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Rhodium Catalyzed Asymmetric Hydrogenation of 2-Pyridine Ketones

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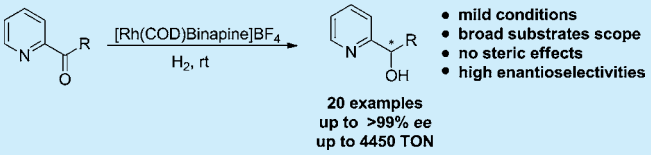
Supporting Information

ABSTRACT: Catalyzed by [Rh(COD)Binapine]BF_4, the asymmetric hydrogenation of 2-pyridine ketones has been achieved with excellent enantioselectivities (enantiomeric excesses up to 99%) under mild conditions. This method is suitable for various kinds of 2-pyridine ketones and their derivatives. A number of enantiomerically pure chiral 2-pyridine-aryl/alkyl alcohols were prepared through hydrogenation, which can be used directly in organic synthesis.



Along with the considerable progress made in asymmetric hydrogenation in the past decades, homogeneous asymmetric hydrogenation of prochiral ketones has become one of the most important methods for the preparation of various chiral secondary alcohols.[1] Enantiopure secondary alcohols with 2-pyridine as a substituent group are key intermediates that are widely used in the synthesis of various natural products, pharmaceuticals, agrochemicals, and chiral ligands.[2] For example, carbinoxamine and bepotastine besilate (Figure 1) are two useful histamine H1 antagonists.[3] In 1996,

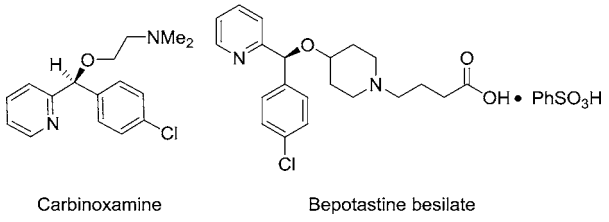
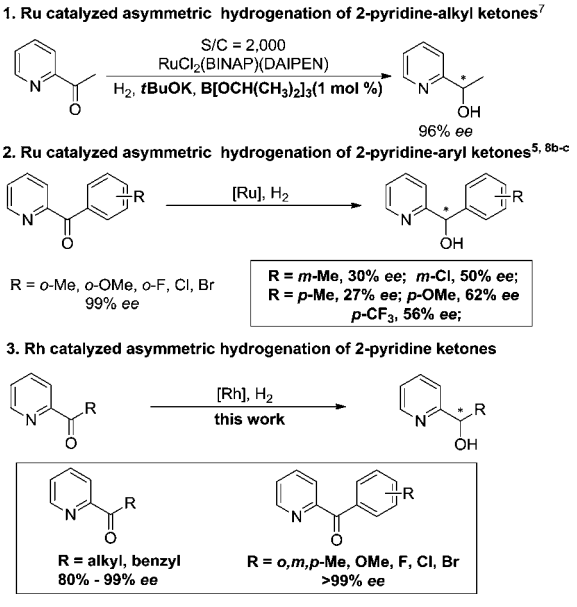


Figure 1. Representative drugs contain aryl-(pyridine-2-yl)-methanol.

Corey realized the reduction of the 2-(4-chlorobenzoyl)-pyridine with oxazaborolidine, but the nitrogen must be protected and the catalyst loading was high.[4] Afterward, Zhang attempted asymmetric hydrogenation. Although high *ee* was obtained with Xyl-SunPhos, the phenyl group must have bromide as an ortho substituent, which was not an efficient process.[5]

In fact, due to the coordination effect of pyridines, direct asymmetric hydrogenation of 2-pyridine ketones was a longstanding problem despite the great progress made in the hydrogenation of simple ketones.[2a,6] Compared to simple aryl ketones, little attention was paid to asymmetric hydrogenation of 2-pyridine ketones. In 2001, Noyori reported the hydrogenation of 2-acetylpyridine with trans-$RuCl_2$[(*R*)-xylBINAP]-[(*R*)-daipen] and with the addition of isopropyl borate to inhibit pyridine coordination, and up to 96% *ee* had been realized (Scheme 1).[7] Afterward, several groups applied the

Scheme 1. Asymmetric Hydrogenation of 2-Pyridine Ketones



$RuCl_2$(diphosphine) (diamine) in the asymmetric hydrogenation of aryl-pyridyl ketones,[5,8] but all the results indicated that, for the 2-pyridyl aryl ketones, only when the phenyl group had an ortho substitution group, the product had excellent *ee* (99%), and many other 2-pyridine aryl ketones offered poor *ee* (27%−62%). This substrate limitation greatly hindered its applications.[9]

Asymmetric hydrogenation of 2-pyridine ketones and their derivatives remains an important but unsolved problem. Recently, the Bristol-Myers Squibb Company realized the

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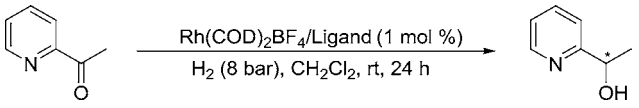
asymmetric hydrogenation of 7,8-dihydro-5-*H*-cyclohepta-pyridin-e-5,9-dione with [Rh(COD)Binapine]BF_4 during the synthesis of a CGRP antagonist.[10] We envisioned that the Rh-diphosphine catalysts may work well with the hydrogenation of the 2-pyridine ketones using the ligands in our "chiral ligands toolbox".[11] Herein, we report a very efficient route for the asymmetric hydrogenation of 2-pyridine ketones with excellent enantioselectivities and high turnover numbers (TON) not only for 2-pyridine alkyl ketones but also for 2-pyridine aryl ketones regardless of whether there is an ortho substituted group or not.

We initiated the research by screening the catalysts with 2-acetyl pyridine as the standard substrates. As shown in Table 1,

Table 1. Ligand Screening for the [$Rh(COD)_2BF_4$] Catalyzed Asymmetric Hydrogenation of 2-Acetyl Pyridine[a]



entry	ligand	conversion[b] (%)	ee[c] (%)
1	(*R*)-BINAP	0	–
2	Josiphos	14	−12
3	(1*S*,1*S*′,2*R*,2*R*′)-TangPhos	98	−95
4	(*Rc*, *Sp*)-DuanPhos	7	34
5	(*R*)-Binapine	>99	>99

[a]Unless otherwise noted, all reactions were carried out with a [$Rh(COD)_2BF_4$]/ligand/substrate (0.2 mmol) ratio of 1:1.1:100 in 2 mL of CH_2Cl_2 at room temperature under hydrogen (8 bar) for 24 h. [b]Determined by ^1H NMR. [c]Determined by HPLC analysis using a chiral stationary phase.

different chiral diphosphine ligands displayed obviously different activities with $Rh(COD)_2BF_4$ (Figure 2). To our delight,

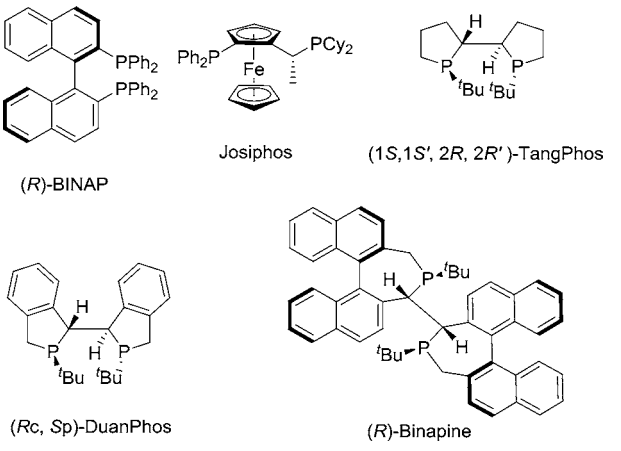
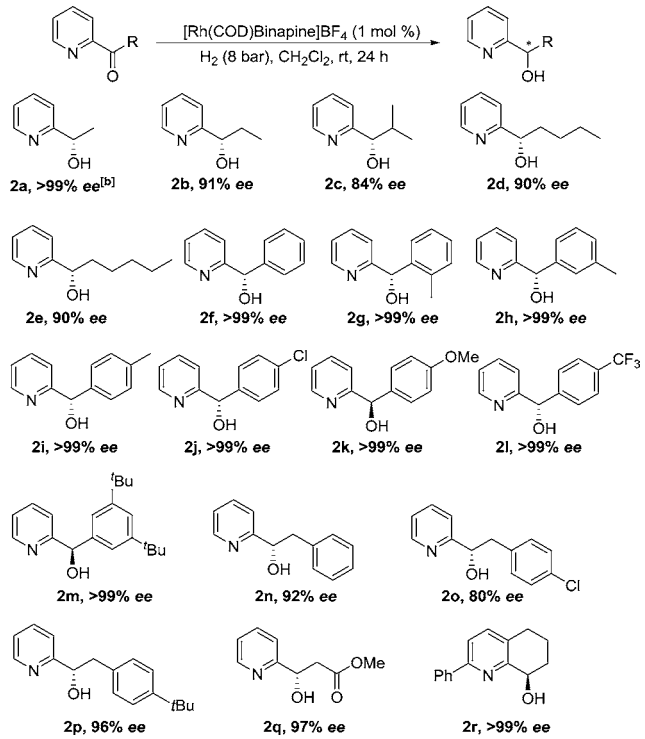


Figure 2. Ligands screened in the Rh-catalyzed hydrogenation of 2-acetylpyridine.

the (*R*)-Binapine developed in our lab exhibited excellent results (>99% conversion and >99% *ee*, Table 1, entry 5). In contrast, other ligands except for TangPhos showed low activities.[12] Then, we further screened the solvents (see Supporting Information), and the results indicated that CH_2Cl_2 was the most suitable solvent. This exciting result prompted us to attempt the asymmetric hydrogenation of other 2-pyridine ketones and their derivatives under the optimized conditions. Most of the substrates were synthesized by the corresponding Grignard reagents and 2-cyanopyridine.[5,13] The results are shown in Scheme 2. 2-Pyridine-alkyl ketones were

Scheme 2. [$Rh(COD)Binapine]BF_4$ Catalyzed Asymmetric Hydrogenation of 2-Pyridine Ketones[a]



[a]Unless otherwise noted, all reactions were carried out with a [Rh(COD)Binapine]BF_4/substrate ratio of 1:100 in 2 mL of CH_2Cl_2 at room temperature under hydrogen (8 bar) for 24 h; full conversion in all cases. [b]Determined by HPLC analysis using a chiral stationary phase.

good substrates for this reaction, but the *ee* value gradually decreased as the alkyl groups become bulkier (99%−84% *ee*, Scheme 2, **2a**−**2e**). For the 2-pyridine-aryl ketones, in the case of either electron-donating or -withdrawing groups on the aromatic rings, all gave excellent *ee* and conversion (Scheme 2, **2f**−**2m**). It was worth noting that the steric effects of the substituent didn't impact the enantioselectivities. It may be because the nitrogen atom of the pyridine could coordinate with the catalysts well, which played an important role in asymmetric hydrogenation. These results suggested hydrogenation of 2-pyridine-aryl ketones could proceed successfully with a broad substrate scope.

However, for the 2-pyridine-benzyl ketones, the substituent group had important effects on the enantioselectivities. The halogen atom on the benzyl group dramatically decreased the *ee* (Scheme 2, **2o**), while large substituent groups such as *tert*-butyl improved the *ee* (Scheme 2, **2p**). We also utilized another functionlized 2-pyridine ketone (Scheme 2, **2q**),[14] which gave satisfactory results as well. With this method, chiral 2-phenyl-5,6,7,8-tetrahydroquinolin-8-ols (Scheme 2, **2r**) and their derivatives, which were key intermediates in the chiral ligands and biologically active compounds synthesis, could be prepared effectively.[15]

Next we explored some other heteroaromatic ketones such as 2-acetyl furan and 2-acetyl thiophene (Table 2, entries 1, 2). To our surprise, there was no reaction at all. We proposed that the

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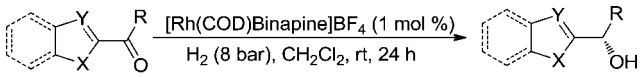
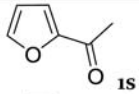
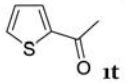
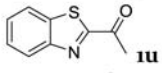
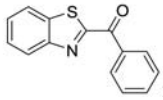
Table 2. [Rh(COD)Binapine]BF_4 Catalyzed Asymmetric Hydrogenation of Other Heteroaromatic Ketone Derivatives[a]



entry	substrates	product	conversion[b] (%)	ee[c] (%)
1	 1s	2s	0	-
2	 1t	2t	0	-
3[d]	 1u	2u	90(83[e])	92
4	 1v	2v	>99	>99

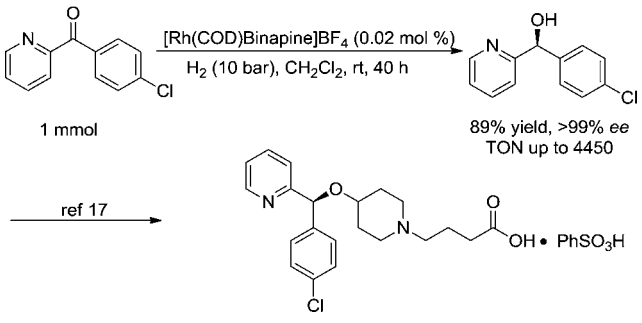
[a]Unless otherwise noted, all reactions were carried out with a [Rh(COD)Binapine]BF_4/substrate ratio of 1:100 in 2 mL of CH_2Cl_2 at room temperature under hydrogen (8 bar) for 24 h. [b]Determined by ^1H NMR. [c]Determined by HPLC analysis using a chiral stationary phase. [d]0.1 mmol of **1u** was hydrogenated because the poor solubility of 2-acetyyl benzothiazole in CH_2Cl_2. [e]Isolated yield.

oxygen and sulfur atoms could not coordinate well with the catalysts compared to the nitrogen. Then we synthesized the 2-acetyl benzothiazole and 2-benzoyl benzothiazole, and the hydrogenation results were in agreement with our initial hypothesis. 2-Acetyl benzothiazole mostly converted to the product with 92% *ee*, and 2-benzyoyl benzothiazole underwent total conversion with 99% *ee* (Table 2, entries 3, 4).[16]

To demonstrate the practical utility of current methodology, we synthesized the key intermediate of bepotastine besilate **2j** by asymmetric hydrogenation with excellent *ee* and high TON (Scheme 3). As shown in Scheme 3, when the hydrogenation of ketone **1j** was conducted under S/C = 5000, we achieved an 89% yield and >99% *ee*.

In summary, we have developed an effective method for the asymmetric hydrogenation of 2-pyridine alky/aryl ketones using [Rh(COD)Binapine]BF_4 as the catalyst, affording 2-pyridine alky and aryl alcohols with excellent yields and excellent enantioselectivities. A broad substrate scope has been realized. This protocol can be directly used in the synthesis of bepotastine besilate with high TON and high *ee*, exhibiting great potential in the practical synthesis of pharmaceuticals. The hydrogenation of other heteroaryl ketones is underway in our laboratory.

Scheme 3. Asymmetric Synthesis of Bepotastine Besilate with High TON



■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01878.

Experimental details and characterization data (PDF)

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Author Contributions

†H.Y. and N.H. contributed equally

Notes

The authors declare no competing financial interest.

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