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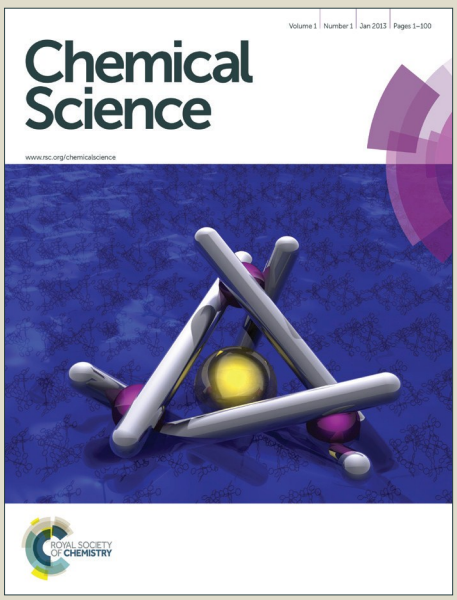

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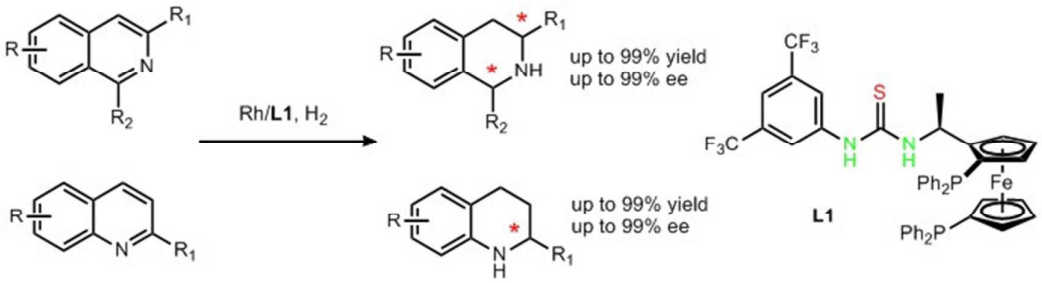
Catalyzed by a Rh/bisphosphine-thiourea(**L1**) complex, isoquinolines and quinolines are hydrogenated with high conversions and high enantioselectivities.



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ARTICLE

Strong Brønsted acid promoted asymmetric hydrogenation of isoquinolines and quinolines catalyzed by a Rh-thiourea chiral phosphine complex via anion binding†

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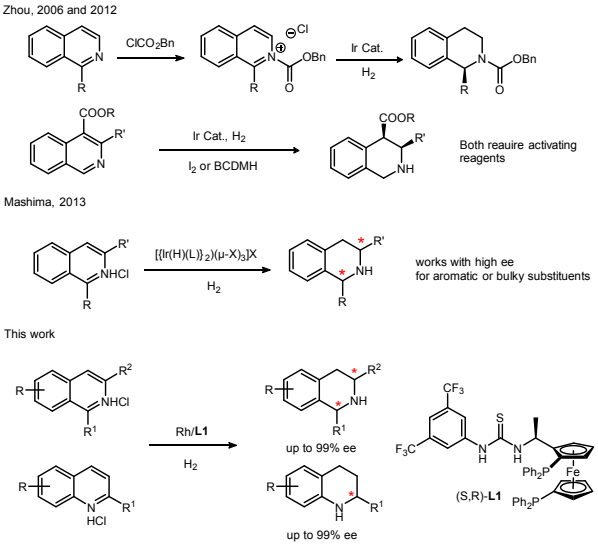
Rhodium catalyzed asymmetric hydrogenation of both isoquinolines and quinolines provides a new method to synthesize chiral tetrahydroisoquinolines and tetrahydroquinolines. By introducing strong Brønsted acid HCl, anion binding between the substrate and the ligand was established to achieve high reactivity and high enantioselectivity (up to 99% conversion and 99% ee). NMR study suggests an anion binding between the catalyst and the substrate. Deuterium labeling experiments reveal a plausible reaction pathway.

Introduction

As one of the important non-covalent interactions in nature, especially in biological system, anion binding has been demonstrated as a powerful tool in organocatalysis. [1] Triggered by the pioneering work done by Jacobsen and other groups, many successful asymmetric catalytic systems involving anion binding have been developed in recent years. [2] On the other hand, utilizing the secondary interaction has been one of the fundamental ideas in catalyst design, which combines more catalytic centers (transition metal catalysis, organocatalysis and enzyme catalysis) in single molecules to provide an efficient chiral environment. Inspired by this strategy, we recently developed a novel ferrocene-thiourea chiral bisphosphine ligand (**L1**). Through a covalent linker, cooperation of transition metal catalysis and organocatalysis could be achieved. This strategy has been successfully applied in rhodium-catalyzed asymmetric hydrogenation of nitroalkenes and unprotected iminiums. [3,4,5] Control experiments implied that the covalent linker was essential for high activities and enantioselectivities. [4,5]

Tetrahydroquinolines (THQs) and tetrahydroisoquinolines (THIQs) are an important family of biologically active molecules, including natural alkaloids and important pharmaceutical products. [6] Among various synthetic approaches to synthesizing chiral THQs and THIQs, direct hydrogenation, with high atom economy, relatively simple procedure and easy work-up, deserves special attention. To our best knowledge, however, asymmetric hydrogenation of *N*-heteroaromatics, especially isoquinolines, remains a challenging task. [7] Although quinolines have been successfully hydrogenated in several cases, [8] there were only few examples of isoquinolines. Zhou's group used iridium-bisphosphine catalyst to obtain high enantioselectivity, but this transformation needs activation by chloroformate or addition of BCDMH. [9] By introducing chiral phosphoric acid, transfer hydrogenation of isoquinoline was achieved by Zhou in 2014 and *N*-protected 1,2-dihydroisoquinolines were synthesized with moderate enantioselectivities. [10] In 2013, Mashima's group synthesized chiral THIQ using a dinuclear iridium(III)-bisphosphine complex, but the substrate scope is still limited to aromatic or bulky substituents (schemie 1). [11] Isoquinolines with less hindered alkyl substituents on the prochiral carbons are still challenging. Most of these catalysis cases for *N*-heteroaromatics are performed with ruthenium, iridium and palladium complexes. [6] Rhodium was rarely reported in direct



Scheme 1. Asymmetric hydrogenation of isoquinolines

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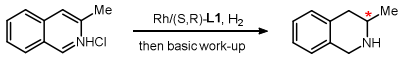
asymmetric hydrogenation of *N*-heteroaromatics with high turnovers and ee's. [7] This is in sharp contrast to the broad application of Rh complex in asymmetric hydrogenation of olefins, enamides and imines. [12]

As continuing research on the ferrocene-based thiourea chiral phosphine system, we herein report a highly reactive and enantioselective example of rhodium/bisphosphine-catalyzed asymmetric hydrogenation of isoquinolines and quinolines. In this catalysis system, a secondary interaction between the catalyst and the substrates was believed to occur via anion binding of ion-pair intermediates. We envision that the introduction of a strong Brønsted acid such as HCl, brings dual benefits: (1) activating the aromatic ring, [13] (2) establishing a salt bridge between the catalyst and the substrates.

Result and discussion

Table 1, Optimization of condition. [a]



1a 2a

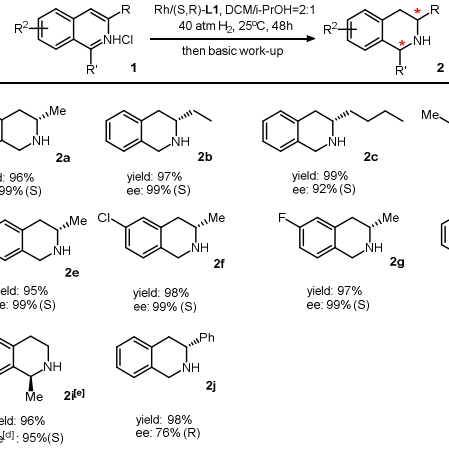
Entry	Metal	Solvent	conversion[b]	ee[c]
1	[Rh(COD)Cl]2	i-PrOH	>99%	70%
2	[Rh(COD)Cl]2	MeOH	85%	30%
3	[Rh(COD)Cl]2	DCM	>99%	92%
4	[Rh(COD)Cl]2	Dioxane	95%	90%
5	[Rh(COD)Cl]2	Dioxane/i-PrOH=2:1	>99%	90%
6[d]	[Rh(COD)Cl]2	DCM/i-PrOH=2:1	>99%	99%
7[d]	[Rh(COD)I]2	DCM/i-PrOH=2:1	99%	93%
8	[Ir(COD)Cl]2	Dioxane/i-PrOH=2:1	>99%	83%

[a] Reaction condition: **1a** (0.1 mmol) in 1.0 ml solvent, **1**/[Rh(COD)Cl]2/**L1** ratio=100/0.5/1, 40 atm H2, 40 °C, 24 h; [b]conversion was determined by ^{1}H NMR analysis, no by product was observed; [c]ee was determined by GC with a chiral stationary phase; [d]performed at 25 °C.

Our study was initiated with 3-methylisoquinoline hydrochloride as a model substrate. The Rh catalyst was prepared *in situ* by mixing the metal precursor $[Rh(COD)Cl]_2$ with (S,R)-**L1**. In accordance with our previous reports, [4,5] this catalysis system is solvent-dependent. After screening of alkyl halide, alcohols and ethers, we found that under 40 atm H_2 pressure at 40 °C, dichloromethane gives the best result (>99% conversion and 92% ee were observed with 1% catalyst loading). In addition to using single solvents, solvent pairs were also tested. The mixture of dichloromethane and isopropanol (2:1, v/v) at 25 °C gives the optimal condition with 99% ee and full conversion. Iridium complex $[Ir(COD)Cl]_2$/**L1** also shows high activity with, but lower enantioselectivity than its Rh counterpart (table 1, entry 5 vs entry 8). Halide effect, which causes considerable difference in some cases,[14] was evaluated as well. Using $[Rh(COD)I]_2$ as a metal precursor resulted in small changes in conversion and enantioselectivity (table 1, entry 6 vs entry 7).

Counterion effects were also investigated. Bromide or iodide anion do not bring significant influence on the conversion or enantioselectivity, while fluoride anion dramatically inhibits this reaction (For more details, see supporting information, Section 6).

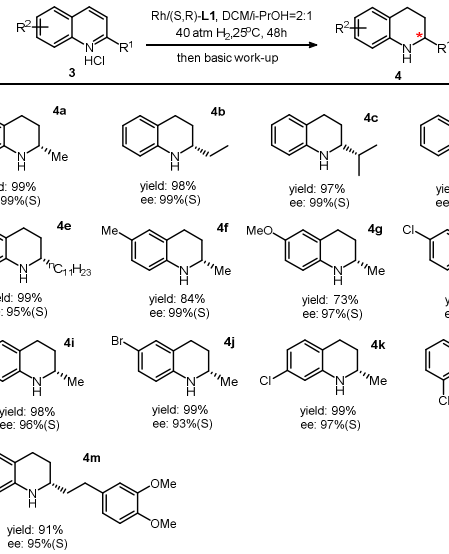
Table 2, Substrate scope for isoquinolines. [a]



[a] reaction condition: **1** (0.2 mmol) in 1.2 ml solvent, **1**/[Rh(COD)Cl]$_2$/**L1** ratio = 100/0.5/1; yield was determined with isolated THIQ products; ee was determined by GC or HPLC with a chiral stationary phase; [e]performed in Dioxane/iPrOH = 2:1(v/v) at 60 °C under 60 atm H_2 with 2% catalyst.

Then we applied this method to synthesize various chiral THIQs. Different alkyl substituents at 3-position or benzo ring do not show obvious changes in yields and enantioselectivities. Aryl substituent, such as phenyl group, on 3- position leads to full conversion and moderate enantioselectivity (76% ee). In addition to 3-alkyl isoquinolines, 1-methylisouinoline was also hydrogenated with high enantioselectivity (Table 2).

Table 3, Substrate scope for quinolines. [a]



[a] reaction condition: **3** (0.2 mmol) in 1.2 ml solvent, **3**/[Rh(COD)Cl]$_2$/**L1** ratio = 100/0.5/1; yield was determined with isolated THQ products; ee was determined by GC or HPLC with a chiral stationary phase.

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As far as we know, few catalysis systems can be applied in asymmetric hydrogenation of both isoquinolines and quinolines with both high turn-overs and excellent enantioselectivities. [7, 8] Then a question merged to us: can this synthetic protocol be used to synthesize chiral THQs with high ee? By employing the optimized condition (DCM/iPrOH=2:1, v/v) in the case asymmetric hydrogenation of isoquinolines, we found that the enantioselectivity was dramatically increased to 99% ee[5]. This observation, in return, suggests that this thiourea-Rh-bisphosphine catalysis system is highly solvent-dependent. Substrate scope of asymmetric hydrogenation of quinolines is broad. High enantioselectivities have been obtained with various substituents (Table 3).

The potential application of this synthetic protocol was estimated: we have scaled up this asymmetric hydrogenation reaction into gram scale. No significant sign of changes in conversion or enantioselectivity was observed with 0.5% catalyst loading. [15] In addition, the role of strong Brønsted acid HCl is essential in this chemical transformation. Without HCl, no hydrogenation product was observed. [16]

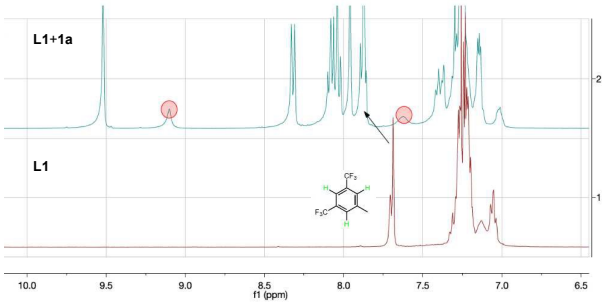
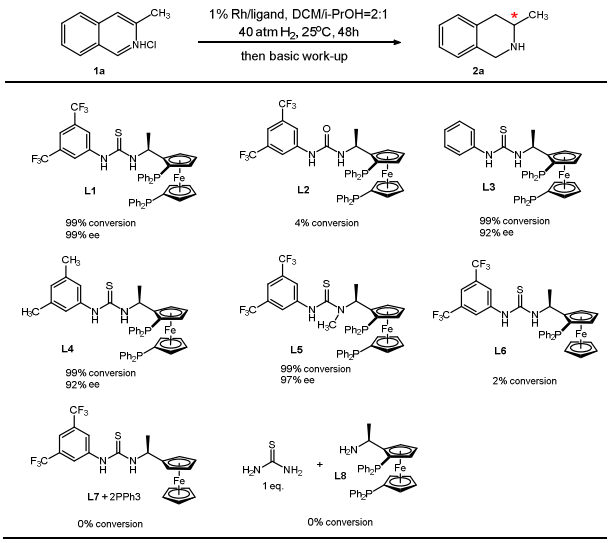


Figure 1. NMR study for the interaction of L1 and 1a.

To gain evidence of a secondary interaction of **L1** with chloride anion of substrates, we mixed **L1** and **1a** (3 eq.) in $CDCl_3$. The ^{1}HNMR showed similar obvious changes of chemical shifts (Figure 1). The original thiourea N-H peaks (hidden in the aromatic peaks within 7.3~7.0 ppm) shift downfield to 9.10 and 7.62 (marked with red circles in Figure 1). In addition, the three protons on the 3,5-bis(trifluoromethyl)phenyl group also shift downfield a little by 0.19 ppm (marked by arrow in Figure 1). These changes of chemical shifts, consistent with the case of **L1** with Cl^- from TBAC, [5] suggest the anion binding between the ligand and the substrate.

We synthesized a series of analogues of **L1** and conducted control experiments to evaluate the collaboration manner of each unit of **L1** (Table 4). Urea bisphosphine ligand **L2** only gives trace product, and this sharp contrast suggests the crucial role of thiourea moiety in **L1**. Compared to H (**L3**) and methyl (**L4**), more electron-withdrawing trifluoromethyl group at 3- and 5- position on the phenyl ring increases the enantioselectivity, which is probably due to the stronger acidity of N-H proton on the thiourea. After *N*-methylation of the less acidic thiourea N-H proton, enantioselectivity results in a minor decrease. This observation reveals that the more acidic thiourea N-H proton contributes mostly in anion binding with chloride. Furthermore, monophosphine ligand **L6** and the mixture of ferrocene-thiourea compound **L7** with triphenylphosphine can hardly catalyzed the hydrogenation reaction. On the other hand, the mixture of thiourea molecule and bisphosphine-Ugi's amine **L8** failed to show catalytic activity. These results (**L1** vs **L7**/PPh_3 and **L8**/thiourea) demonstrate the importance of a covalent incorporation of bisphosphine moiety and thiourea. The idea of secondary offers an alternative strategy for asymmetric hydrogenation.

Table 4. Ligand evaluation and control experiment.



[a] reaction condition: **1** (0.1 mmol) in 0.6 ml solvent, **1**/[Rh(COD)Cl]$_2$/ligand ratio = 100/0.5/1; conversion was determined by ^{1}H NMR analysis; ee was determined by GC with a chiral stationary phase.

In order to obtain insight of this transformation, deuterium labeling experiments was conducted. First, 3-methylisoquinoline hydrochloride was reduced by deuterium gas in methanol (Scheme 2, Eq. 1). D atoms are added only at 1- and 3- position respectively. This indicates that the hydrogen atom at 4- position of the product comes from the methanol solvent. Second, 3-methylisoquinoline deuterochloride was reduced with hydrogen gas in deuterated methanol (Scheme 2, Eq. 2). Hydrogen atoms are added at 1- and 3- position. The original H at 4- position, however, was exchanged with D, resulting two D atoms at 4- position. This indicates that D atoms at 4- position come from the Methanol-d_4 solvent. A tautomerization is probably responsible for this H-D exchange. Interestingly, H-D exchange also occurs on the methyl group (53% original H was replaced by D). This observation, in return, proves the existence of tautomerization. Based on this results, we proposed a possible path in this transformation (Scheme 2). After addition of a hydrogen at 1- position, the substrate is partially reduced, leading to conjugate enamine, which could not be further reduced in this rhodium-thiourea-bisphosphine catalytic system. After a tautomerization follows, giving an iminiums intermediate, which could be easily hydrogenated. [5] Another tautomer, a terminal enamine is less preferred than its conjugate counterpart, because the latter is more stable. This explains why H atoms on methyl group was partially replaced

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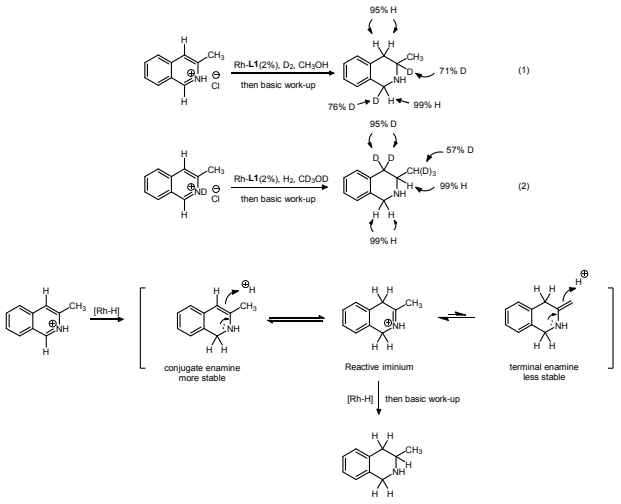
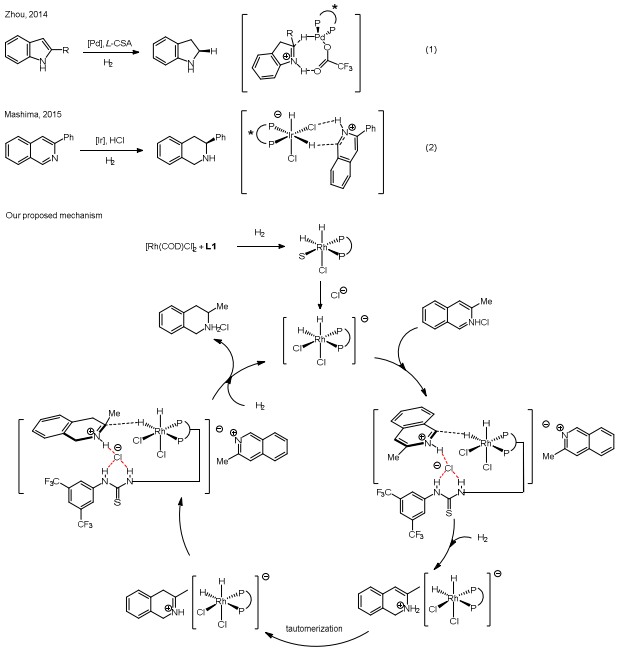
by D (but H at 4- position is almost replaced by D). (For details, please see supporting information.)



Scheme 2. Deuterium labeling experiment and proposed transformation path.

Recent reports revealed an outer-sphere mechanism for bisphosphine-transition metal catalyzed hydrogenation. In 2014, Zhou reported a series of detailed studies on palladium catalyzed asymmetric hydrogenation of protonated indoles. After careful evaluation, hydride transfer from a Pd-H complex to an iminium intermediate was proposed. (Scheme 3, Eq. 1) [17] In 2015, Mashima's group proposed a mechanism on iridium-catalyzed asymmetric hydrogenation of isoquinoline hydrogen halide salts. Strong experimental evidence was presented to favor an outer-sphere mechanism, in which hydrogen bonding between Ir-Cl complex and N-H proton was proposed. (Scheme 3, Eq. 2) [18] Both of these mechanism studies above were focused on hydrogenation of the halide salts of aromatic compounds. Similarly, the nature of protonated (iso)quinolines suggests that it seems not possible for the substrates to coordinate to the rhodium complex in this case, no matter in a σ-bonding or a π-bonding manner. A hydride transfer mechanism is more possible in this catalytic case, instead of the traditional inner-sphere mechanism that involves the direct coordination of unsaturated bonds to the metal. Based on previous reports and our deuterium labeling experiments, we propose a catalytic cycle to explain a plausible outer-sphere mechanism (scheme 3). After oxidative addition of H_2, a dihydride rhodium (III) complex is formed. The chloride anion of the isoquinolinium salt will bind with the hydrogen of thiourea, forming a Rh dichloro-dihydride anionic complex. The equatorial hydride of the active rhodium complex will be transferred to the isoquinolinium due to strong trans effect of a phosphine. After this 1,2- addition, a tautomerization step will follow, giving an iminium intermediate. The iminium, instead of an enamine, will undergo the insertion of hydride from a rhodium dihydride complex. The chirality of the product is originated in this step. Another molecule of hydrogen will react and form the active rhodium dihydride species, finishing the catalytic cycle. In order to approve the mechanism of this rhodium catalyzed asymmetric hydrogenation of (iso)quinolinium salts, further study is needed in the future.



Scheme 3. Outer-sphere mechanism in asymmetric hydrogenation of *N*-heteroaromatics.

Conclusions

In summary, we report a successful example of Rh-catalyzed asymmetric hydrogenation of both isoquinolines and quinolines. Compared with previous catalysis systems, this method has broader substrates scope. The strong Brønsted acid HCl activates the *N*-heteroaromatic substrates and introduces anion binding into the catalysis system, which played an important role in this transformation. Deuterium labeling experiments revealed an enamine-iminium tautomerization equilibrium after the first hydride transfer step.

Acknowledgements

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