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Cobalt pincer complex-catalyzed highly enantioselective hydrogenation of quinoxalines

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ABSTRACT

A cobalt pincer complex bearing both P and C-stereogenic centers has been designed and synthesized, allowing for the development of the first cobalt-catalyzed asymmetric hydrogenation of quinoxalines under relatively mild conditions. Valuable chiral 1,2,3,4-tetrahydroquinoxalines could be obtained with high yields and excellent eantioselectivities (35 examples, up to >99% *ee*).

Compounds containing chiral 1,2,3,4-tetrahydroquinoxalines have been discovered as core structure in a wide range of bioactive molecules and natural products [1-6]. As a result, the development of various approaches to synthesizing these chiral heterocycles has been ongoing for many years [7]. Homogeneous asymmetric hydrogenation (AH) of quinoxalines is a direct and atom economic method for the preparation of chiral tetrahydroquinoxaline [8-11]. Early in 1987, Murata reported the first rhodium-catalyzed AH of 2-methylquinoxalines, but with only 3% enantioselectivity observed [12]. Later, the *ee* value increased to 90% with an orthometalated dihydride iridium complex by Bianchini in 1998 [13]. Although some progress was made in the following several years [14-16], the reactions generally suffered from low conversions and/or low *ee* values. A breakthrough was achieved with an easily accessible Ir-diphosphinite catalyst by Chan in 2009, disclosing up to 98% enantioselectivity and unprecedented high catalytic activity (TOF up to 5620 h^{-1}) [17]. Thereafter, the AH of quinoxaline derivatives with various transition metal catalysts, mainly based on Ir [18-23], Rh [24], Ru [25-28], and Mo [29] complexes, or using frustrated Lewis pairs (FLPs) [30], has been successfully demonstrated, providing good enantioselectivities and yields. However, given the high cost, limited supply and toxicity of late transition metals, and the often-complex synthetic processes and high loading of FLP catalysts, establishing a more sustainable and environmentally benign transition metal catalytic system is highly desirable.

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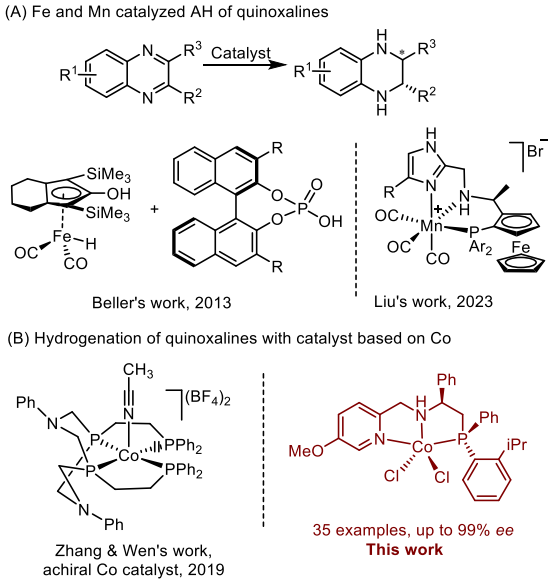


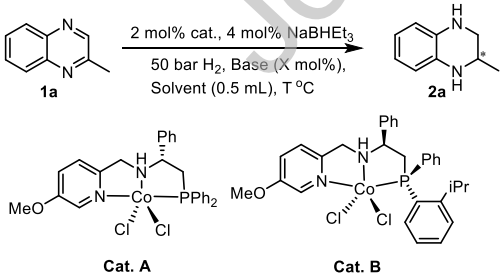
Scheme 1. Catalysts based on 3d transition metals for the hydrogenation of quinoxalines.

The replacement of precious metals with earth-abundant metals in asymmetric reactions has become an important topic [31-39]. Many catalysts comprised of one of the 3d transition-metals and a suitable chiral ligand have been reported, allowing for the AH of unsaturated substrates with C=C, C=O and C=N bonds [40-43]. However, for the AH of quinoxaline compounds, it remains a challenging task. In 2013, Beller reported an iron-catalyzed AH of quinoxalines, exploiting the concept of metal and chiral BrØnsted acid cooperative catalysis (Scheme 1A, left) [44-46]. Ten years later, Liu developed an efficient manganese-catalyzed AH of quinoxalines, using a chiral tridentate PNN ligand derived from ferrocene and an imidazole group (Scheme 1A, right) [47]. Cobalt, a congener of rhodium and iridium, is a promising transition metal for AH reactions because of its easier availability and reduced toxicity [43,48-66]. However, concerning the hydrogenation of quinoxalines, only one achiral Co catalyst has been reported until now (Scheme 1B, left) [58].

Recently, we developed a cobalt catalyst bearing a chiral PNN pincer ligand based on an amino phosphine skeleton [54]. Whilst the cobalt catalyst showed low enantioselectivity in catalytic AH of aryl ketones, introducing an achiral monodentate phosphine ligand increased significantly the product enantioselectivity. This could be due to the coordination of the phosphine ligand to the cobalt, creating additional steric hindrance around the metal and thus enhancing the stereo-differentiating ability of the PNN ligand. We therefore thought that by increasing the steric bulkiness and the stereo-differentiating quality of the PNN ligand, we may be able to achieve higher enantioselectivities in AH reactions with a cobalt catalyst having such a PNN ligand. Herein, we present a new cobalt complex derived from a chiral pincer PNN ligand featuring both P and C-stereogenic centers (Scheme 1B, right). With this cobalt complex, the first examples of Co-catalyzed enantioselective hydrogenation of 2-substituent quinoxalines have been achieved, affording up to 99% *ee* values and full conversions under relatively mild reaction conditions.

Table 1

Optimization of reaction conditions for cobalt-catalyzed hydrogenation of 2-methylquinoxaline.[a]

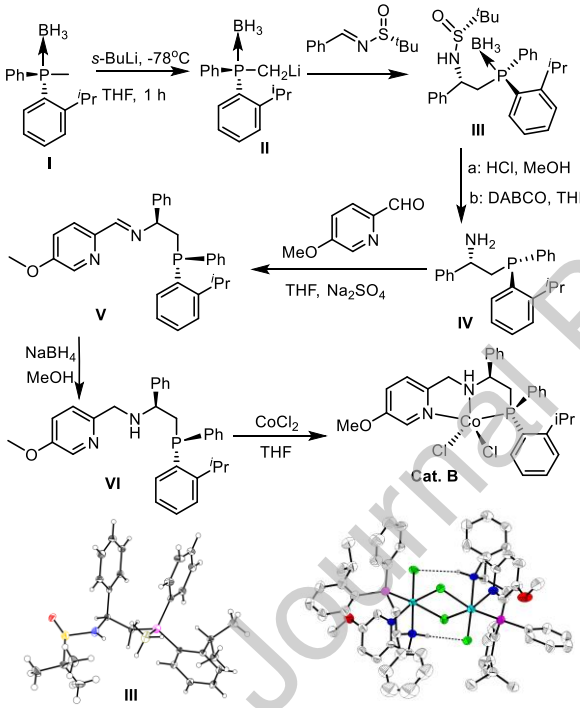


Entry	Solvent	Base (mol%)	Cat.	T. (ºC)	Conv. (%)[b]	*ee* (%)[b]
1	THF	Cs_2CO_3 (20)	**A**	30	ND	-
2	THF	NaOMe (20)	**A**	30	75	62 (*R*)
3	THF	NaOEt (20)	**A**	30	95	76 (*R*)
4	THF	NaO^{t}Bu (20)	**A**	30	20	72 (*R*)
5	THF	NaOEt (10)	**A**	30	49	80 (*R*)
6	THF	NaOEt (30)	**A**	30	96	72 (*R*)
7	Tol	NaOEt (20)	**A**	30	65	66 (*R*)
8	Dioxane	NaOEt (20)	**A**	30	13	ND
9	THF	NaOEt (20)	**A**	40	96	78 (*R*)

10	THF	NaOEt (20)	**B**	40	97	93 (*S*)

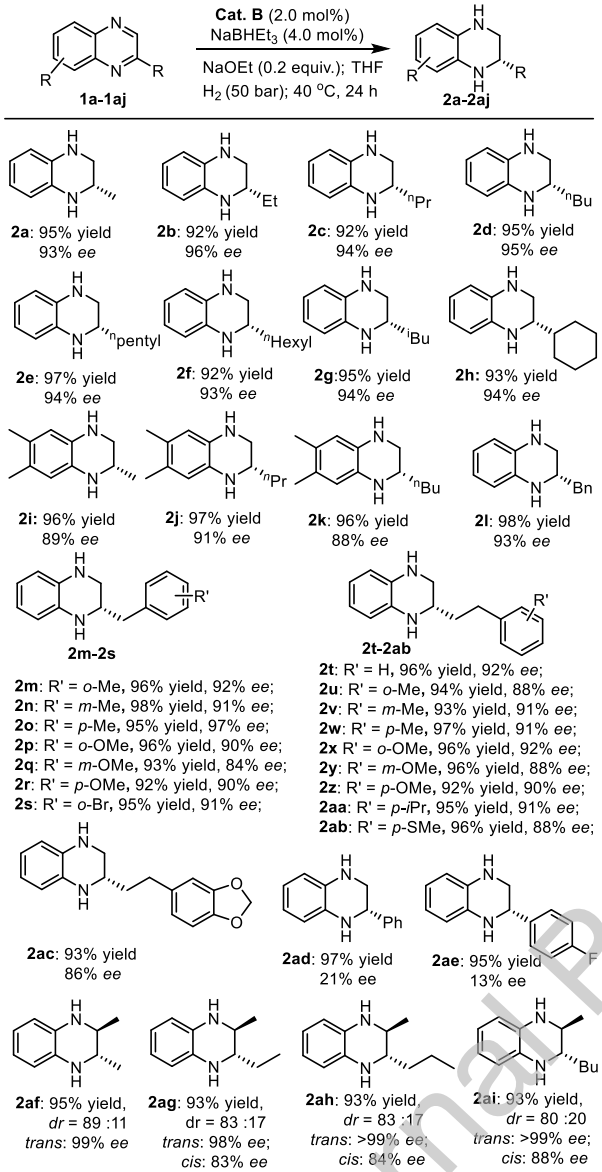
[a] Reaction conditions: 2-methylquinoxaline (0.25 mmol), catalyst (2 mol%), solvent (0.5 mL), base, 50 bar H_2, 24 h; ND: not detected.
[b] The yields were determined by ^{1}H NMR with 1,3,5-trimethoxybenzene as an internal standard and the *ee* values were determined by HPLC (OD-H column) analysis.

Following our pursuit of cobalt-catalyzed enantioselective hydrogenation reactions, we initially examined the AH of 2-methylquinoxaline (**1a**) with our previously reported cobalt catalyst **Cat. A** under conditions similar to those previously described for AH of ketones [54]. The **Cat. A** was firstly activated with a reducing reagent $NaBHEt_3$, possibly giving a Co(I)-H complex from **Cat. A** [67,68]. Disappointingly, no reaction was observed (Table 1, entry 1). Changing the weak base $CsCO_3$ to a strong one, NaOMe, led to a significant change, with **2a** being formed in 75% yield and 62% *ee* (Table 1, entry 2). Following this lead, a series of parameters were screened (Table 1, entries 1-9; see Supporting information for more details), and we eventually found that when using NaOEt as the base in THF at 50 bar, the AH afforded full conversion of **1a**, although the enantioselectivity remained unsatisfactory, at 78% *ee* (Table 1, entry 9). In order to improve the enantioselectivity, we opted to alter the structure of the PNN ligand. With the thought to make the ligand sterically more demanding and differentiating, a stereogenic phosphorus atom was introduced to replace the original achiral phosphine moiety. [69] To this end, a new chiral PNN ligand **VI** bearing a P as well as a C-stereogenic center was synthesized and the corresponding cobalt complex, **Cat. B**, was prepared by reacting the ligand with $CoCl_2$ in THF. The details of the ligand and complex synthesis are outlined in Scheme 2 (see Supporting information for experiment details) [70-73]. The absolute configurations of compound **III** (CCDC: 2355942) and **Cat. B** (CCDC: 2355923) have been confirmed by X-ray crystallographic analysis. As with **Cat. A** (CCDC: 1997410) [54], the complex **Cat. B** exists as a dimer in the solid state with the two Co(II) centers bridged by two chloride ions and each Co(II) in a distorted octahedral geometry. The bridge is strengthened by each of the axial chloride hydrogen bonding with the neighboring NH proton. However, the dimer is expected to dissociate into a monomeric form in catalysis.



Scheme 2. Synthesis of a new chiral PNN ligand **VI** and its complex with Co(II), **Cat. B**. The X-ray structures of compound **III** and the dimeric form of **Cat. B** are shown.

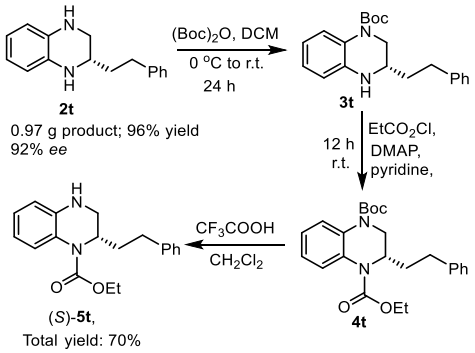
The newly synthesized **Cat. B** was tested for the hydrogenation of **1a** under the optimized reaction conditions for **Cat. A**. Delightfully, the enantioselectivity increased from 78% to 93% *ee* with **1a** fully converted (Table 1, entries 9 *vs.* 10). Further optimization of the reaction condition did not lead to better enantioselectivities (see Supporting information for details).



Scheme 3. Scope of substrates. Reaction conditions: quinoxaline (0.25 mmol), **Cat. B** (0.005 mmol), $NaBHEt_3$ (0.01 mmol), NaOEt (0.05 mmol), THF (0.5 mL), 40 °C, H_2 (50 bar), 24 h, isolated yields. The *ee* values were determined by HPLC analysis.

With the optimized reaction conditions in hand, we subsequently turned attention to examining the substrate scope of the AH reaction enabled by **Cat. B** (Scheme 3). 2-Alky substituted quinoxalines were firstly studied. All the tested 2-alky substituted quinoxalines could undergo smooth hydrogenation under the optimized reaction conditions, giving excellent yields and enantioselectivities (Scheme 3, **1a**-**1h**). The enantioselectivity was relatively insensitive to the length (**2a**-**2f**) or bulkiness (**2g**-**2h**) of alkyl substituents. With increased steric bulkiness, the 6,7-dimethyl quinoxalines (**1i**-**1k**) could still be hydrogenated smoothly, affording excellent yields; however, the enantioselectivities decreased somewhat (**2i**-**2k**). For quinoxalines with 2-benzyl-substituted groups (**1l**-**1s**), the yields were excellent and the enantioselectivities were high, regardless of whether the phenyl ring contains an electron-donating group (**1m**-**1r**) or electron-withdrawing one (**1s**). The enantioselectivity of the product with a *meta*-substituted phenyl ring is slightly lower than *para*- or *ortho*-substituted ones (**2q** *vs.* **2p** and **2r**). The best enantioselectivity was observed for product **2o** with a 2-*para*-methyl benzyl group (97% *ee*). Quinoxalines containing 2-substituted phenethyl groups were also investigated under the standard reaction conditions (**1t**-**1ac**). The substrates were hydrogenated smoothly, affording excellent yields (92%-97%), with the enantiomeric excesses varied between 86% and 92%. Interestingly, the substrate with a *para*-SMe group (**1ab**) underwent the AH smoothly with **2ab** obtained in 88% *ee*, demonstrating the robustness of the Co(II) catalyst. For 2-aryl substituted quinoxalines, the enantioselectivities were reduced considerably. Examples are seen in the AH of **1ad**-**1ae**, which afforded **2ad**-**2ae** in 21% and 13% *ee*, respectively, although the yield was excellent. Clearly, the chiral environment created by the PNN ligand **VI** around Co(II) cannot effectively recognize the two arene faces when there is a 2-aryl group; the reason remains to be elucidated though. We also explored some 2,3-disubstiuted quinoxalines (**1af**-**1ai**) [27,74]. As can be seen from Scheme 3, diastereomeric products were formed, with *trans* isomers being the major products (**2af**-**2ai**). The ratios of *trans*/*cis* products ranged from 80:20 to 89:11. It is worth noting that the enantioselectivities of the *trans*-products are excellent, reaching up to >99%

ee, and are much higher than those of the *cis* isomers.



Scheme 4. A gram scale AH reaction and product derivatization.

Finally, considering the importance of tetrahydroquinoxaline derivatives as biologically relevant molecules, the hydrogenation of **1t** was carried out on a gram scale followed by the conversion to a potentially bioactive compound. Using the optimized reaction conditions, product (*S*)-**2t** was isolated in a high yield of 96% with 92% *ee* (Scheme 4). Following Ohshima's method [19], chemoselective *N*-Boc protection resulted in compound **3t**, which was then treated with ethylchoroformate to give **4t**. The deprotection of **4t** with trifluoroacetic acid in dichloromethane led to the formation of **5t** in 70% overall yield, which is an analogue of an inhibitor of cholesteryl ester transfer protein (CETP) [75].

In conclusion, we have developed the first cobalt-catalyzed AH of quinoxalines, with the asymmetry induced by a chiral PNN ligand featuring both a P and a C-stereogenic center. The introduction of chirality to the phosphine unit of the PNN ligand is critical for achieving high enantioselectivities in the AH of quinoxalines. The cobalt catalyst demonstrated a broad scope of quinoxalines and good to excellent enantioselectivities. The design strategy of combining P and C-stereogenic centers in a pincer ligand could shed a new light on the development of more effective chiral 3*d* metal catalysts for asymmetric catalysis in general.

Acknowledgments

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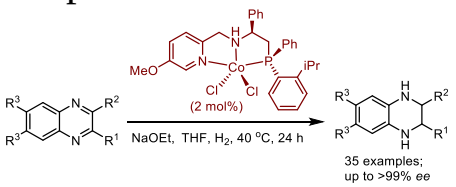
Graphical abstract



A cobalt pincer complex bearing both P and C-stereogenic centers has been developed, which catalyzes asymmetric hydrogenation of subtituted quinoxalines, affording good to excellent enantioselectivities.

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Declarations of interest: none