Asymmetric Hydrogenation

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Facile Synthesis of Chiral Cyclic Ureas through Hydrogenation of 2-Hydroxypyrimidine/Pyrimidin-2(1*H*)-one Tautomers

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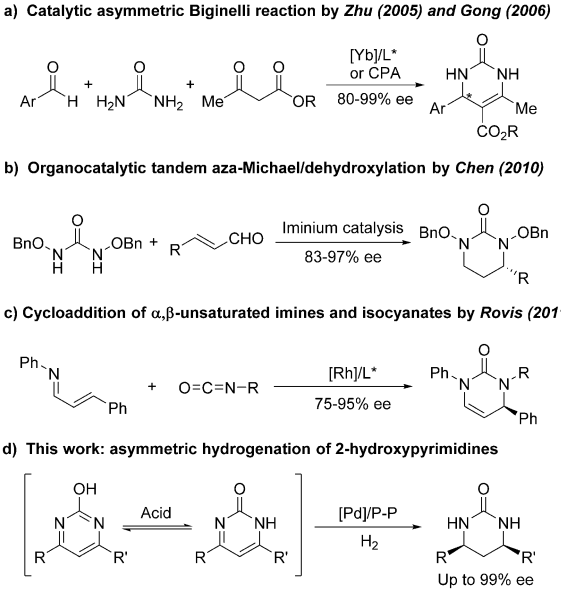
Abstract: *A facile access to optically active cyclic ureas was developed through palladium-catalyzed asymmetric hydrogenation of pyrimidines containing tautomeric hydroxy group with up to 99 % ee. Mechanistic studies indicated that reaction pathway proceed through hydrogenation of C=N of the oxo tautomer pyrimidin-2(1H)-one, acid-catalyzed isomerization of enamine–imine, and hydrogenation of imine pathway. In addition, the chiral cyclic ureas are readily converted into useful chiral 1,3-diamine and thiourea derivatives without loss of optical purity.*

Ureas are commonly found in biologically active compounds, pharmaceuticals, agricultural pesticides, dyes for cellulose fibers, antioxidants in gasoline, as well as chiral catalysts for organic synthesis.[1] Especially, as an important pharmacophore, cyclic urea skeleton has been widely embedded in many bioactive molecules and pharmaceutical agents, such as calcium channel blocker SQ32926,[1d] tubulin inhibitors PPB-SOs[1e] and α_{1a}-receptor antagonist (*S*)-L-771688[1f] (Figure 1).

Traditional syntheses of the chiral ureas often use phosgene or isocyanates which cause tremendous toxicological and environmental problems.[2] The development of environmentally friendly methods to prepare urea-containing compounds without using harmful reagents has attracted considerable attention and obtained certain achievements.[3] However, there are only a few reports on direct asymmetric synthesis of chiral cyclic ureas (Scheme 1). In 2005, Zhu and co-workers described an asymmetric catalytic Biginelli reaction with a chiral ytterbium catalyst, providing chiral cyclic ureas, 3,4-dihydropyrimidinones (DHPMs) in high yields with



Scheme 1. Catalytic asymmetric synthesis of chiral cyclic ureas.

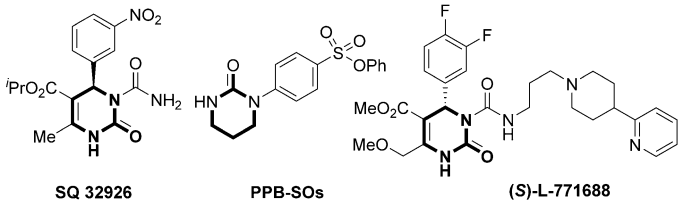


Figure 1. Selected bioactive molecules containing cyclic urea motifs.

excellent enantioselectivities.[4] Shortly after, Gong and co-workers reported the first asymmetric organocatalytic Biginelli reaction catalyzed by a BINOL-derived chiral phosphoric acid catalyst, affording the chiral DHPMs in high enantioselectivities.[5] Notably, in 2010, a method for the asymmetric synthesis of chiral cyclic urea derivatives via an organocatalytic tandem aza-Michael addition–hemiaminal formation and dehydroxylation cascade was successfully developed by Chen and co-workers.[6] Very recently, Rovis' group developed an elegant rhodium-catalyzed [4+2] cycloaddition between α,β-unsaturated imines and isocyanates to generate the chiral DHPMs in good yields and high enantioselectivities.[7] Despite these successful examples, given the great importance of chiral cyclic ureas, it remains indispensable to find new effective approaches to prepare structurally diverse chiral cyclic ureas derivatives with excellent enantioselectivity.

Asymmetric hydrogenation of heteroaromatics is one of efficient methods for synthesis of chiral heterocycles. Although catalytic asymmetric hydrogenation of heteroarenes has been well documented,[8] most successful examples in this field are limited to bicyclic and a few of monocyclic

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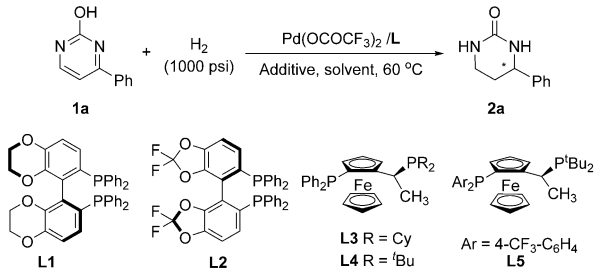
heteroaromatic compounds.[9] Particularly, six-membered N-aromatics, such as pyridine, pyrimidine, pyrazine and so on, still remain challenging. Tautomerism of N-heteroarenes containing potential tautomeric functional group (OH, SH, NHR, acylmethyl, etc) is intimately relative to the aromaticity, chemical reactivity[9k,l] and biological activity.[10] Introducing a hydroxy substituent on α or γ to pyridine-like nitrogen atom of N-heteroarene leads to the hydroxy–oxo tautomerism to weaken aromaticity. This property might supply a potential solution for enantioselective hydrogenation of those heteroarenes with high stability. Tautomeric equilibria for 2- and 4-hydroxypyrimidines in gas or solution phase has been well studied in detail.[10a,11] As such, in most solvents, the lactam–lactim equilibrium of 2-hydroxypyrimidine is more toward the oxo form in pyrimidin-2(1*H*)-one. This oxo tautomer preserves aromatic character but lower than hydroxy tautomer. Thus, it is reasonable to envision that oxo tautomer with lower aromaticity might be amenable to asymmetric hydrogenation condition, giving the chiral cyclic ureas (Scheme 1). To the best of our knowledge, only one successful example on asymmetric hydrogenation of pyrimidines was reported by Kuwano group.[12] Substoichiometric achiral Lewis acid was employed to promote the hydrogenation of pyrimidines. Interestingly, chiral cyclic amidines as the reduced product were obtained with excellent enantioselectivities and yields. Herein, we report a highly enantioselective palladium-catalyzed hydrogenation of pyrimidines containing tautomeric hydroxy group, giving the chiral cyclic ureas with up to 99% of enantioselectivity.

Under the assumption that the oxo form of the 2-hydroxypyrimidine tautomer is more reactive due to its relatively lower aromaticity, we started the investigation of a proper asymmetric hydrogenation catalyst system for this concept. Previous research have demonstrated that Brønsted acids often play as promoter to facilitate the hydrogenation through activating substrate[13] and accelerating imine–enamine[9f] or hydroxy–oxo tautomerization.[14] In addition, much progresses have been successfully achieved in palladium-catalyzed asymmetric hydrogenation, which feature a robust hydrogenation catalyst with high toleration to the strong Brønsted acid, oxygen and moisture.[15–17] Thus, initially, we choose readily available 4-phenylpyrimidin-2-ol (**1a**) as model substrate, $Pd(OCOCF_3)_2$/(*S*)-Synphos (**L1**) complex as hydrogenation catalyst and trifluoroacetic acid (TFA) as additive. The hydrogenation was run in toluene at 60 °C under 1000 psi of hydrogen. Disappointedly, hydrogenation did not occur (Table 1, entry 1). Subsequently, the solvent effect was examined (entries 1–3). The reaction experienced significant solvent effects and a dramatic enhancement was observed when trifluoroethanol (TFE) was used. **1a** could be hydrogenated in full conversion to give the chiral cyclic urea **2a** with poor 26% *ee* (entry 3). It is noteworthy that the reactivity decreased in the absence of Brønsted acid (entry 4). Next, various acid additives were tested and gave similar *ee* values in the range of 25–31% (entries 5–8). Next, we tested the effect of some commercially available bisphosphine ligands on reactivity and enantioselectivity (entries 9–11). It was turned out that electron-donating ferrocene-derived Josiphos-type ligand (*R*,*S*)-PPF-P^{t}Bu$_2$ (**L4**) was the best in view of both reactivity and enantioselectivity (entry 11). Delightedly, elevating the temperature to 80 °C afforded slightly higher 94% of enantioselectivity (entry 12). Thus, the optimized conditions were established as: $Pd(OCOCF_3)_2$ (3.0 mol%)/(*R*,*S*)-PPF-P^{t}Bu$_2$ (3.3 mol%)/$PhCO_2H$ (10 mol%)/TFE/H_2 (1000 psi)/80 °C.

Table 1: Condition optimization.[a]

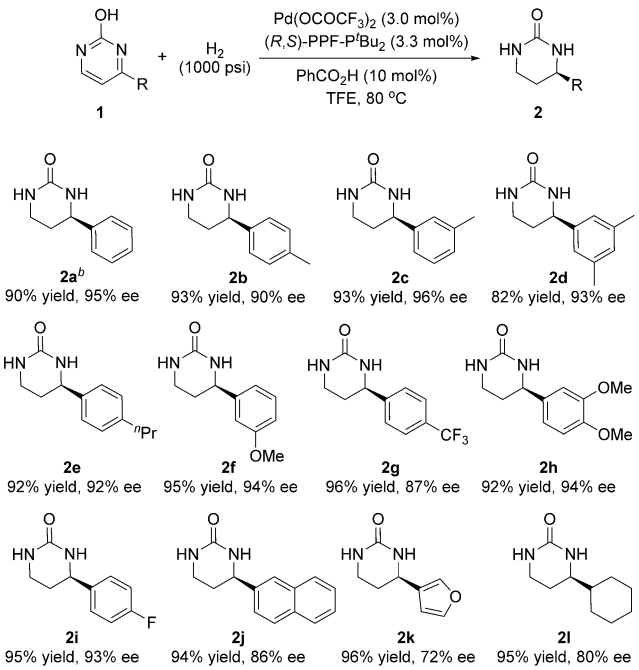


Entry	Solvent	Additive	Ligand	Conv. [%][b]	*ee* [%][c]
1	PhMe	TFA	**L1**	<5	NA
2	THF	TFA	**L1**	<5	NA
3	TFE	TFA	**L1**	>95	26 (*S*)
4	TFE	–	**L1**	83	32 (*S*)
5	TFE	$PhCO_2H$	**L1**	>95	31 (*S*)
6	TFE	$TsOH{\cdot}H_2O$	**L1**	>95	25 (*S*)
7	TFE	(*D*)-CSA	**L1**	>95	30 (*S*)
8	TFE	(*L*)-CSA	**L1**	>95	30 (*S*)
9	TFE	$PhCO_2H$	**L2**	>95	36 (*R*)
10	TFE	$PhCO_2H$	**L3**	>95	74 (*R*)
11	TFE	$PhCO_2H$	**L4**	>95	89 (*R*)
12[d]	TFE	$PhCO_2H$	**L4**	>95 (91)[e]	94 (*R*)

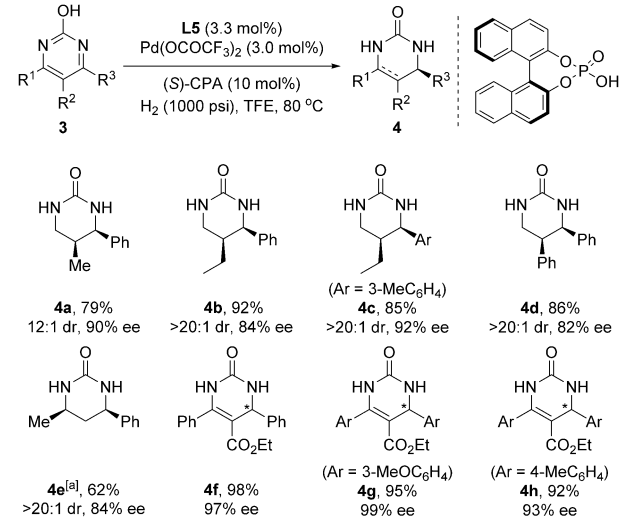
[a] Conditions: **1a** (0.20 mmol), $Pd(OCOCF_3)_2$ (3.0 mol%), ligand (3.3 mol%), additive (10 mol%), H_2 (1000 psi), solvent (3.0 mL), 24 h, 60 °C. [b] Determined by ^{1}H NMR spectroscopy. [c] Determined by HPLC analysis of the corresponding *N*-benzoyl derivatives. [d] 80 °C. [e] Isolated yield.

With the optimal condition in hand, we next examined the substrate scope, and the results are summarized in Scheme 2. A series of 4-aryl substituted 2-hydroxypyrimidines could be hydrogenated smoothly, giving the corresponding chiral cyclic ureas with excellent yields and excellent enantioselectivities (**2a**–**2j**). This reaction is not sensitive to the electronic character or steric hindrance effect of the substituent on C4 aromatic ring, and the corresponding products were obtained in 82–96% yields and 86–96% *ee*. Furthermore, the asymmetric hydrogenation of **1k** possessing the heterocyclic ring substituent proceeded with full conversion and moderate 72% *ee* (**2k**). Fortunately, 4-alkyl 2-hydroxypyrimidine can also give the corresponding chiral cyclic urea in moderate 80% *ee* (**2l**) under the standard condition. It was noteworthy that the gram scale experiment of **1a** was performed under the standard condition without loss of reactivity (90% vs. 91% yield) and enantioselectivity (95% *ee* vs. 94% *ee*).

Encouraged by these results obtained, we turned our attention to more complex di- and trisubstituted 2-hydroxypyrimidines. After a slightly modification of condition (using more acidic phosphoric acid instead of benzoic acid), this strategy turned out to be successful, and a range of disubstituted 2-hydroxypyrimidines (**4a**–**4e**, Scheme 3) could be well hydrogenated in the presence of chiral



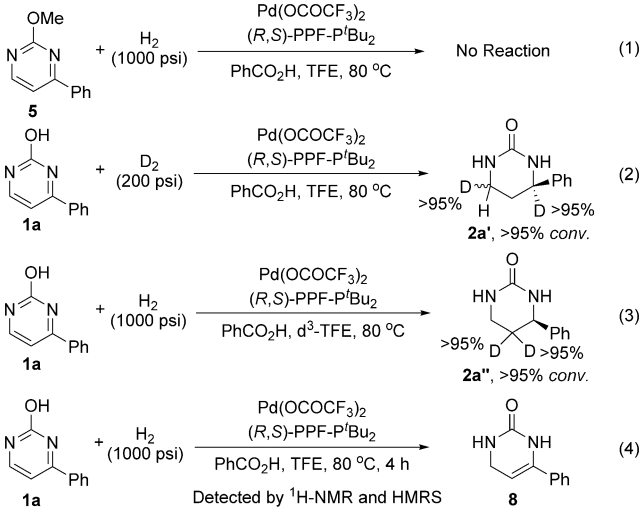
Scheme 2. Pd-catalyzed asymmetric hydrogenation of 2-hydroxypyrimidines **1**.[a] [a] Conditions: 2-hydroxypyrimidines **1** (0.30 mmol), $Pd(OCOCF_3)_2$ (3.0 mol%), **L4** (*R*,*S*)-PPF-P^{t}Bu$_2$ (3.3 mol%), $PhCO_2H$ (10 mol%), H_2 (1000 psi), TFE (3.0 mL), 80°C, 24 h, [b] 5.9 mmol scale.



Scheme 3. Palladium-catalyzed asymmetric hydrogenation of di- and trisubstituted 2-hydroxypyrimidines. [a] $Pd(OCOCF_3)_2$ (5.0 mol%), (*R*,*S*)-PPF-P^{t}Bu$_2$ (5.5 mol%) was used instead of **L5**, $PhCO_2H$ (10 mol%) was used instead of (*S*)-CPA, H_2 (1200 psi), TFE (3.0 mL), 100°C, 72 h.

phosphoric acid with high diastereoselectivities and 82–92% of enantioselectivities. Notably, asymmetric hydrogenation of trisubstituted 2-hydroxypyrimidines **3f–3h** furnished the partial hydrogenation 3,4-dihydropyrimidinones **4f–4h** in 92–98% yield and 93–99% of enantioselectivities.[18] It should be noted that the configuration of BINOL-derived chiral phosphoric acid would not affect the enantioselectivity and absolute configuration (see Table S1 in the Supporting Information).

To gain insight into the mechanism of this reaction, some control experiments were carried out (Scheme 4). As expected, no reaction was observed for the hydroxy protected substrate **5** [Eq. (1)]. When the isotopic labeling experiment

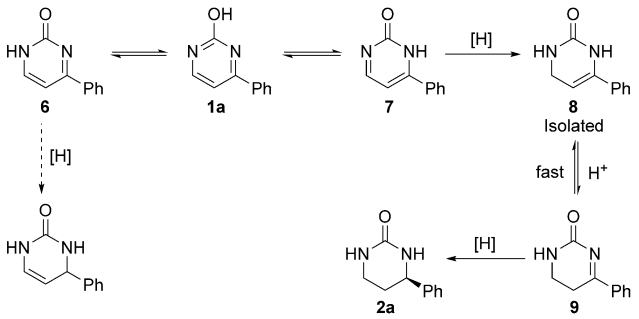


Scheme 4. Mechanistic investigation.

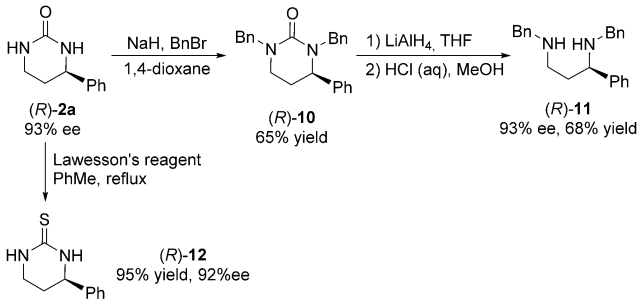
was carried out by the reaction of **1a** with D_2, the deuterium atoms were incorporated on the C4 and C6 position (>95% and >95%) [Eq. (2)]. The above result suggested that asymmetric hydrogenation of imine happened twice on C4 and C6, respectively. Then, the hydrogenation of **1a** was carried out in d^3-TFE [Eq. (3)], ^{1}H NMR analysis of the crude hydrogenation product showed that the deuterium atoms were taken up to C5 with >95% incorporation, which was possibly caused by the fast enamine–imine tautomerization during hydrogenation process. To further explore the mechanism, the hydrogenation reaction of **1a** was carried out and was stopped just after 4 hours. Gratifyingly, analysis of the crude hydrogenation mixture showed the existence of partially hydrogenation intermediate enamine **8** with ^{1}H NMR and HRMS.

Based on the above experimental results, a plausible stepwise hydrogenation process was proposed (Scheme 5). In the reaction system, the 2-hydroxypyrimidine mainly exists in two tautomeric oxo forms **6** and **7**. Firstly, the N1=C6 double bond of **7** is hydrogenated to give the intermediate dihydropyrimidin-2(1*H*)-one **8**. Next, the intermediate **8** proceeds the acid-catalyzed tautomerization process of enamine to imine **9**, followed by palladium-catalyzed asymmetric hydrogenation of imine **9** to give the final chiral cyclic urea **2a**.

After establishing the facile approach for the synthesis of chiral cyclic ureas by asymmetric hydrogenation, we further evaluated the practical utility (Scheme 6). Firstly, the ring opening experiments of products have been conducted. According to the reported method, cleavage of the urea failed to give the free diamines under acidic conditions.[3b]



Scheme 5. Proposed reaction pathway.



Scheme 6. Product elaboration: synthesis of chiral 1,3-diamine and cyclic thiourea.

Fortunately, the chiral cyclic urea **2a** can be readily protected with benzyl bromide, followed by reduction by $LiAlH_4$ and hydrolysis could provide the desired chiral 1,3-diamine **11** with 93% *ee*.[19] This result demonstrated direct synthesis of important chiral 1,3-diamine skeleton and may deliver practical application in enantioselective synthesis, organocatalysis, and medicinal chemistry.[20] Significantly, treatment of the **2a** with Lawesson's reagent afforded chiral cyclic thiourea **12** without loss of optical purity (Scheme 6).[21]

In summary, an efficient palladium-catalyzed asymmetric hydrogenation of 2-hydroxypyrimidines has been successfully developed for the facile synthesis of chiral cyclic ureas with up to 99% *ee*. The current catalytic system exhibits an impressive broad substrate scope, mono-, di- and trisubstituted 2-hydroxypyrimidines can be easily hydrogenated with good yields and enantioselectivities. The practicability of the reaction has been demonstrated by the easy scalability and synthesis of important chiral 1,3-diamines and cyclic thioureas. Further investigations on the hydrogenation of related challenging heteroaromatic compounds are ongoing in our laboratory.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: 1,3-diamines · cyclic ureas · palladium · pyrimidines · tautomerization

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