Organic LETTERS

Letter

Cite This: Org. Lett. 2018, 20, 2143−2147

pubs.acs.org/OrgLett

Brønsted-Acid-Promoted Rh-Catalyzed Asymmetric Hydrogenation of N-Unprotected Indoles: A Cocatalysis of Transition Metal and Anion Binding

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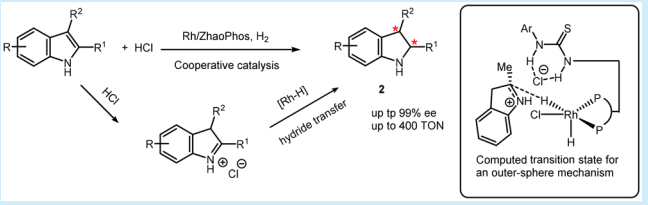
Supporting Information

ABSTRACT: The incorporation of Brønsted acid, thiourea anion binding, and transition metal catalysis enables an efficient method to synthesize chiral indolines via hydrogenation of indoles. Catalyzed by a rhodium/ZhaoPhos complex, asymmetric hydrogenation of unprotected indoles is performed smoothly with excellent enantioselectivities (up to 99% ee, up to 400 TON). Brønsted acid HCl activates indoles to form iminium ion intermediates. Mechanistic studies support the assumption that anion binding plays a crucial role as a secondary interaction. DFT calculations reveal an outer-sphere mechanism in this chemical transformation.



A proton is the simplest and a powerful catalyst. The last two decades have witnessed the prosperity of Brønsted acid catalysis.[1] Asymmetric Brønsted acid catalysis has been demonstrated as a powerful tool in organic synthetic methodologies.[2] In the meanwhile, thiourea hydrogen bonding, with unique characteristics, such as moderate bonding energy and directionality,[3] plays an important role in the field of organocatalysis. The combination of thiourea/urea derivatives and simple Brønsted acids offers a broader acidity range than chiral phosphoric acids. Moreover, tunable substituents on bifunctional thiourea/urea catalysts can introduce many kinds of secondary interactions, such as cation−π interaction and π−π stacking[3c,d,4] (Figure 1). The strategy of cooperative catalysis emerged in recent years, aiming to combine two or more catalytic centers to achieve a single reaction.[5] The integration of transition-metal-catalyzed hydrogenation and small-molecule organocatalysis has shown its potential application in synthetic chemistry.[6]

We recently developed a bisphosphine-thiourea ligand, ZhaoPhos.[7] Within this ligand, a covalent linker connects a ferrocene-based bisphosphine unit with a thiourea moiety (Figure 1). We aimed to utilize the hydrogen bonding between the thiourea and substrate to introduce a secondary interaction, enabling chemical transformations with high enantioselectivities. The hydrogenations of nitroolefins,[7,8] N-unprotected iminium ions,[9] α,β-unsaturated carbonyl compounds,[10] isoquinolines, and quinolines[11] are among its successful applications in asymmetric catalysis.

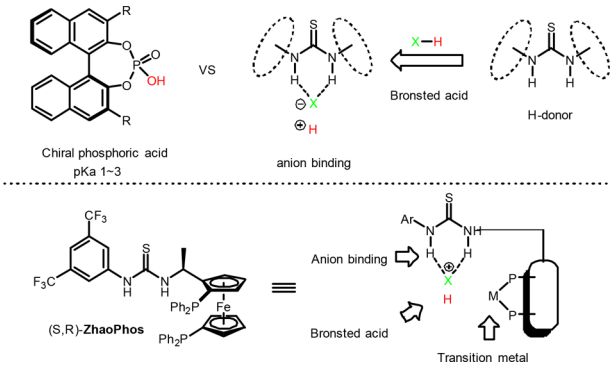


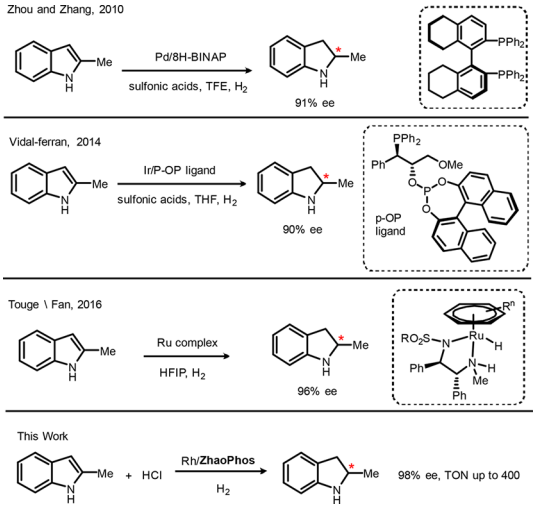
Figure 1. Chiral Brønsted acid catalysis and thiourea anion binding with simple Brønsted acid and Zhaophos.

Chiral indolines are ubiquitous N-heterocycles. This structural motif could be widely found in natural alkaloids and drugs.[12] Efficient synthetic methods to prepare optically pure indolines are in high demand. Compared with other synthetic approaches, hydrogenation of indoles is a straightforward method to obtain chiral indolines (Scheme 1). N-

Received: January 29, 2018
Published: March 30, 2018

DOI: 10.1021/acs.orglett.8b00312
Org. Lett. 2018, 20, 2143−2147

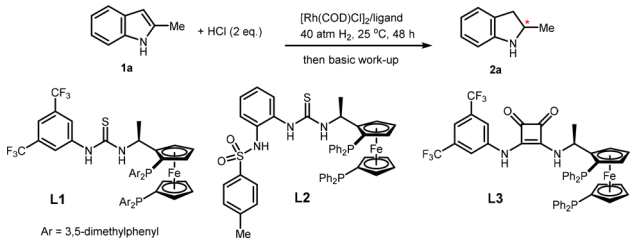
Scheme 1. Asymmetric Hydrogenation of N-Unprotected Indole



Protected indoles have been successfully reduced with ruthenium, iridium, or rhodium complexes.[13] However, the removal of protecting groups requires extra steps and leads to loss of yields, thus increasing the cost for synthetic chemistry. Due to their unique nature,[13] N-unprotected indoles are still a challenging class of hydrogenation substrates. The limited successful examples for unprotected indoles were reported with palladium,[14] iridium,[15] and ruthenium.[16] In these cases, either the relatively moderate enantioselectivity or the use of expensive fluorinated alcohol limits their application in industry. Therefore, we were looking forward to developing a simple and economic synthetic method to afford chiral indoles with excellent enantioselectivities and lower cost.

We envisioned that a strong Brønsted acid could activate this kind of aromatic substrates, while the thiourea moiety of the ligand forms a secondary interaction with the substrates. Based on this theoretical rationale, we initiated our research with hydrogenation of 2-methylindole with (*S*,*R*)-ZhaoPhos and $[Rh(COD)Cl]_2$. Hydrogen chloride in diethyl ether solution (2 M) was introduced as the Brønsted acid. After screening of solvents, we found that dichloromethane and 1,2-dichloroethane gave the highest conversion with the highest enantiomeric excess (Table 1, entries 7 and 8). ^{1}H NMR analysis showed no byproducts (e.g., dimerization products), which are usually found in acidic conditions. Diethyl ether, however, is extraordinarily volatile, and therefore, its HCl solution is difficult to handle and measure in a glovebox. In addition, the concentration of HCl in ether can hardly be maintained in the reaction condition. Isopropanol and acetic acid, with much higher boiling point, might be desirable alternatives. When we applied HCl (5 M) in isopropanol, the conversion was driven up to nearly 100% with the retention of high enantioselectivity (Table 1, entry 9). Finally, hydrochloric acid in acetic acid was chosen to be the acid source (entry 10, 99% conversion and 98% ee). [For further acid screening and the rationale, please see Supporting Information.] A series of analogues of ZhaoPhos were prepared and tested afterward. They did not show superiority to ZhaoPhos (**L1**, **L2**, and **L3**). This reaction was conducted smoothly with catalyst loading as low as 0.25% (entry 14), giving a turnover number of approximately 400. In addition, the equivalent of hydrogen chloride to indole substrate is wide-ranging.[17] These advantages

Table 1. Condition Optimization for 2-Methylindole[a]



entry	ligand	solvent	conversion[b]	ee[c]
1	(*S*,*R*)-ZhaoPhos	MeOH	56%	27%
2	(*S*,*R*)-ZhaoPhos	i-PrOH	>99%	60%
3	(*S*,*R*)-ZhaoPhos	CF_3CH_2OH	21%	84%
4	(*S*,*R*)-ZhaoPhos	toluene	26%	91%
5	(*S*,*R*)-ZhaoPhos	THF	14%	84%
6	(*S*,*R*)-ZhaoPhos	1,4-dioxane	trace	N.D.
7	(*S*,*R*)-ZhaoPhos	DCM	76%	94%
8	(*S*,*R*)-ZhaoPhos	1,2-DCE	71%	95%
9[d]	(*S*,*R*)-ZhaoPhos	DCM	>99%	95%
10[d]	**L1**	DCM	68%	89%
11[d]	**L2**	DCM	65%	80%
12[d]	**L3**	DCM	0	N.D.
13[e]	(*S*,*R*)-ZhaoPhos	DCM	99%	98%
14[f]	(*S*,*R*)-ZhaoPhos	DCM	97%	98%
15[g]	(*S*,*R*)-ZhaoPhos	DCM	0	N.D.

[a]Reaction condition: **1a** (0.1 mmol) in 1.0 mL of solvent, **1a**/$[Rh(COD)Cl]_2$/ligand ratio = 100/0.50/1.0, 0.1 mL of HCl (2 M) in Et_2O solution was added. [b]Conversion was determined by ^{1}H NMR analysis, and no side product was observed. [c]ee was determined by GC with a chiral stationary phase. [d]0.04 mL of HCl (5 M) in *i*-PrOH solution was added. [e]0.2 mL of HCl (1 M) in AcOH solution was applied. [f]0.25 mol % of Rh catalyst. [g]No acid was added.

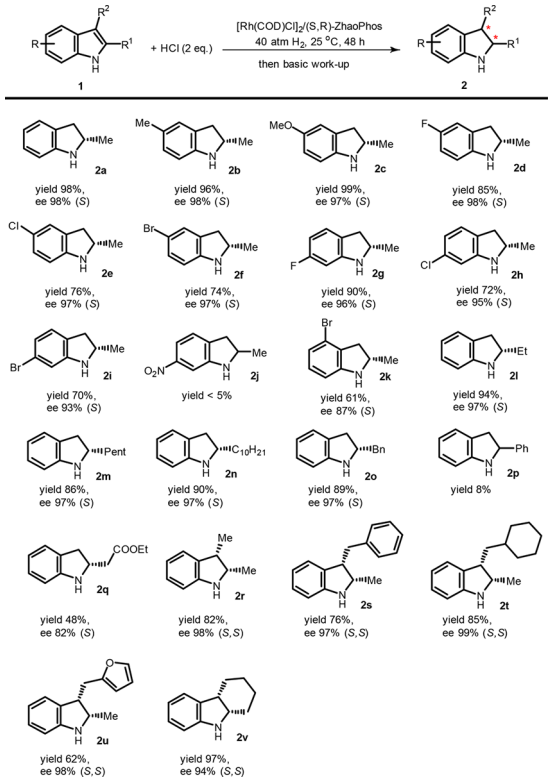
make the ZhaoPhos/Rh catalytic system easy in organic synthesis communities. However, without Brønsted acid HCl, no product was observed, leading to almost 100% recovery of starting material (entry 15).

The substrate scope of this chemical transformation was explored under the optimized conditions (Scheme 2). By adding hydrogen chloride in acetic acid as the Brønsted acid source, 2-monosubstituted indoles and 2,3-disubstituted indoles were hydrogenated smoothly with high enantioselectivities (82% ~ 99% ee). Various substituents at the C-2 position or on the benzene ring brought no significant influence on the enantioselectivity, while the yields vary from case to case. Due to the extraordinary electron-withdrawing effect, the nitro group on the fused benzo ring may cause difficulty in the protonation step, leading to a low yield (**2j**). Substrate **2p** remains a challenge, and this might be caused by a highly stable enamine structure conjugate with phenyl on the 2-position, which is difficult to protonate. 2,3-Disubstituted indoles were also hydrogenated successfully with both high diastereoselectivities (>25:1) and high enantioselectivities.

In order to gain insight into the reaction pathway, isotope labeling experiments (Scheme 3) were conducted. When the reaction was performed in deuterated solvent with hydrogen gas, D atoms were located only at the C-3 position and H atoms at the C-2 position. When regular solvents and deuterium gas were applied, D atoms were located exclusively at the C-2 position, and no significant signal of D atoms was observed at the C-3 position. These results suggested that it is the C═N bond, rather than C═C, that is hydrogenated. A

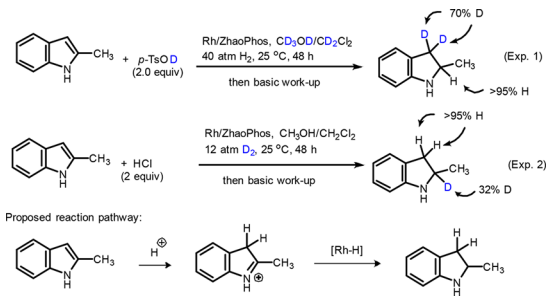
DOI: 10.1021/acs.orglett.8b00312
Org. Lett. 2018, 20, 2143−2147

Scheme 2. Substrate Scope for Asymmetric Hydrogenation of Indoles[a]



[a]Reaction condition: **1** (0.1 mmol) in 1.0 mL of solvent, **1**/[Rh(COD)Cl]$_2$/ligand ratio = 100/0.50/1.0; isolated yields ee's were determined by HPLC with a chiral stationary phase.

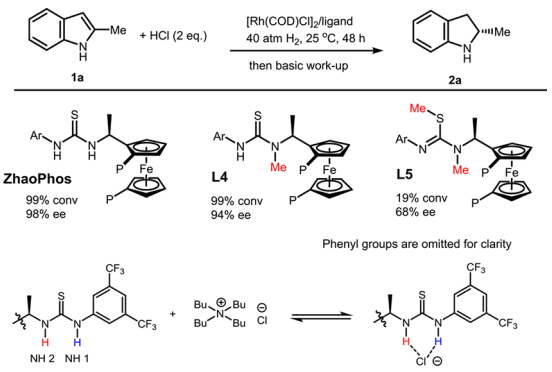
Scheme 3. Deuterium Labeling Experiments and Proposed Reaction Pathway



protonation and the following enamine−iminium transformation probably occur prior to the hydrogenation. A noteworthy finding is the reduced abundance of the deuterium atom at the 2-position in exp. 2, which is probably caused by H/D exchange.[18]

The anion binding of ZhaoPhos with the chloride ion was already observed in our previous NMR studies.[9,11] Control experiments were conducted to examine the cooperation of the thiourea moiety and the bisphosphine scaffold. Each unit of ZhaoPhos was demonstrated to be necessary for efficient asymmetric hydrogenation of 2-methylindole. [For experimental details of ligand evaluation, see SI.] Substitution of the less acidic proton in the thiourea with the methyl group (Scheme 4, **L4**) led to only a minor decrease of ee. Replacement of both protons (**L5**), however, lead to a sharp decrease in both conversion and ee. We assume that the more acidic proton in

Scheme 4. Control Experiments to Demonstrate the Importance of Thiourea



the thiourea dominates the anion binding, while the less acidic one contributes much less.[19] Counterion effect was also examined:[20] fluoride anion dose not bring a significant influence to this asymmetric reaction, while bromide and iodide ions lower both the reactivity and enantioselectivity. These results demonstrated that the thiourea−chloride anion binding plays a crucial role in this chemical transformation. Further investigation on binding manner between ZhaoPhos and the chloride ion was undertaken. A Job plot was drawn, and the curve suggests a 1:1 binding pattern (Figure 2).[21] In addition, high-resolution mass spectroscopy supports this ZhaoPhos−chloride ion complex.[22]

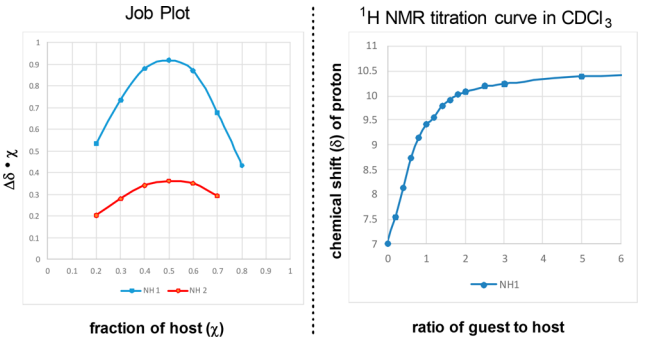
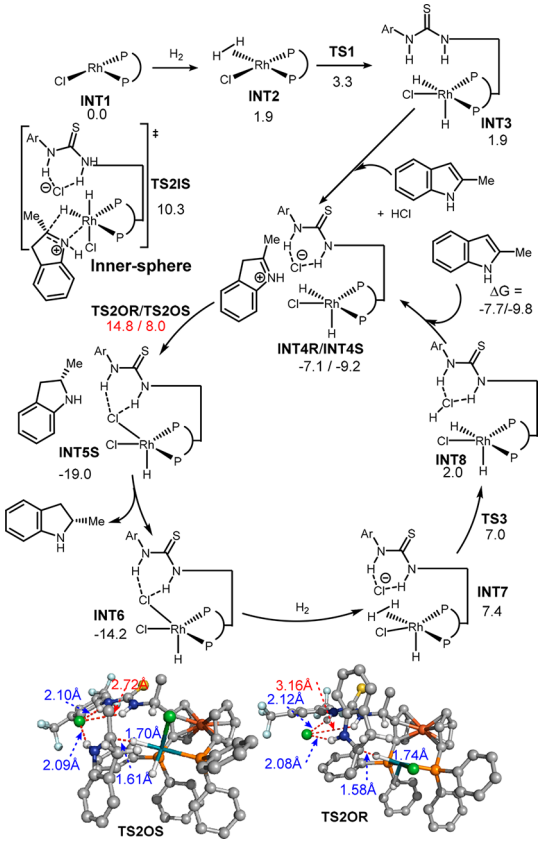


Figure 2. Job plot and NMR titration curves.

To gain insight into the reaction mechanism, DFT (PCM B3LYP-D3/def2-SVP method) calculations have been performed by using the Rh(I)/ZhaoPhos complex and substrate **1a**. The computed possible pathway was initiated with oxidative addition of H_2 to the Rh(I) to form an active Rh(III) dihydride intermediate. A five-coordinate Rh(III) is less usual than an octahedral one in homogeneous hydrogenation reaction,[23] but it will be highly crowded (much higher in energy) if another ligand is introduced in this rhodium complex. After the protonation of indole by HCl, a catalyst−substrate complex is formed (**INT4**). Hydride transfer then preferentially occurs to the *Re*- face at C-2 of the protonated indole in an outer-sphere manner[24] (**TS2OS**). **TS2OS** is computed to be lower in free energy than **TS2IS** (inner-sphere) and **TS2OR** by 2.3−6.9 kcal/mol in solution, partly due to a larger distortion of the metal−ligand part in **TS2OR** (Scheme 5 and Figure S1). The chloride ion forms hydrogen bonds with the thiourea of ZhaoPhos and the protonated indole NH group in **TS2OS**. After dissociation of indoline and coordination of another H_2

DOI: 10.1021/acs.orglett.8b00312
Org. Lett. 2018, 20, 2143−2147

Scheme 5. Proposed Possible Mechanism with Computed Relative Free Energies (kcal·mol^{-1}) by the B3LYP-D3 Method in Solution



molecule, the chloride ion facilitates heterolytic cleavage of dihydrogen to regenerate the active dihydride species and HCl, which was computed to be the rate-determining step. Our computational results are qualitatively consistent with the experimental observations and support the cooperative effect of Rh, Brønsted acid, and anion binding in the asymmetric hydrogenation. However, other possible models, such as the one involving the electrostatic interaction between an anionic Rh complex and the cationic indolinium substrate,[24b,25] could not be excluded.

In summary, we developed an efficient catalytic system that works well under acidic conditions. This method was successfully applied to synthesize chiral indolines. Catalyzed by a Rh/ZhaoPhos complex, various 2-substituted and 2,3-disubstituted indoles were hydrogenated with high enantioselectivities. By employing a Brønsted acid HCl, an indolinium ion active intermediate is formed and reduced afterward. Thiourea−chloride anion binding proved to be crucial for high enantioselectivity and reactivity. DFT calculation studies suggested an outer-sphere mechanism in the hydrogenation step.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00312.

Experimental and computational details, characterization data, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful for Prof. Warmuth's constructive discussion about hydrogen bonding, Mr. Yang Gao's technical support, and Dr. Tian Zhou's computational support for modeling study (all at Rutgers University). We gratefully acknowledge the financial support from the NSFC and SUSTech.

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DOI: 10.1021/acs.orglett.8b00312
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DOI: 10.1021/acs.orglett.8b00312
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