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Iridium-Catalyzed Asymmetric Hydrogenation of 4,6-Disubstituted 2-Hydroxypyrimidines

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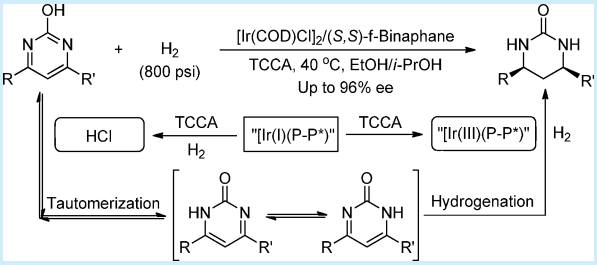
Supporting Information

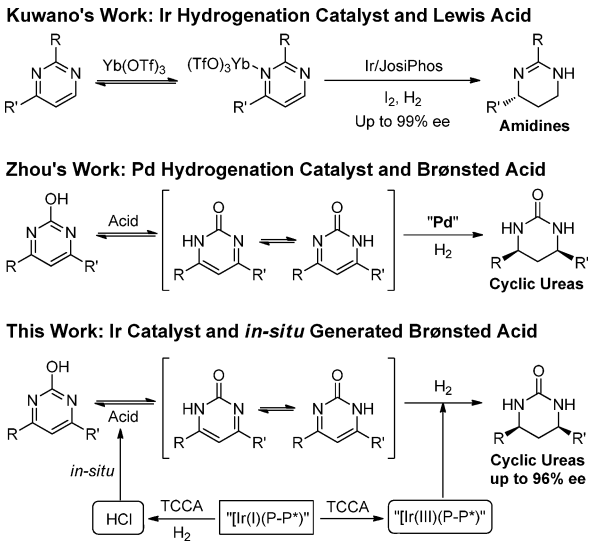
ABSTRACT: An efficient iridium-catalyzed hydrogenation of 4,6-disubstituted 2-hydroxypyrimidines has been achieved, giving chiral cyclic ureas with excellent diastereoselectivities and up to 96% ee of enantioselectivities. In the presence of the *in situ* generated hydrogen halide, the equilibrium of the lactame−lactime tautomerism of 2-hydroxypyrimidine is more toward the oxo form with lower aromaticity, which effectively improves the reactivity to facilitate hydrogenation. Moreover, the cyclic ureas could be readily converted into chiral 1,3-diamine derivatives without loss of optical purity.



Asymmetric hydrogenation of aromatic compounds has been considered as an efficient method for the synthesis of a variety of chiral cyclic compounds.[1] So far, significant progress on asymmetric hydrogenation of aromatics has been successfully implemented for substrates such as quinolines,[2] isoquinolines,[3] quinoxalines,[4] pyridines,[5] indoles/pyrroles,[6] furans,[7] imidazoles,[8] thiophenes,[9] and even carbocycles.[10] Despite these achievements, most successful examples in this field are limited to bicyclic heteroaromatic and polycyclic compounds with relatively low aromaticity.

There still remain some challenging substrates to be overcome in this field, especially pyrimidines, a six-membered ring *N*-heteroaromatic compound. The inherent problems are apparent: First, pyrimidine is one of the most stable aromatic structures. Second, substrates and the corresponding reduced products that possess strong coordination ability might cause deactivation of the chiral catalysts. Therefore, only a few examples of hydrogenation of pyrimidine derivatives have been reported. In 2014, Kuwano and co-workers first documented highly enantioselective hydrogenation of pyrimidines by using an iridium catalyst.[11] It is noteworthy that substoichiometric Lewis acid as an activator was crucial for achieving the high enantioselectivity and reactivity (Scheme 1). Very recently, an efficient palladium-catalyzed asymmetric hydrogenation of 2-hydroxypyrimidines was successfully realized in our laboratory. The key to success in this case was the hydroxyl-oxo tautomerism of 2-hydroxypyrimidine causing certain loss of aromaticity (Scheme 1).[12] However, harsh conditions (1000 psi, 80 °C) and high loading of palladium catalyst (3−5 mol %) are necessary in order to obtain satisfactory yields and enantioselectivities. Additionally, for some bulky substrates, especially 4,6-disubstituted 2-hydroxypyrimidines, the reactivity decreased, and only 62% yield was obtained even with 5 mol % palladium catalyst under 1200 psi of hydrogen at 100 °C. Given the fact that asymmetric hydrogenation of 2-hydroxypyrimidines provides a simple approach to chiral cyclic ureas, a more efficient catalytic system is highly imperative.

Scheme 1. Asymmetric Hydrogenation of Pyrimidines



An iridium complex is also an effective catalyst frequently used for enantioselective hydrogenation of heteroaromatics. For the iridium-catalyzed hydrogenation, the halogenide additive was often used to improve the reactivity through oxidizing iridium(I) to iridium(III) and *in situ* generating the hydrogen halide as substrate activator.[1d,e] We envisioned that the equilibrium of the lactame−lactime tautomerism of 2-

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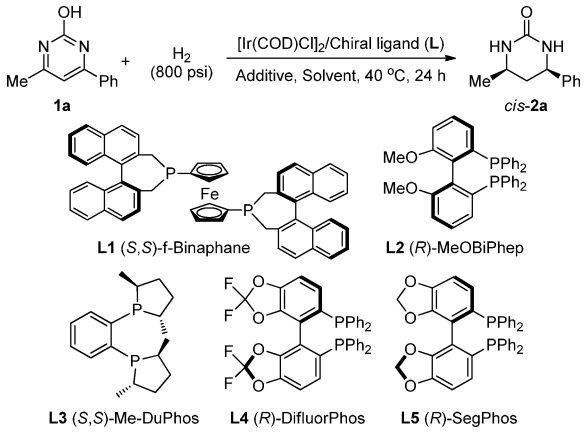
hydroxypyrimidine is more toward the oxo form in the presence of acid under the iridium-catalyzed hydrogenation condition, which would effectively improve the reactivity to facilitate the hydrogenation (Scheme 1).[13] Herein, we report an efficient iridium-catalyzed asymmetric hydrogenation of 4,6-disubstituted 2-hydroxypyrimidines with up to 96% ee, which is complementary to the previous palladium-catalyzed asymmetric hydrogenation of 2-hydroxypyrimidines.[12]

4-Methyl-6-phenylpyrimidin-2-ol (**1a**) was chosen as a model substrate to start our study, and we tested asymmetric hydrogenation of **1a** with 1,3,5-trichloroisocyanuric acid (TCCA) as additive and $[Ir(COD)Cl]_2$/(*S*,*S*)-f-Binaphane as catalyst in tetrahydrofuran (THF). To our delight, the reaction could proceed smoothly under the conditions (40 °C, 800 psi H_2) with full conversion and moderate 76% ee (Table 1, entry 1). In contrast, only moderate yield was obtained with a previous palladium catalyst system.[12] Encouraged by this promising result, the reaction condition was optimized systematically. First, different solvents were screened (entries 2−5), and ethanol was observed to be optimal in terms of enantioselectivity and reactivity (87% ee and full conversion, entry 5). Next, some other halogen sources were tested and resulted in an obvious decrease of the ee (entries 6−7). Some commercially available chiral bisphosphine ligands were also evaluated (entries 8−11), and (*S*,*S*)-f-Binaphane still emerged as the most favorable one (87% ee, entry 5). Finally, excellent 95% ee and full conversion were achieved when a mixture solvent of ethanol and isopropanol with the ratio of 1/2 was used (entry 13). Therefore, the optimal reaction condition was established as $[Ir(COD)Cl]_2$/(*S*,*S*)-f-Binaphane (1:2.2), TCCA (10 mol %), ethanol:isopropanol (1:2), and H_2 (800 psi), at 40 °C.

Having identified a highly enantioselective catalytic system, exploration of the substrate scope was carried out to test the generality, and the results are summarized in Scheme 2. A variety of 4,6-disubstituted 2-hydroxypyrimidine derivatives **1** could be converted into cyclic ureas **2** with high enantioselectivities and yields. The effect of electronic properties of the substrates on the enantioselectivities was investigated. Both electron-donating and electron-withdrawing groups were well tolerated, affording the chiral ureas with good yields and ee's (Scheme 2, **2b**−**2k**). When the phenyl ring contains a strong electron-withdrawing trifluoromethyl group in the *para* position (**2l**), 86% yield and 83% ee were also achieved at an elevated reaction temperature (80 °C). The isopropyl group instead of the methyl group at the 6-position led to slight erosion of the ee, but yields and diastereoselectivity were still maintained at a high level (**2n**). Notably, the

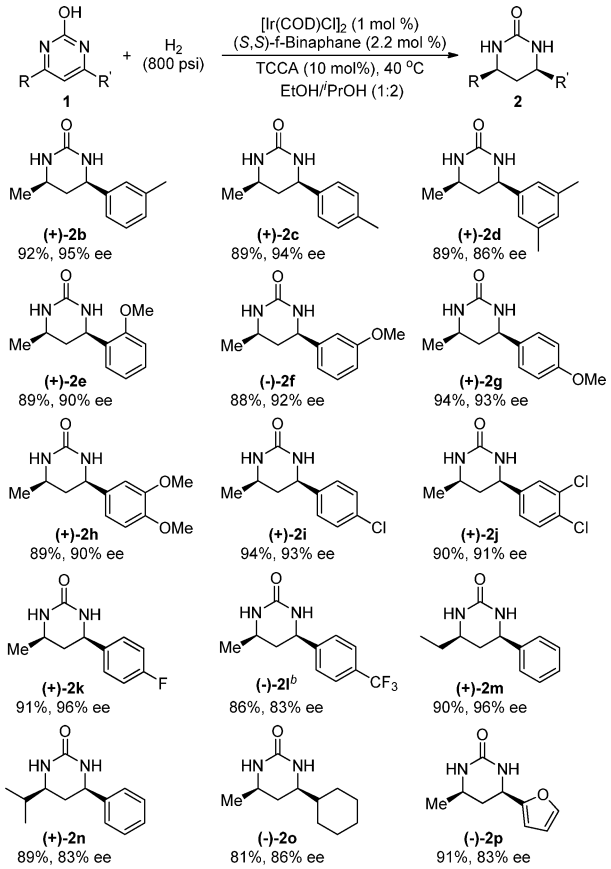
Table 1. Evaluation of Reaction Parameters[a]



entry	solvent	additive	ligand	ee (%)[b]
1	THF	TCCA	**L1**	76 (*R*,*R*)
2	PhMe	TCCA	**L1**	58 (*R*,*R*)
3	DCM	TCCA	**L1**	85 (*R*,*R*)
4	^{i}PrOH (P)	TCCA	**L1**	79 (*R*,*R*)
5	EtOH (E)	TCCA	**L1**	87 (*R*,*R*)
6	EtOH	NBS	**L1**	58 (*R*,*R*)
7	EtOH	I_2	**L1**	52 (*R*,*R*)
8	EtOH	TCCA	**L2**	53 (*R*,*R*)
9[c]	EtOH	TCCA	**L3**	NA
10	EtOH	TCCA	**L4**	57 (*R*,*R*)
11	EtOH	TCCA	**L5**	75 (*R*,*R*)
12	E:P (1:1)	TCCA	**L1**	88 (*R*,*R*)
13[d]	E:P (1:2)	TCCA	**L1**	95 (*R*,*R*)
14	E:P (2:1)	TCCA	**L1**	94 (*R*,*R*)

[a]Reaction conditions: **1a** (0.2 mmol), $[Ir(COD)Cl]_2$ (1.0 mol %), ligand (2.2 mol %), H_2 (800 psi), solvent (3.0 mL), and additive (10 mol %), 24 h, 40 °C. Reaction conversion and dr were determined by ^{1}H NMR spectroscopy. Unless noted, in all cases, the reaction conversion is >95% and the dr > 20:1. [b]Determined by HPLC analysis of the corresponding *N*-benzoyl derivative. [c]The conversion is <5%. [d]92% isolated yield. TCCA = 1,3,5-trichloroisocyanuric acid, NBS = *N*-bromosuccinimide, NA = not available.

Scheme 2. Substrate Scope: 4,6-Disubstituted Pyrimidines[a]



[a]Conditions: **1** (0.30 mmol), $[Ir(COD)Cl]_2$ (1.0 mol %), (*S*,*S*)-f-binaphane (2.2 mol %), TCCA (10 mol %), H_2 (800 psi), EtOH/^{i}PrOH (1.0 mL/2.0 mL), at 40 °C, 24 h. [b]Performed at 80 °C.

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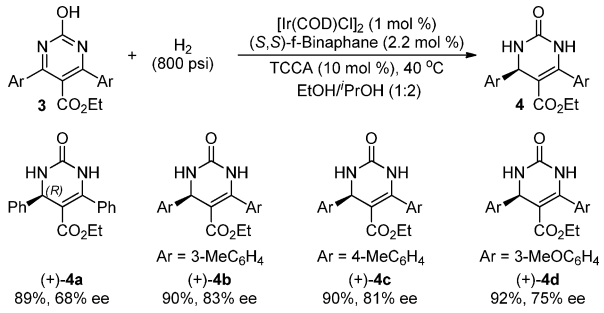
substrate containing a furyl group was also suitable, affording the desirable product with 91% yield and 83% ee (**2p**). To demonstrate the practicality of this methodology, asymmetric hydrogenation of **1a** was smoothly performed on a gram scale (1.026 g) under the standard conditions without loss of reactivity and enantioselectivity (92% yield and 95% ee).

Afterward, the more challenging trisubstituted 2-hydroxypyrimidines were subjected to the above standard hydrogenation conditions. Pleasingly, our strategy also turned out to be successful; a range of 4,5,6-trisubstituted 2-hydroxypyrimidines could be well partially hydrogenated to deliver the chiral 3,4-dihydropyrimidin-2-(1*H*)-ones (DHPMs) with moderate ee values (68−83% ee) and good reactivities (89−92%) (Scheme 3, **4a**−**4d**). This method provides an efficient protocol to construct biologically important architecture DHPMs in an enantioselective manner.

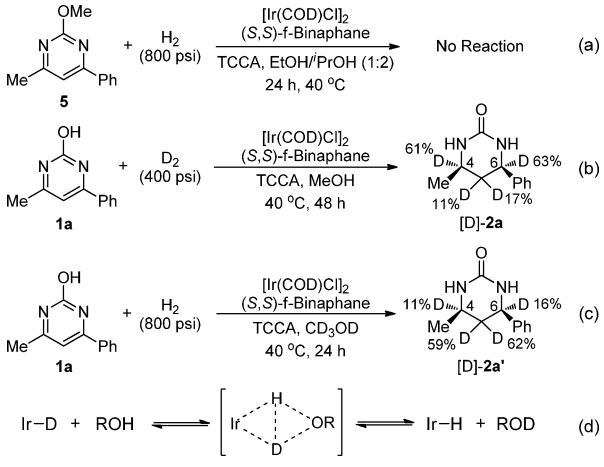
Scheme 3. Substrate Scope: Trisubstituted Pyrimidines[a]



[a]Conditions: **3** (0.30 mmol), $[Ir(COD)Cl]_2$ (1.0 mol %), (*S*,*S*)-f-binaphane (2.2 mol %), TCCA (10 mol %), H_2 (800 psi), EtOH/^{i}PrOH (1.0 mL/2.0 mL), 40 °C, 48 h.

Several experiments have been performed to probe the reaction mechanism. As expected, no product was observed for the hydroxyl-protected substrate **5** (Scheme 4, a). An isotopic

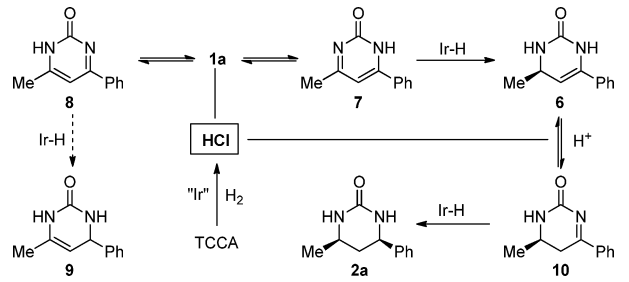
Scheme 4. Controlled and Deuterium Labeling Experiments



labeling experiment was carried out by hydrogenation of **1a** with D_2 gas. To our surprise, the deuterium atoms were incorporated in only moderate rate on the C4 and C6 (61% and 63%) (Scheme 4, b). During the deuteration of **1a**, the Ir−D could exchange proton with alcohol solvent through a Ir−(D−H) transition state (Scheme 4, d).[14] As a result, this H/D exchange process would cause erosion of the deuterium rate. Meanwhile, hydrogen/deuterium scrambling took place on the C5 atom, which possibly was caused by fast enamine/iminium tautomerization. When the reduction of **1a** was performed in deuterium solvent CD_3OD, the deuteration was also accompanied by a similar H/D exchange phenomenon (C5:59% and 62% D), which further confirms the existence of a fast enamine/iminium tautomerization (Scheme 4, c).

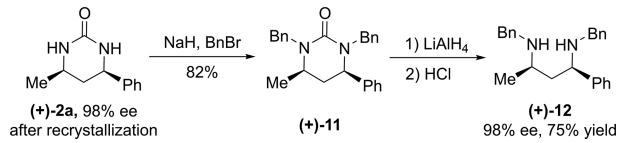
Based on the above experimental results, a plausible stepwise hydrogenation process was proposed (Scheme 5). 2-Hydroxypyrimidine can readily tautomerize into two oxo forms (**7** and **8**)[12] in the presence of *in situ* generated HCl. Next, an initial reduction of the N3−C4 double bond of **7** gives the key intermediate dihydropyrimidin-2(1*H*)-one **6**. Then, the intermediate **6** proceeds in the acid-catalyzed isomerization of enamine to imine **10**, followed by asymmetric hydrogenation of imine **10** to give the chiral cyclic urea **2a**.

Scheme 5. Proposed Reaction Pathway



Finally, the application of chiral cyclic urea for preparation of the corresponding chiral 1,3-diamine is depicted in Scheme 6.

Scheme 6. Elaboration: Synthesis of Chiral 1,3-Diamine



The chiral cyclic urea **2a** with 98% ee can be easily protected with benzyl bromide, followed by $LiAlH_4$ reduction and hydrolysis to provide the desired chiral 1,3-diamine **12** without any loss of ee.[15] This approach gave new access to chiral 1,3-diamine and may find useful applications in organic synthesis, medicinal chemistry, and asymmetric synthesis.[16]

In conclusion, an efficient iridium-catalyzed asymmetric hydrogenation of 4,6-disubstituted 2-hydroxypyrimidines has been developed for the facile synthesis of chiral cyclic ureas with up to 96% ee. The iridium catalytic system exhibits a broad substrate scope for 4,6-disubstituted and more complex trisubstituted 2-hydroxypyrimidine substrates, which is an important complement to a palladium-catalyzed asymmetric hydrogenation system. The unexpected H/D exchange phenomenon between Ir−D with protic solvent was observed, which was different from the palladium-catalyzed hydrogenation system. The practicability of the reaction has been demonstrated by the easy scalability and chiral 1,3-diamine synthesis. Related works using this strategy to extend the other challenging heteroaromatics will be described in due course.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02723.

Experimental procedures, characterization data, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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