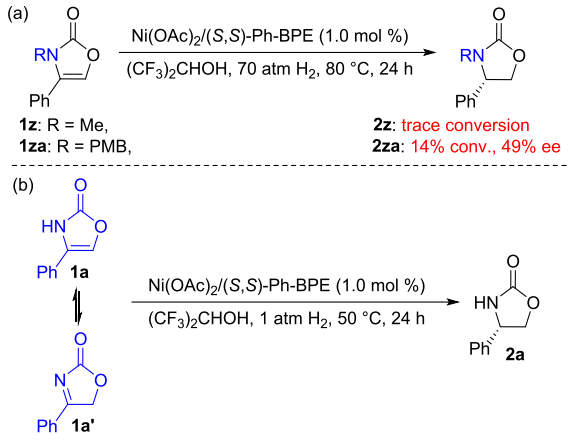
Scheme 4. Deuterium labelling experiments.



Based on these observations, we speculated that there should be existed an equilibrium between our substrate enamine 4-phenyloxazol-2(3H)-one **1a** and its isomer imine 4-phenyloxazol-2(5H)-one **1a'** in the reaction system. Control experiments were then carried out (Scheme 5). Substrates **1z** and **1za** containing methyl and 4-methoxybenzyl protecting groups on the nitrogen atom were investigated, which could not form the corresponding imine isomers. And poor reactivities

and enantioselectivities were observed, which demonstrated that there should be an equilibrium between our substrate enamine and its isomer imine, and the imine isomer may work as the more preferred substrate in this Ni-catalyzed asymmetric process.

Scheme 5. Control experiments.



To shed light on reaction mechanism for this Ni-catalyzed asymmetric hydrogenation of 2-oxazolones, DFT calculations have been carried out using B3LYP-D3 method (Figure 4). The catalytic cycle initiates from the acetate-assisted nickel complex intermediate **I**. Then H_2 coordinates with intermediate **I** and undergoes heterolytic cleavage to overcome an energy barrier of 26.0 kcal/mol, generating a Ni(II)-H complex intermediate **III**. Enamines can be converted into imines under mild conditions, and the conversion of **1a** and **1a'** requires a low energy barrier of 0.6 kcal/mol. The favored pathway proceed through catalytic imine cycle since the insertion between Ni(II)-H complex and imine takes place to form intermediate **VII** *via* transition state **TSIII** with lower energy barrier than the formation of intermediate **VI** *via* transition state **TSII**. 1,2-Addition of Ni(II)-H and imine preferentially formed intermediate **VII**s with an energy demand of 33.2 kca/mol, which is 3.8 kcal/mol lower than the generation of intermediate **VII**$_R$, implying an accessible pathway to generate desired (*S*)-product. Subsequently, there are two possible pathways for the protonation of the intermediate **VII**s, which can re-coordinate with AcOH *via* transition state **TSV**s with a barrier of -8.5 kca/mol or protonate with H_2 *via* transition state **TSVI**s by 22.0 kca/mol energy barrier. The former pathway is more possible attributed to its lower energy, which is consistent with the experimental results and isotope labelling shown in Scheme 4.

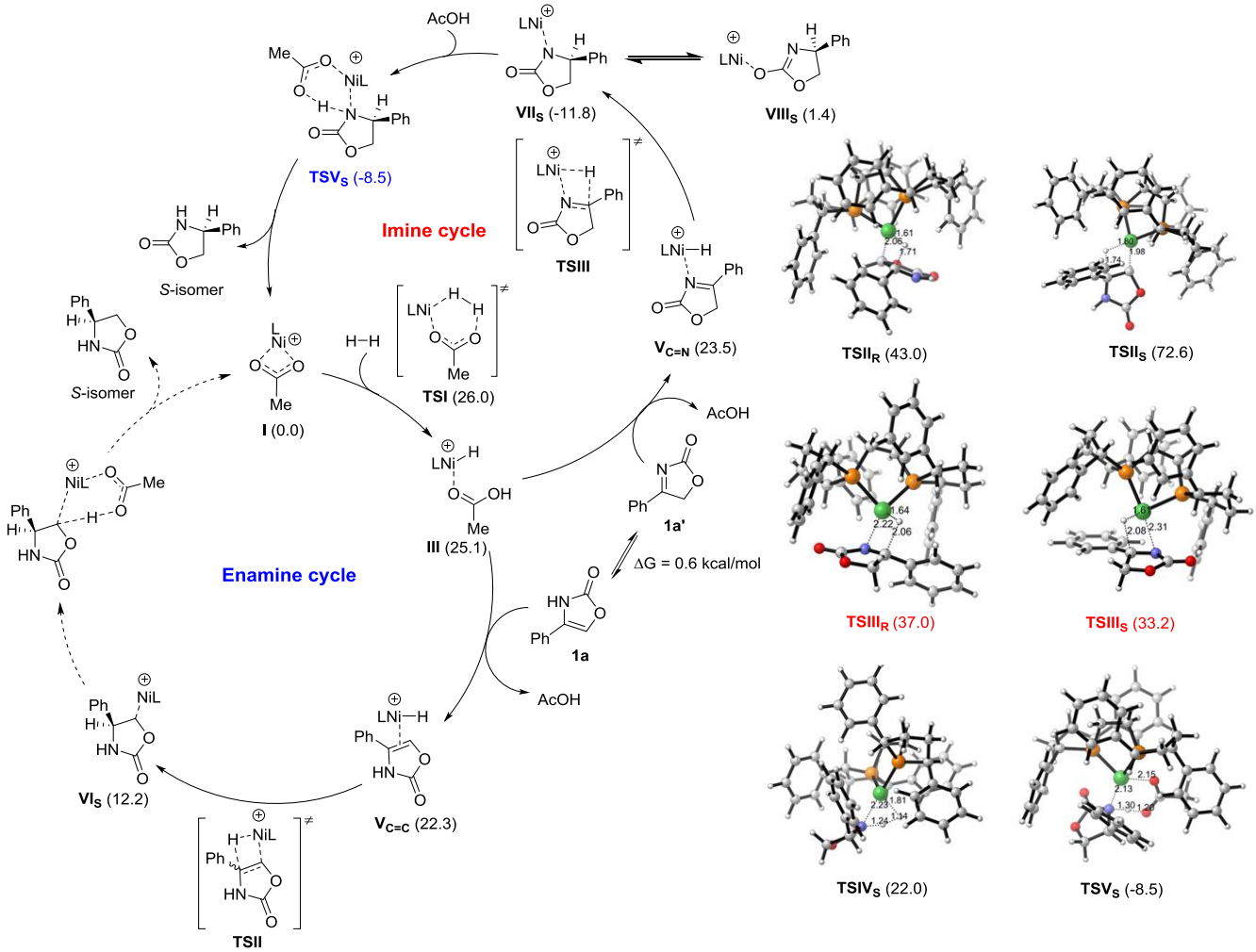
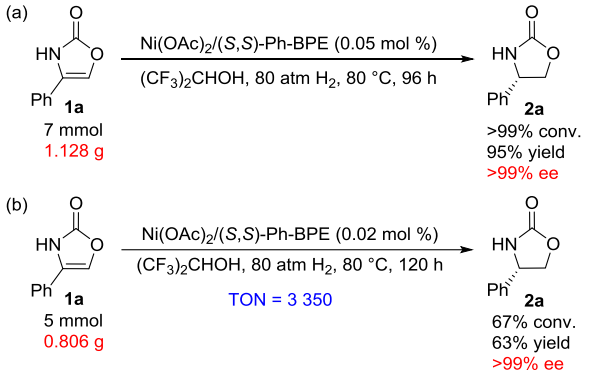


Figure 4. DFT-calculated reaction energy profile for the proposed catalytic cycle for Ni-catalyzed asymmetric hydrogenation of 2-oxazolones (ΔG: kcal·mol^{-1}).

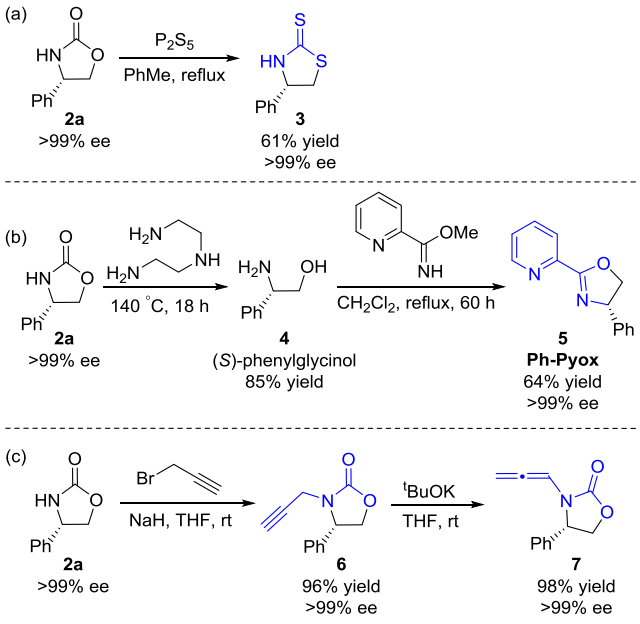
In order to demonstrate the synthetic application potentiality of this methodology, the gram-scale Ni-catalyzed asymmetric hydrogenation of model substrate **1a** was performed smoothly. As shown in Scheme 6a, this asymmetric hydrogenation with 7 mmol model substrate **1a** could be proceeded efficiently in the presence of 0.05 mol% catalyst loading (S/C = 2 000), which led to the desired product **2a** with full conversion, 95% yield and >99% ee. Moreover, the gram-scale reduction were also implemented well with only 0.02 mol% catalyst loading (S/C = 5 000) with moderate conversion and excellent enantioselectivity (Scheme 6b, 67% conversion, 63% yield, >99% ee, TON = 3 350). These results exhibited the practical potentiality of this catalytic synthetic protocol.

Scheme 6. Gram-scale and high TON of Ni-catalyzed asymmetric hydrogenation of **1a**.



The hydrogenation products chiral 2-oxazolidinones are important intermediates in asymmetric synthesis, several transformations were further carried out to construct a series of significant chiral compounds. The compound **2a** was easily treated with P_2S_5 to generate (*S*)-4-phenylthiazolidine-2-thione **3** with 61% yield and no erosion of ee value (Scheme 7a).[16] The enantioenriched (*S*)-Phenylglycinol **4** was efficiently afforded by the cleavage of compound **2a** in the presence of diethylenetriamine, which is an important intermediate in the field of asymmetric synthesis. For example, it can be further converted to chiral pyridine-oxazoline (Pyox) ligands without decrease of ee value, such as Ph-Pyox **5** (Scheme 7b).[17] The hydrogenation product **2a** also can be alkylated with propargyl bromide followed by base-induced isomerization to obtain chiral allenamide **7**, which was versatile synthon in organic synthesis and involved various types of reactions.[18] For example, it can be went through inverse demand [4+2] cycloaddition reactions with heterodienes to prepare highly functionalized pyranyl heterocycles.[18b]

Scheme 7. Synthetic transformations of hydrogenation product **2a**.



In conclusion, we have developed a general and direct method for the preparation of a variety of enantioenriched 2-oxazolidinones through Ni-catalyzed asymmetric hydrogenation of 2-oxazolones with high yields and excellent enantioselectivities (95%-99% yields, 97%->99% ee, almost all products with >99% ee). In addition, the linear effect reaction results disclosed that there should be no catalyst self-aggregation or ligand-substrate agglomeration in the catalytic system. More significantly, deuterium labelling studies, control experiments and DFT calculations were conducted to reveal a reasonable catalytic mechanism for this hydrogenation, which indicated that there should be existed an equilibrium between our substrate enamine and its isomer imine in the reaction process, and the imine isomer worked as the more preferred substrate. The synthetic utility of this protocol was further demonstrated by a gram-scale hydrogenation in the presence of very low catalyst loading (TON = 3 350). A series of synthetic transformations have been easily conducted to provide some other important organic compounds, such as chiral dihydrothiophene-2(3H)-thione, amino alcohol, oxazoline ligand and allenamide.

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Notes

The authors declare no competing financial interest.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge *via* the Internet at http://pubs.acs.org.
Experimental procedures and compound characterization (PDF) are attached.

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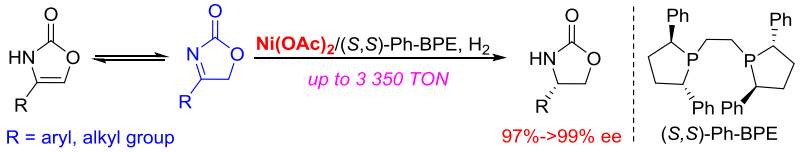
cheap transition metal nickel catalytic system



R = aryl, alkyl group

97%->99% ee

(*S*,*S*)-Ph-BPE

- cheap transition metal Ni-catalyzed system
- reasonable catalytic mechanistic explanation
- excellent reactivity and enantioselectivity
- mild reaction condition
- wide substrate scope
- gram-scale synthesis