Asymmetric Catalysis

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Rhodium-Catalyzed Asymmetric Hydrogenation of Unprotected NH Imines Assisted by a Thiourea**

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Abstract: *Asymmetric hydrogenation of unprotected NH imines catalyzed by rhodium/bis(phosphine)-thiourea provided chiral amines with up to 97% yield and 95% ee. ^1H NMR studies, coupled with control experiments, implied that catalytic chloride-bound intermediates were involved in the mechanism through a dual hydrogen-bonding interaction. Deuteration experiments proved that the hydrogenation proceeded through a pathway consistent with an imine.*

Chiral amines are powerful pharmacophores of biologically active molecules for pharmaceuticals and agrochemicals, such as the elastase inhibitor DMP 777, calcimimetic agent Sensipar (Cinacalcet), and type II calcimimetics NPS *R*-568. (Figure 1).[1] As one of the most efficient synthetic approaches, metal-catalyzed asymmetric hydrogenation deserves special attention. Many successful catalytic systems have been developed, including asymmetric reductive amination and asymmetric hydrogenation of enamines and imines.[1–7] However, owing to the complex interactions between catalysts and substrates/products, that is, imine–enamine tautomerization and the *E*/*Z* interconversion of imines, asymmetric hydrogenation of enamines and imines is still a largely underdeveloped area in contrast to the advances of olefins and ketones.[1b] Unprotected NH imines and enamines are attractive but challenging substrates.[3–5] Asymmetric hydrogenation of such substrates eliminates the use of N-protecting groups and has broad potential applications in industry. To date, although there are several successful examples of unprotected enamines in academic research and industrial utilization,[3] the unprotected imines are rarely studied.[4,5] Our group reported the first example of iminium salts[5] involved in a substrate activation strategy[1e,3–7] with well-studied iridium-based catalysts. We aimed to develop a novel and efficient rhodium-based catalytic system for this transformation.

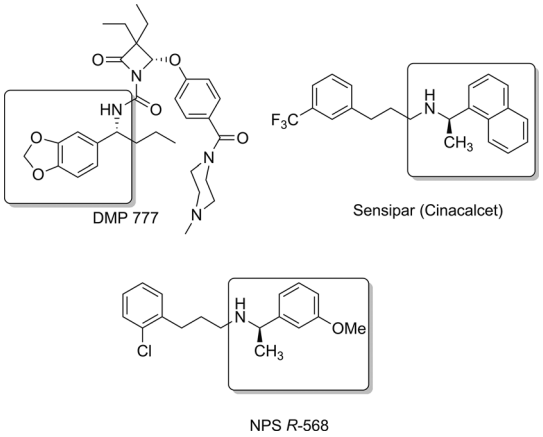

Figure 1. Related drugs (candidates) containing chiral amines.

Thiourea has been widely used as a hydrogen-bond donor in organocatalysis.[8] Most research focuses on the direct activation of neutral substrates by hydrogen bonding while recent studies take advantage of the anion binding of ion-pairing intermediates.[9] Inspired by the strategies developed in organocatalysis[10–12] and our previous research on the rhodium/bisphosphine-catalyzed asymmetric hydrogenation of nitroalkenes assisted by thiourea,[13] we sought to extend anion-binding catalysis to the transition-metal-catalyzed asymmetric hydrogenation. We envisioned that thiourea could interact with a counterion in the catalytic pathway (Figure 2).

Herein, we describe the first example of rhodium/bisphosphine-catalyzed asymmetric hydrogenation of unprotected NH imines, assisted by thiourea, with up to 97% yield and 95% *ee*.

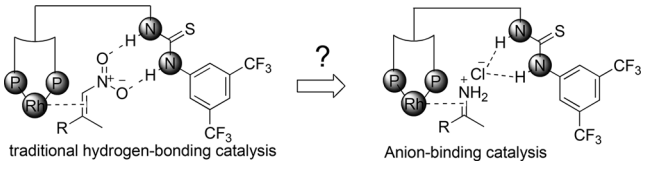

Figure 2. Extension of our rhodium/bis(phosphine) thiourea catalytic system.

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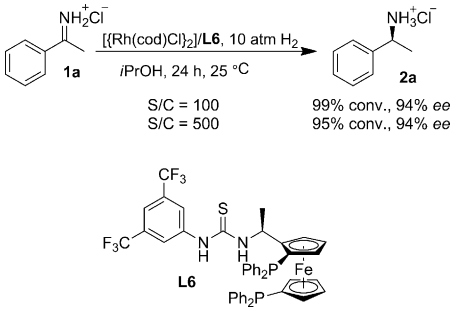
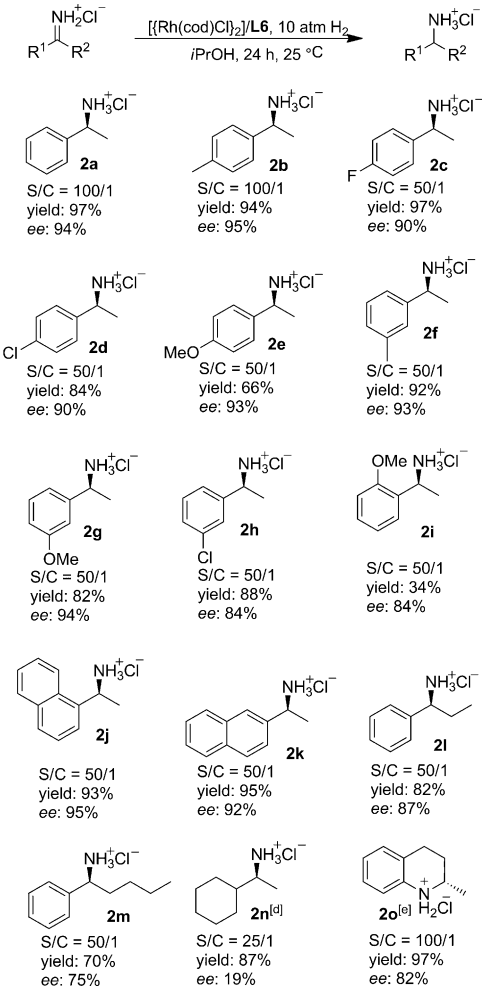


Scheme 1. **1a** (0.1 mmol) and a Rh/L ratio of 1:1.1 in 1.0 mL solvent. The *ee* values and conversion were determined by GC analysis of the corresponding acetamides using a chiral stationary phase.

As we reported previously,[13] the catalytic system was solvent dependent and poor results were given when using iridium, palladium, and ruthenium.[14] In addition, pressures, temperatures, and additives were examined to study the turnover number (TON) limit of this transformation.[14] A 99% conversion and 94% *ee* was observed with 1 mol% catalyst at 25°C under 10 atm H_2 (Scheme 1). Even if 0.2 mol% catalyst was used, 95% conversion and 94% *ee* was obtained. This system provided remarkably higher TONs than our previous iridium/f-Binaphane catalytic system (5 mol% catalyst).[5]

Under the optimized reaction conditions, a variety of NH imines were tested (Scheme 2). Most substrates with *meta* and *para* substitutions on the phenyl ring afforded high yields and enantioselectivities (92–97% yield and 90–95% *ee*). However, the chloro and methoxy group resulted in an obvious decrease of the yields. The *ortho*-methoxy group on the phenyl ring resulted in 34% yield and 84% *ee* (**2i**). 1-naphthyl and 2-naphthyl amines were obtained with 95% and 92% *ee*, respectively (**2j** and **2k**). Changing the R^2 group had a significant effect on the outcome. When R^2 was ethyl, both lower conversion and enantioselectivity were observed (**2l**). As R^2 was changed to a bulkier butyl group, further loss of conversion and enantioselectivity was observed (**2m**). The catalytic system displayed low activity and enantioselectivity for the dialkyl ketimine **2n** and diaryl ketimine.[15] Otherwise, 2-methyl quinolinium chloride was hydrogenated in 97% yield with 82% *ee* at 25°C under 5 atm H_2 with 1 mol% catalyst (**2o**).

To obtain insight into this catalytic system, a series of chiral ligands were prepared and control experiments were undertaken (Table 1). Consistent with our recent report,[13] the rhodium/bisphosphine complex without the (thio)urea motif (**L1**) showed very low activity and enantioselectivity (Table 1, entry 1). The urea **L2** provided 22% conversion and 66% *ee*, which is in sharp contrast to the thiourea **L6** (Table 1, entry 2 versus 6). The CF_3 group on the 3,5-bis(trifluoromethyl)phenyl moiety remained important in the catalytic system (Table 1, entries 3–5).[16] The N methylation of **L6** led to a dramatic decrease of the conversion and enantioselectivity (Table 1, entry 7), which suggested that the NH was involved in the activation of iminium salts and the stereoselectivity of hydrogenation. Furthermore, the low conversion

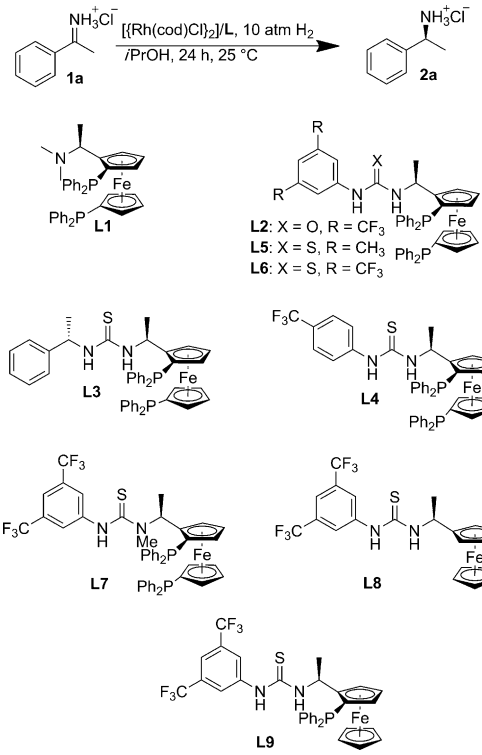


Scheme 2. Substrate scope.[a–c] [a] Reaction conditions: **1** (0.2 mmol) and a Rh/L ratio of 1:1.1 in 2.0 mL solvent. [b] Yield of isolated product. [c] The *ee* values were determined by GC analysis of the corresponding acetamides using a chiral stationary phase. [d] 45°C, 50 atm H_2. [e] 25°C, 5 atm H_2; *ee* value was determined by GC analysis of the free amines using a chiral stationary phase.

and enantioselectivity obtained with monodentate phosphorus ligands implied that the bis(phosphine) moiety was essential (Table 1, entry 9). Importantly, neither the combination of the chiral phosphine with the thiourea, nor the combination of the chiral thiourea with the simple phosphine improved this reaction (Table 1, entry 1 versus 11, and entry 8 versus 10), thus pointing to the importance of the covalent linker for high activity and enantioselectivity.

Different counterions and additives were also investigated (Table 2). When the chloride counterion in **1a** was replaced with trifluoromethanesulfonate, only 20% conversion and 53% *ee* was observed (Table 2, entry 1). Interestingly, the addition of a chloride counterion from LiCl and tetrabutylammonium chloride (TBAC) increased the conversions and enantioselectivities (Table 2, entries 2 and 3). However, the addition of bromide from tetrabutylammonium bromide (TBAB) and iodide counterions from tetrabutylammonium iodide (TBAI) decreased the conversions and enantioselec-

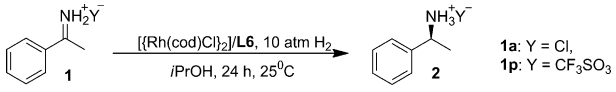
Table 1: Ligands study and control experiments.[a]



Entry	Ligand	Conv. [%][b]	*ee* [%][b]
1	**L1**	2	55
2	**L2**	22	66
3	**L3**	6	11
4	**L4**	72	87
5	**L5**	76	90
6	**L6**	99	94
7	**L7**	26	38
8	**L8**	2	11
9	**L9**	9	84
10[c]	**L8**	5	8
11[d]	**L1**	9	57

[a] Reaction conditions: **1a** (0.1 mmol) and a Rh/L/**1a** ratio of 1:1.1:100 in 1.0 mL solvent. [b] Determined by GC analysis of the corresponding acetamides using a chiral stationary phase. [c] Rh/L/**1a**/Ph_3P = 1:1.1:100:2.2. [d] Rh/L/**1a**/thiourea = 1:1.1:100:1.1.

Table 2: Substrates study and control experiments.[a]



Entry	1	Additive	Conv.[b] [%]	*ee*[b] [%]
1	**1p**	–	20	53
2	**1p**	TBAC	86	94
3	**1p**	LiCl	71	93
4	**1a**	–	99	94
5	**1a**	TBAB	77	90
6	**1a**	TBAI	32	89

[a] **1a** (0.1 mmol) and a Rh/L/**1a**/Additive ratio of 1:1.1:100:100 in 1.0 mL solvent. [b] Determined by GC analysis of the corresponding acetamides using a chiral stationary phase. TBAB = tetra-*n*-butylammonium bromide, TBAI = tetra-*n*-butylammonium iodide.

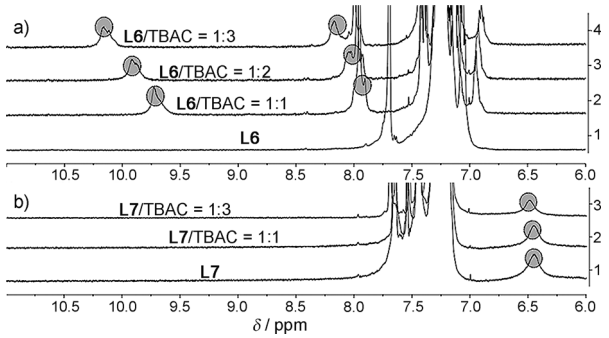
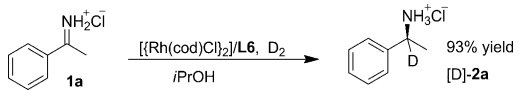


Figure 3. a) ^{1}H NMR spectra of **L6** with TBAC. b) ^{1}H NMR spectra of **L7** with TBAC. The signal for the NH is marked.

tivities (Table 2, entries 4–6). This phenomenon implied that the chloride ion played a crucial role in the catalytic system.

Further information about the reaction was provided by ^{1}H NMR studies of mixtures generated from ligands and TBAC (Figure 3). The addition of varying amounts of TBAC to **L6** in $CDCl_3$ resulted in downfield shifts of the NH proton signals. However, no change was observed for the NH proton signal of **L7**. Analogous experiments employing a series of different ligands gave similar results.[14] This finding was consistent with a dual hydrogen-bonding interaction between the thiourea of the catalyst and chloride ions.[10c,f,12b] This observation, coupled with the fact that optimal yields and *ee* values involved chloride ions, led us to propose that catalytic chloride-bound intermediates were involved in the mechanism through the dual hydrogen-bonding interaction (Figure 2).

To gain further insight into this transformation, the asymmetric hydrogenation was performed under D_2. ^{1}H NMR analysis of the crude reaction mixture showed that **2a** had incorporated deuterium in the α-position (Scheme 3),



Scheme 3. Deuteration experiment.

thus suggesting that the hydrogenation proceeded through a pathway consistent with the imine.[3c,5a,14]

With the ultimate goal being the fast screening of reaction conditions in the future, we initiated collaborative work with the Anslyn group and verified their method to measure *ee* values of chiral amines based on circular dichroism (CD) spectroscopy.[17] Although the accuracy is not ideal (an average absolute error of 9%),[14] it is much faster than the chiral GC analysis and being transitioned to aid in our research.

In conclusion, we report the first rhodium/bis(phosphine) thiourea catalyzed asymmetric hydrogenation of unprotected NH imines. The chiral amines were obtained in high yields and enantioselectivities. Based on the control experiments and ^{1}H NMR studies, we propose that the anion binding

interaction between the thiourea and chloride counterion plays an important role in the catalytic system. Deuteration experiments suggested that the hydrogenation proceeded through a pathway consistent with the imine. Further research on the mechanism of catalysis and other applications is currently under way, as is the use of the high-throughput screening methodology.

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