Organic & Biomolecular Chemistry

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: Y. Liu, F. Chen, Y. He, C. Li and Q. Fan, *Org. Biomol. Chem.*, 2019, DOI: 10.1039/C9OB00770A.

ROYAL SOCIETY OF CHEMISTRY

rsc.li/obc

View Article Online
DOI: 10.1039/C9OB00770A

ARTICLE

Enantioselective Synthesis of Tunable Chiral Pyridine–Aminophosphine Ligands and Their Application in Asymmetric Hydrogenation

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

Youran Liu,[a] Fei Chen,[a] Yan-Mei He,[a] Chenghao Li,[a] and Qing-Hua Fan*[a,b]

A small library of tunable chiral pyridine–aminophosphine ligands were enantioselectively synthesized based on chiral 2-(pyridin-2-yl)-substituted 1,2,3,4-tetrahydroquinoline scaffolds, which were obtained in high yields and excellent enantioselectivities via ruthenium-catalyzed asymmetric hydrogenation of 2-(pyridin-2-yl)quinolines. The protocol features wide substrate scope, mild reaction conditions and enabling scalable synthesis. These chiral P,N ligands were successfully applied in the Ir-catalyzed asymmetric hydrogenation of benchmark olefins as well as challenging seven-membered cyclic imines including benzazepines and benzodiazepines. Excellent enantio- and diastereoselectivity (up to 99% ee and >20:1 dr), and/or unprecedented chemoselectivity were obtained in the asymmetric hydrogenation of 2,4-diaryl-*3H*-benzo[*b*]azepines and 2,4-diaryl-*3H*- benzo[*b*][1,4]diazepines.

Introduction

Advances in transition-metal catalyzed asymmetric catalysis are closely related to the development of new chiral ligands, which can lead to excellent enantioselective control in catalysis and even enable previously impossible asymmetric transformations. To date, a huge number of chiral ligands and their transition metal complexes have been developed for different organic transformations.[1] However, only a few of them have demonstrated high generality for various asymmetric reactions.[1b,1c,1g] The development of new tunable chiral ligands is still one of the central themes in asymmetric catalysis. On the other hand, preparation of chiral ligands relies heavily on optical resolution of racemic backbones using resolving agents or the use of the available pool of chiral building blocks. This classical approach often suffers from a long synthetic route and/or difficulty in tuning the electronic and steric effect of ligands. In this context, alternative methodologies for efficient catalytic enantioselective synthesis of chiral ligands remain rare[1h,2] and thus highly desirable.

The iridium complexes of chiral P,N ligands have been recognized as powerful catalysts in the asymmetric hydrogenation of unfunctionalized olefins and imines[3] since the pioneering work of Pfaltz and co-workers,[1e] who developed chiral PHOX ligands to mimic Crabtree's catalyst.[4] To date, a number of chiral P,N ligands have been developed by combining phosphorus units with oxazoline or other nitrogen-containing heteroaromatic rings as the chelating moieties.[1e,1f,5] Among them, only a few examples are the P,N ligands derived from pyridine,[5] more closely matching the Crabtree's catalyst. The representative examples were chiral ligands **1** ~ **3** reported by Pfaltz and co-workers (Figure 1a). All these ligands showed excellent enantioselective control in the iridium-catalyzed asymmetric hydrogenation. Particularly, the iridium complexes of bicyclic P,N ligand **3** are highly efficient catalysts for the asymmetric hydrogenation of challenging purely alkyl-substituted olefins and furan derivatives.[5c,5d] Intrigued by the excellent performance of these pyridine-containing P,N ligands, we report herein a facile synthesis of a new type of tunable chiral pyridine-aminophosphine ligands **4** derived from chiral tetrahydroquinoline backbones (Figure 1b).

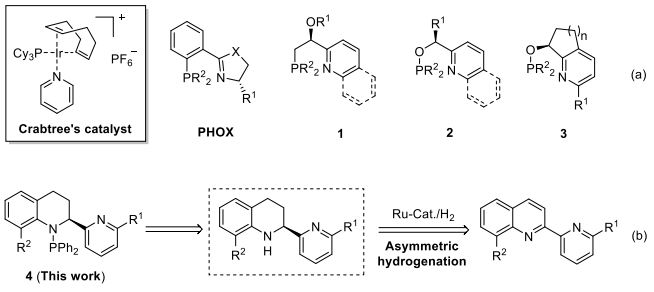


Figure 1. Representative chiral pyridine-containing P,N ligands (a) and a designed synthetic route to new pyridine-aminophosphine ligands **4** (b).

Recently, we have demonstrated that the ruthenium complexes of chiral monosulfonated diamines[6] are excellent catalysts for the asymmetric hydrogenation of quinolines and

[a] *Beijing National Laboratory for Molecular Sciences, CAS Key Laboratory of Molecular Recognition and Function, Institute of Chemistry, Chinese Academy of Sciences (CAS), and University of Chinese Academy of Sciences, Beijing 100190, P. R. China; E-mail: fanqh@iccas.ac.cn*
[b] *Collaborative Innovation Center of Chemical Science and Engineering, Tianjin 300072, P. R. China.*
† Electronic Supplementary Information (ESI) available: experimental procedures and characterization for all of the compounds. See DOI: 10.1039/x0xx00000x

other heteroaromatics.[7,8] In particular, this catalytic system was also very effective in the hydrogenation of polycyclic heteroarenes such as 1,10-phenanthrolines, naphthyridines and bisquinolines with excellent enantioselectivity.[8] Intrigued by these results, we envision that these ruthenium complexes could catalyze the asymmetric hydrogenation of challenging 2-(pyridin-2-yl)quinoline derivatives, thus providing a chiral tetrahydroquinoline backbone for the facile synthesis of chiral P,N ligands **4** (Figure 1b). The notable features of these new P,N ligands are their tunability by variation of the substituents on both the pyridyl ring (R^1) and the tetrahydroquinoline backbone (R^2), which would have a great impact on the efficiency and stereoselectivity of their iridium catalysts in the asymmetric hydrogenation of olefins and cyclic imines.

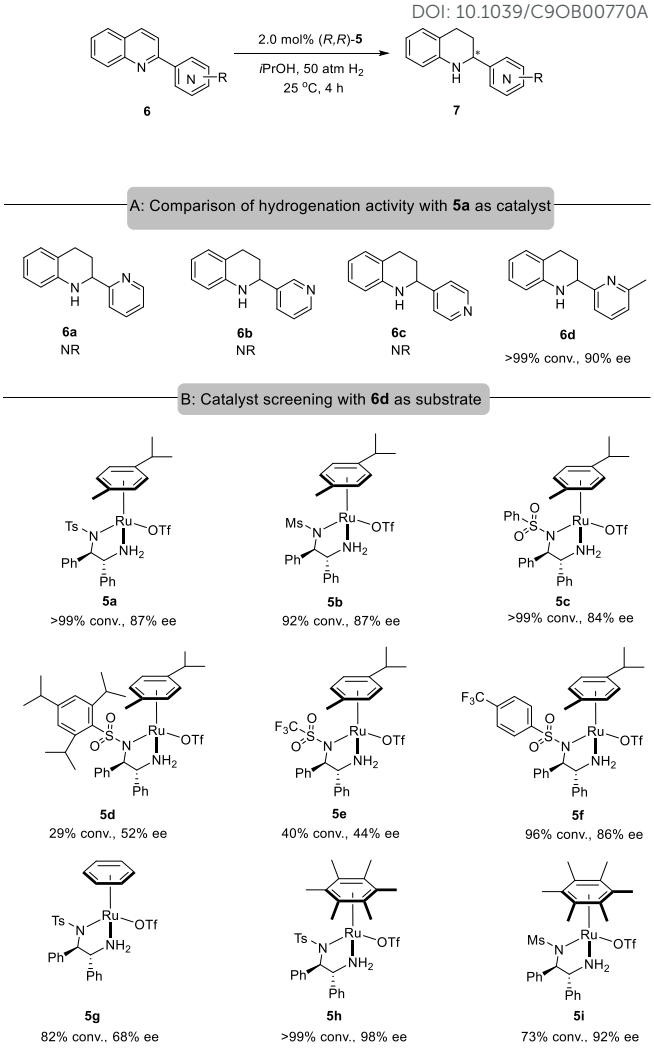
Results and Discussion

Asymmetric Hydrogenation of 2-(Pyridin-2-yl)quinoline Derivatives.

The substrates containing a pyridyl group are difficult to be hydrogenated, because the pyridyl group has strong coordination to the metal center and may thus deactivate the catalyst.[9] As far as we know, the asymmetric hydrogenation of pyridine-substituted quinoline derivatives have not been reported so far, and only a few hydrogenations with achiral catalyst have been reported.[10] In our initial experiment, 2-(pyridin-2-yl)quinoline **6a** was chosen to be hydrogenated with (*R,R*)-**5a** in *i*PrOH under 50 atm H_2. However, the reduced product 2-(pyridin-2-yl)-1,2,3,4-tetrahydroquinoline was not detected. Similarly, hydrogenation of 2-(pyridin-3-yl)quinoline **6b** and 2-(pyridin-4-yl)quinoline **6c** could neither take place. Notably, reaction of 2-(6-methylpyridin-2-yl)quinoline **6d** was hydrogenated smoothly, and full conversation with 90% ee was observed under the same conditions. This was probably due to the steric effect of the *ortho*-substituted methyl group which could reduce the coordinating ability of nitrogen atom.[9c,11] In addition, the introduction of a substituent at the *ortho* position of pyridine ring not only improves the catalytic reactivity, but also enables further tuning of the steric effect of ligand.

The hydrogenation of 2-(6-methylpyridin-2-yl)quinoline (**6d**) was chosen as the model substrate for the optimization of reaction conditions. Firstly, all catalysts described in Table 1 were tested. Generally, the catalytic performance was significantly affected by both the substituents of the η^6-arene ligand and the N-sulfonate substituents. Introducing alkyl substituents into the η^6-arene of the Ru catalysts led to significant increase in enantioselectivity, and the catalyst bearing a hexamethylbenzene ligand (*R,R*)-**5h** offered 97% ee and full conversion. In addition, the influence of solvent was studied and *i*PrOH was selected as the solvent of choice in terms of both reactivity and enantioselectivity (entries 1-7 in Table *S1*, Supporting Information). The influences of temperature and hydrogen pressure were also studied. Reducing the hydrogen pressure or increasing the reaction temperature resulted in a slightly decrease in enantioselectivity (entries 8-10 in Table *S1*).

Table 1. Optimization of Reaction Conditions [a]



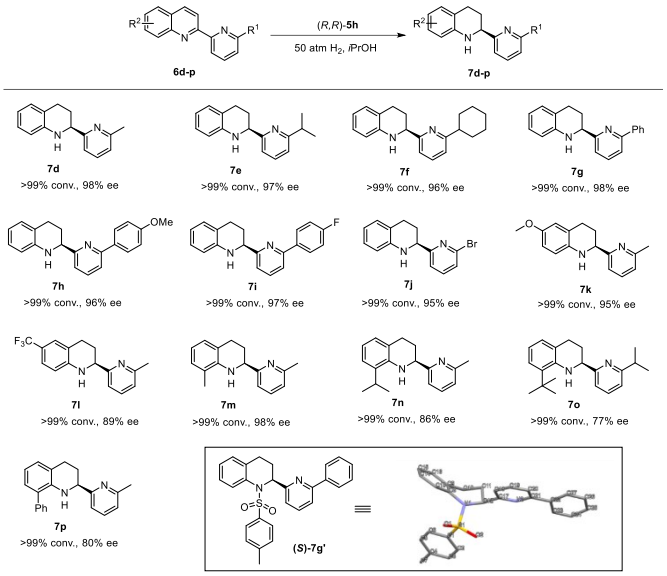
[a]Reaction conditions：substrate **6** (0.1 mmol), *i*PrOH (1 mL), Ru-catalyst **5** (2.0 mol %), H_2 (50 atm), stirred at rt for 4 h. The conversions were determined by ^{1}H NMR spectroscopy of the crude reaction mixture. The ee values were determined by chiral OB-H column.

Having established the optimal reaction condition, we then explored the substrate scope of the hydrogenation reactions (Scheme 1). Generally, all 2-(pyridin-2-yl)quinoline derivatives studied were hydrogenated smoothly in full conversions with good to excellent enantioselectivities (77%-98% ee). Excellent enantioselectivities were achieved with the substrates **6d-6i** bearing either an alkyl or aryl substituents at the 2-position of pyridine ring. Notably, the hydrogenation of substrate **6j** bearing a Br substituent on the pyridine proceeded smoothly with 5.0 mol% catalyst, and 97% ee was observed. Introducing substituents at the 6-position or 8-position of quinoline backbone resulted in lower reactivity, and 5.0 mol% catalyst was needed to achieve full conversion (**6k-6p**). Meanwhile, a lower enantioselectivity was obtained when an electron-withdrawing CF_3 group was located at the 6-position of quinoline backbone (**6l**). In the cases of 8-substituted 2-(pyridin-2-yl)quinolines, the ee value dropped sharply as the steric hindrance of the alkyl side chain increased (**6m-6o**). The hydrogenation of 8-phenyl substituted substrate **6p** proceeded smoothly but giving only

DOI: 10.1039/C9OB00770A

80% ee. In addition, the absolute configuration of **7g'** was determined to be *S* based on single-crystal X-ray analysis.

Scheme 1. Asymmetric Hydrogenation of 2-(Pyridin-2-yl)quinoline Derivatives[a]



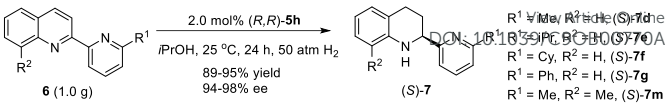
[a]Reaction conditions: substrates **6d-i** (0.2 mmol), *i*PrOH (2 mL), 2.0 mol % of (*R,R*)-**5h**, H_2 (50 atm), stirred at 25 °C for 12 h; substrates **6j-p** with 5.0 mol % of (*R,R*)-**5h**. The conversions were determined by ^{1}H NMR spectroscopy of the crude reaction mixtures. The enantiomeric excesses were determined by HPLC with a chiral HPLC column. The absolute configuration of **7g'** was determined to be *S* on the basis of single-crystal X-ray analysis.[12]

The Synthesis of P,N-Ligands 4 and Their Ir-Complexes 8.

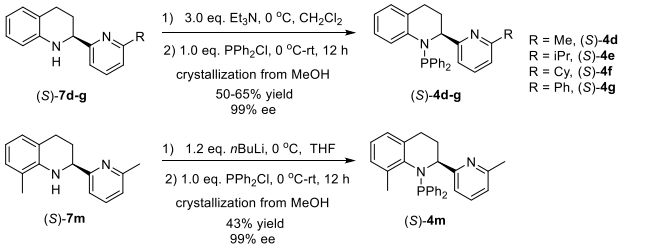
On the basis of the hydrogenation results, the reduced products **7d-7g** and **7m** which have excellent ee values were chosen for the further synthesis of chiral P,N ligands. As illustrated in Scheme 2, the synthesis of enantiopure P,N-ligands and catalysts are quite simple and straightforward. First, the hydrogenation of 2-(pyridin-2-yl) quinolines **6** on gram-scale with (*R,R*)-**5h** under the optimal reaction conditions gave chiral products **7** with excellent yields (89-95%) and well maintained enantioselectivities (94-98%). Then, the resulting chiral 1,2,3,4-tetrahydroquinolines **7** were readily converted into P,N-ligands **4** by treatment with PPh_2Cl in the presence of triethylamine or *n*-BuLi. Moderate isolated yields and unchanged enantioselectivities were obtained. After recrystallization from methanol, all ligands **4** with 99% ee could be obtained. Finally, the iridium complexes **8** were prepared in very good yields (75-85%) by mixing ligand **4** with $[Ir(COD)Cl]_2$ in CH_2Cl_2 followed by anion exchange in the presence of sodium tetrakis-3,5-bis(trifluoromethyl)phenylborate.[13]

Scheme 2. Synthesis of P,N-Ligands **4** and Their Ir-Complexes **8**

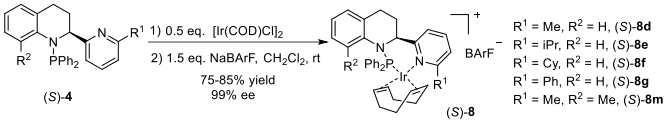
(1) Gram-scale asymmetric hydrogenation



(2) Synthesis of chiral P,N-ligands **4**



(3) Synthesis of chiral Ir-complexes **8**



The synthesized iridium complexes **8d-g** and **8m** were characterized by NMR and ESI-MS. Luckily, the single crystals of the complexes (*S*)-**8f**, (*S*)-**8g** and (*S*)-**8m** were obtained.[14] As shown in Figure 2, in all cases, the Ir-complex adopts a boatlike conformation and the two *P*-phenyl groups adopt the normal axial-equatorial orientations with respect to the coordination plane defined by the P-Ir-N core. The structure of (*S*)-**8f** and (*S*)-**8g** is very similar. The substituents on the pyridine ring in both complexes extend towards the coordination sphere and, therefore, are expected to interact with alkene substrate bounded at the adjacent coordination site. In the case of (*S*)-**8m** bearing another methyl substituent at the 8-position of tetrahydroquinoline backbone, its structure is somewhat different and the tetrahydroquinoline motif extends towards the coordination sphere. This difference in structure may has a great impact on their catalytic performance.

(*S*)-**8f** (*S*)-**8g** (*S*)-**8m**

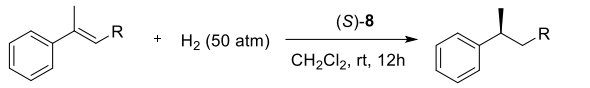
Figure 2. Crystal structures of (*S*)-**8f**, (*S*)-**8g** and (*S*)-**8m**; the anion $BArF^-$ and hydrogen atoms are omitted for clarity. Seleted bond lengths [Å] and angles [°], (*S*)-**8f**: Ir-N 2.142(13), Ir-P 2.303(4); N–Ir–P 83.8(4). (*S*)-**8g**: Ir-N 2.140(8), Ir-P 2.290(2); N–Ir–P 84.3(2). (*S*)-**8m**: Ir-N 2.114(3), Ir-P 2.264(8); N–Ir–P 82.3(8).

Applications in Asymmetric Hydrogenation of Olefins and Cyclic Imines

DOI: 10.1039/C9OB00770A

The *trans*-beta-methylcinnamate **9a** and *E*-1,2-diphenylpropene **9b** were chosen as the model substrates to test the performance of catalysts **8**. The reactions were performed in CH_2Cl_2 under 50 atm hydrogen pressure at 25 °C. As shown in Table 2, in the hydrogenation of **9a**, catalyst (*S*)-**8d**, **8e** and **8f** bearing an alkyl group on the pyridine ring gave similar enantioselectivity around 88-92% ee (entries 1-3). Much lower conversion and ee value were observed by using catalyst **8g** bearing a aryl group on the pyridine ring (entry 4). Notably, catalyst (*S*)-**8m** bearing another methyl group at the 8-position of tetrahydroquinoline backbone, led to remarkable increase in enantioselectivity (90% ee *vs* 99% ee) but with high catalyst loading (entry 1 *vs* 5). For substrate **9b**, similar results were obtained with these iridium catalysts (entries 6-10), and excellent enantioselecivity (99% ee) was achieved with catalyst (*S*)-**8m** (entry 10). Theses results indicate that the new Ir-P,N-ligand complexes **8** are efficient catalysts for the hydrogenation of trisubstituted olefins.

Table 2. Asymmetric hydrogenation of Ethyl *trans*-beta-Methylcinnamate and *E*-Methysibene[a]



9a: R = CO_2Et
9b: R = Ph

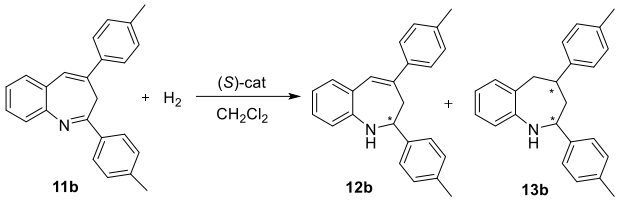
S-**10a:** R = CO_2Et
S-**10b**: R = Ph

Entry	Substrate	Catalyst	Sub/Cat	Conv. (%)[b]	Ee (%)[c]
1	**9a**	(*S*)-**8d**	100	>99	90
2	**9a**	(*S*)-**8e**	100	>99	88
3	**9a**	(*S*)-**8f**	100	>99	92
4	**9a**	(*S*)-**8g**	100	39	54
5	**9a**	(*S*)-**8m**	50	>99	>99
6	**9b**	(*S*)-**8d**	100	>99	94
7	**9b**	(*S*)-**8e**	50	>99	87
8	**9b**	(*S*)-**8f**	50	>99	82
9	**9b**	(*S*)-**8g**	25	32	42
10	**9b**	(*S*)-**8m**	25	>99	>99

[a]Reaction conditions: substrate **9** (0.1 mmol) in CH_2Cl_2 (1.0 mL), Ir-catalyst, H_2 (50 atm), stirred at rt for 12 h. [b]The conversions were determined by ^1H NMR spectroscopy of the crude reaction mixtures. [c]The enantiomeric excesses were determined by HPLC with a chiral column, and the absolute configuration was determined by comparison of optical rotation with literature data.

Having established these complexes as effective catalyts in the reduction of olefins, we then turned our attention to the asymmetric hydrogenation of some challenging seven-membered cyclic imines. The resulting chiral nitrogen hetercycles such as benzoazepines and benzodiazepines are versatile pharmacophores in medicinal chemistry.[15] In sharp contrast to simple olefins and acyclic imines, asymmetric hydrogenation of such benzo-fused cyclic imines remains less explored.[16] We first studied the asymmetric hydrogenation of benzoazepine derivatives containing both C=C and C=N bonds. Considering the facts that iridium complexes of P,N-ligands are effective catalysts for both C=C and C=N bonds, it is thus a challenge to precisely control the chemoselectivity, enantioselectivity and diastereoselectivity.[4]

Table 3. Optimization of Reaction Conditions for the Hydrogenation of 2,4-Diaryl-3*H*-benzo[*b*]azepines [a]



Entry	Cat. (mol%)	Conv. (%)[b]	Ratio (**12b:13b**)	Ee (%)[c] (**12b/13b**)	Dr (**13b**)[d]
1	(*S*)-**8d** (1.0)	>99	>99 : nd	58/--	--
2	(*S*)-**8e** (1.0)	>99	>99 : nd	90/--	--
3	(*S*)-**8f** (2.0)	>99	>99 : nd	54/--	--
4	(*S*)-**8g** (4.0)	>99	87 : 13	16/--	--
5	(*S*)-**8m** (2.0)	>99	>99 : nd	20/--	--
6	(*S*)-**8e** (3.0)	>99	nd : > 99	--/84	3:1
7[e]	(*S*)-**8e** (3.0)	>99	nd : >99	--/90	12:1
8[f]	Ir-PHOX (4.0)	>99	>99 : nd	69/--	--

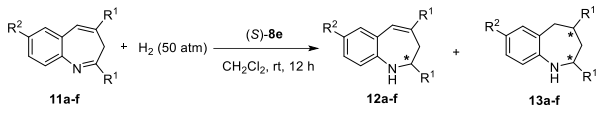
[a]Reaction conditions: substrate **11b** (0.05 mmol) in CH_2Cl_2 (0.5 mL), Ir-catalyst **8**, H_2 (50 atm), stirred at rt for 12 h. [b]The conversions were determined by ^1H NMR spectroscopy of the crude reaction mixtures. [c]The enantiomeric excesses were determined by HPLC with a chiral OD-H column. [d]The dr was determined by ^1H NMR spectroscopy. [e]Two-step one-pot process: **11b** was hydrogenated with 1.0% mol (*S*)-**8e** for 12 h, and then released the hydrogen gas and added another 2.0% mol (*S*)-**8e** followed by hydrogenation for another 12 h. [f] With 1.0 mol% Ir-PHOX, 92% conversion with the same chemo- and enantioselectivity.

In our previous study,[16b,16g] the asymmetric hydrogenation of 2,4-diaryl-*3H*-benzo[*b*]azepines with chiral Ru- and Ir-catalyst only gave the partially hydrogenated products 2,4-diaryl-2,3-dihydro-*1H*-benzo[*b*]azepines, in which the C=C bond cound not be reduced. We firstly examined the asymmetric hydrogenation of 2,4-di-*p*-tolyl-*3H*-benzo[*b*]azepine (**11b**) catalyzed by 1.0 mol % of (*S*)-**8d** in CH_2Cl_2 under 50 atm H_2 pressure at 25 °C for 12 h. The reaction proceeded smoothly, and only the partially hydrogenated product **12b** was observed in full conversion with 58% ee (entry 1 in Table 3). Encouraged by this result, we subsequently screened other iridium catalysts (entries 2-5). It was found that the catalytic performance was significantly affected by both the substituents on the pyridine ring and tetrahydroquinoline backbone. Among these iridium catalysts, (*S*)-**8e** bearing an isopropyl substitution on the pyridine ring exhibited the best enantioselectivity (90% ee, entry 2). In contrast, the best catalyst (*S*)-**8m** in the hydrogenation of olefins gave much lower enantioselectivity (entry 5). It was noted that the fully reduced product **13b** was observed when 4.0 mol% (*S*)-**8g** was used (entry 4). We thus increased the catalyst loading of (*S*)-**8e** from1.0 to 3.0 mol%, and **13b** was obtained as the sole product with 84% ee and 3:1 dr (entry 6). Interestingly, when this reaction was carried out through a two-step one-pot process (entry 7), obviously higher enantio- and diastereoselectivity was obtained (90% ee and 12:1 dr). In comparison, when 4.0 mol% Ir-PHOX was used as the catalyst under

DOI: 10.1039/C9OB00770K

otherwise the same conditions, only **12b** were observed with moderate enantioselectivity (entry 8).

Table 4. Asymmetric Hydrogenation of Benzazepines Catalyzed by (*S*)-**8e**[a]



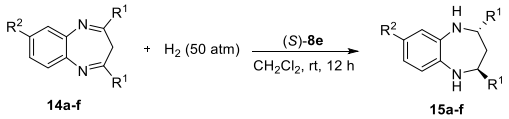
Entry	R^2/R^1 (substrate)	Conv. (%)[b]	Ratio (**12:13**)	Ee (%)[c]	Dr[d]
1	H/Ph (**11a**)	>99	>99:nd	86 (-)	-
2	H/*p*-tolyl (**11b**)	>99	>99:nd	90 (-)	-
3	H/4-MeO-Ph (**11c**)	>99	>99:nd	95 (*S*)	-
4	H/4-Cl-Ph (**11d**)	>99	>99:nd	92 (-)	-
5	H/4-Br-Ph (**11e**)	>99	>99:nd	88 (-)	-
6[e]	MeO/Ph (**11f**)	>99	70:30	90 (-)	-
7[f]	H/Ph (**11a**)	>99	nd:>99	90 (+)	12:1
11[f]	H/*p*-tolyl (**11b**)	>99	nd:>99	88 (+)	8:1
9[f,g]	H/4-MeO-Ph (**11c**)	>99	nd:>99	99(*2S,4S*)	16:1
10[f]	H/4-Cl-Ph (**11d**)	>99	nd:>99	94 (+)	20:1
11[f]	H/4-Br-Ph (**11e**)	>99	nd:>99	90 (+)	5:1
12[f]	MeO/Ph (**11f**)	>99	nd:>99	88 (+)	11:1

[a]Reaction conditions: substrate **11** (0.2 mmol) in CH_2Cl_2 (2.0 mL), 1.0 mol % (*S*)-**8e**, H_2 (50 atm), stirred at rt for 12 h. [b]The conversions were determined by ^{1}H NMR spectroscopy of the crude reaction mixtures. [c]The enantiomeric excesses were determined by HPLC with a chiral OD-H column. The absolute configuration of **12c** was determined to be *S* based on single-crystal X-ray analysis,[17] and the absolute configuration of **13c** was determined to be (2*S*,4*S*) based on the absolute configuration of **12c** and 2D-NOESY spectrum. [d]The dr were determined by ^{1}H NMR. [e]With 0.5 mol% (*S*)-**8e** and H_2 (20 atm). [f]Hydrogenation through two-step one-pot process (entry 7 in Table 3). [g]In the second step, 3 mol % (*S*)-**8e** was added and stirred for 18 h.

With the optimizing conditions in hand (entries 2 and 7 in Table 3), we further explored the scope of the Ir-catalyzed asymmetric hydrogenation of benzazepines (Table 4). In the presence of 1.0 mol% (*S*)-**8e**, full conversions and excellent enantioselectivities were observed in all cases (entries 1-6). Notably, hydrogenation of **11f** bearing a methoxy substituent at the 7-position gave a mixture of both products **12f** and **13f** even under low hydrogen pressure and catalyst loading (entry 6). In addition, the fully reduced products could be obtained through a two-step one-pot process with excellent enantioselectivities (up to 99% ee) and moderate to high diastereoselectivities (entries 7-12).

Encouraged by the above excellent results, we then extended this catalytic system to the asymmetric hydrogenation of benzodiazepines (Table 5). To our delight, the optimal reaction conditions selected for the hydrogenation of benzazepines could also work well for benzodiazepines. Several 2,4-diaryl-substituted benzodiazepines (**14**) were hydrogenated smoothly (entries 1–5), affording the reduced products in very good yields with excellent enantio- and diastereoselectivities (up to 99% ee and >20:1 dr), regardless of either the electronic effect or the position of substituents at the phenyl ring. Notably, the hydrogenation of substrate **14f** bearing a CH_3 substituent gave a much lower enantio- and diastereoselectivity (entry 6). In comparison, when Ir-PHOX complex was used as the catalyst for substrate **14a**, much lower enantioselectivity and diastereoselectivity were obtained (entry 1 vs 7)

Table 5. Asymmetric Hydrogenation of Benzodiazepines Catalyzed by (*S*)-**8e**[a]



Entry	R^2/R^1 (substrate)	Conv. (%)[b]	Ee (%)[c]	Dr[d]
1	H/Ph (**14a**)	>99	99 (*2S,4S*)	16:1
2	H/4-Cl-Ph (**14b**)	>99	97 (*2S,4S*)	10:1
3	H/4-Br-Ph (**14c**)	>99	99 (*2S,4S*)	>20:1
4	MeO/Ph (**14d**)	>99	99 (*2S,4S*)	20:1
5	Cl/Ph (**14e**)	>99	99 (*2S,4S*)	>20:1
6	H/Me (**14f**)	>99	10 (*2R,4R*)	1:2
7[e]	H/Ph (**14a**)	>99	84 (*2R,4R*)	4:1

[a]Reaction conditions: substrate **14** (0.2 mmol) in CH_2Cl_2 (2 mL), 4.0 mol% (*S*)-**8e**, H_2 (50 atm), stirred at rt for 12 h. [b]The conversions were determined by ^{1}H NMR spectroscopy of the crude reaction mixtures. [c]The enantiomeric excesses were determined by HPLC with a chiral OD-H column; and the absolute configuration was determined by comparison of optical rotation with literature data. [d]The dr were determined by ^{1}H NMR. [e]With 4.0 mol% (*S*)-PHOX-Ir catalyst under otherwise the same conditions.

Conclusions

In summary, the first asymmetric hydrogenation of 2-(pyridin-2-yl)quinoline derivatives was developed with up to 98% ee by using chiral cationic Ru(Ⅱ) diamine catalysts. Based on these chiral 2-(pyridin-2-yl)-1,2,3,4-tetrahydroquinoline scaffolds, a small library of tunable chiral pyridine–aminophosphine ligands (*S*)-**4** and their iridium complexes (*S*)-**8** were readily synthesized. The steric properties of the ligands **4** could be fine-tuned by simply changing the substituents on the chiral tetrahydroquinoline backbone and/or the pyridine ring, thereby providing a facile approach for catalysts optimization. These iridium catalysts were found to be efficient in the asymmetric hydrogenation of benchmark alkene substrates as well as challenging seven-membered cyclic imines including benzazepines and benzodiazepines. Excellent enantio- and diastereoselectivity (up to 99% ee and >20:1 dr), and/or unprecedented chemoselectivity were obtained in the asymmetric hydrogenation of 2,4-diaryl-*3H*-benzo[*b*]azepines and 2,4-diaryl-*3H*-benzo[*b*][1,4]diazepines. Further applications of these new ligands in other asymmetric catalysis are currently underway in our laboratory.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We thank the National Natural Science Foundation of China (NSFC, 21790332, 21521002 and 21672218) and CAS (QYZDJSSWSLH023) for financial support.

Notes and references

1. For selected reviews, see: (a) R. Noyori, Asymmetric Catalysis in Organic Synthesis, Wiley, New York, 1993; (b) T. P. Yoon and E. N. Jacobsen, *Science*, 2003, **299**, 1691; (c) Q.-L. Zhou, Privileged Chiral Ligands and Catalysts, Wiley, 2011; (d) W. Tang and X. Zhang, *Chem. Rev.,* 2003, **103**, 3029; (e) G. Helmchen and A. Pfaltz, *Acc. Chem. Res.,* 2000, **33**, 336; (f) J. J. Verendel, O. Pàmies, M. Diéguez and P. G. Andersson, *Chem. Rev.,* 2014, **114**, 2130, and references cited therein; (g) X. Liu, S. Dong, L. Lin and X. Feng, *Chin. J. Chem.*, 2018, **36**, 791; (h) X. Wang and K. Ding, *Chin. J. Chem.*, 2018, **36**, 899. (i) J. F. Teichert and B. L. Feringa, *Angew. Chem., Int. Ed.* 2010, **49**, 2486.
2. (a) D. S. Glueck, *Chem.-Eur. J.,* 2008, **14**, 7108; (b) J. Wencel-Delord, A. Panossian, F. R. Leroux and F. Colobert, *Chem. Soc. Rev*., 2015, **44**, 3418; (c) S. Li, J.-W. Zhang, X.-L. Li, D.-J. Cheng and B. Tan, *J. Am. Chem. Soc.,* 2016, **138**, 16561; (d) L. Yin, J. Xing, Y. Wang, Y. Shen, T. Lu, T. Hayashi and X. Dou, *Angew. Chem., Int. Ed.,* 2019, **58**, 2474.
3. For selected reviews, see: (a) S. J. Roseblade and A. Pfaltz, *Acc. Chem. Res.,* 2007, **40**, 1402; (b) X. Cui, and K. Burgess, *Chem. Rev.,* 2005, **105**, 3272; (c) C. Margarita and P. G. Andersson, *J. Am. Chem. Soc.,* 2017, **139**, 1346; (d) S.-F. Zhu and Q.-L. Zhou, *Acc. Chem. Res,* 2017, **50**, 988.
4. R. H. Crabtree, *Acc. Chem. Res.,* 1979, **12**, 331.
5. For selected examples, see: (a) T. Bunlaksananusorn, K. Polborn and P. Knochel, *Angew. Chem., Int. Ed.,* 2003, **42**, 3941; (b) W. J. Drury III, N. Zimmermann, M. Keenan, M. Hayashi, S. Kaiser, R. Goddard and A. Pfaltz, *Angew. Chem., Int. Ed.,* 2004, **43**, 70; (c) S. Kaiser, S. P. Smidt and A. Pfaltz, *Angew. Chem., Int. Ed.* 2006, **45**, 5194; (d) S. Bell, B. Wüstenberg, S. Kaiser, F. Mengens, T. Netscher and A. Pfaltz, *Science,* 2006, **311**, 642; (e) D. H. Woodmansee, M.-A. Müller, M. Neuburger and A. Pfaltz, *Chem. Sci.,* 2010, **1**, 72; (f) M. Bernasconi, M.-A. Müller and A. Pfaltz, *Angew. Chem., Int. Ed.,* 2014, **53**, 5385; (g) P. Tosatti and A. Pfaltz, *Angew. Chem., Int. Ed.,* 2017, **56**, 4579; (h) Q.- B. Liu, C.-B. Yu and Y.-G. Zhou, *Tetrahedron Letters,* 2006, **47**, 4733; (i) X. Quan, V. S. Parihar, M. Bera and P. G. Andersson, *Eur. J. Org. Chem.,* 2014, 140; (j) B. Qu, L. P. Samankumara, J. Savoie, D. R. Fandrick, N. Haddad, X. Wei, S. Ma, H. Lee, S. Rodriguez, C. A. Busacca, N. K. Yee, J. J. Song and C. H. Senanayake, *J. Org. Chem.,* 2014, **79**, 993.
6. (a) R. Noyori and S. Hashiguchi, *Acc. Chem. Res.*, 1997, **30**, 97; (b) S. Hashiguchi, A. Fujii, J. Takehara, T. Ikariya and R. Noyori, *J. Am. Chem. Soc.,* 1995, **117**, 7562; (c) N. Uematsu, A. Fujii, S. Hashiguchi, T. Ikariya and R. Noyori, *J. Am. Chem. Soc.,* 1996, **118**, 4916; (d) T. Ohkuma, N. Utsumi, K. Tsutsumi, K. Murata, C. Sandoval and R. Noyori, *J. Am. Chem. Soc.,* 2006, **128**, 8724.
7. (a) D.-S. Wang, Q.-A. Chen, S.-M. Lu and Y.-G. Zhou, *Chem. Rev.,* 2012, **112**, 2557; (b) D. Zhao, L. Candish, D. Paul and F. Glorius, *ACS Catal.,* 2016, **6**, 5978; (c) Y.-M. He, F.-S. Song and Q.-H. Fan, *Top. Curr. Chem.,* 2014, **343**, 145; (d) W.-B. Wang, S.-M. Lu, P.-Y. Yang, X.-W. Han and Y.-G. Zhou, *J. Am. Chem. Soc.,* 2003, **125**, 10536; (e) H. Zhou, Z. Li, Z. Wang, T. Wang, L. Xu, Y. He, Q.-H. Fan, J. Pan, L. Gu and A. S. C. Chan, *Angew. Chem., Int. Ed.*, 2008, **47**, 8464; (f) T. Wang, L.-G. Zhuo, Z. Li, F. Chen, Z. Ding, Y. He, Q.-H. Fan, J. Xiang, Z.-X. Yu and A. S. C. Chan, *J. Am. Chem. Soc.,* 2011, **133**, 9878.
8. (a) T. Wang, F. Chen, J. Qin, Y.-M. He and Q.-H. Fan, *Angew. Chem. Int. Ed.,* 2013, **52**, 7172; (b) J. Zhang, F. Chen, Y.-M. He and Q.-H. Fan, *Angew. Chem. Int. Ed.,* 2015, **54**, 4622; (c) W. Ma, F. Chen, Y. Liu, Y.-M. He and Q.-H. Fan, *Org. Lett.,* 2016, **18**, 2730; (d) W. Ma, J. Zhang, C. Xu, F. Chen. Y.-M. He and Q.-H. Fan, *Angew. Chem., Int. Ed.,* 2016, **55**, 12891; (e) B. Li, C. Xu, Y.-M. He, G.-J. Deng and Q.-H. Fan, *Chin. J. Chem.*, 2018, **36**, 1169.
9. (a) T. Ohkuma, M. Koizumi, M. Yoshida and R. Noyori, *Org. Lett.,* 2000, **2**, 1749; (b) M. Adamczyk, S. R. Akireddy and R. E. Reddy, *Org. Lett.,* 2001, **3**, 3157; (c) C. Guo, D.-W. Sun, S. Yang, S.-J. Mao, X.-H. Xu, S.-F. Zhu and Q.-L. Zhou, *J. Am. Chem. Soc.,* 2015, **137**, 90; (d) H. Yang, N. Huo, P. Yang, H. Pei, H. Lv and X.-M. Zhang, *Org. Lett.,* 2015, **17**, 4144; (e) B. Wang, H. Zhou, G. Lu, Q. Liu and X. Jiang, *Org. Lett.,* 2017, **19**, 2094; (f) H.-L. Sun, F. Chen, M.-S. Xie, H.-M. Guo, G.-R. Qu, Y.-M. He and Q.-H. Fan, *Org. Lett.,* 2016, **18**, 2260.
10. (a) V. Kouznetsov, L. Y. V. Méndez, B. Tibaduiza, C. Ochoa, D. M. Pereira, J. J. N. Ruiz, C. F. Portillo, S. M. Serrano, A. G. Bahsas and J. Amaro-Luis, *Arch. Pharm. Pharm. Med. Chem.,* 2004**, 337**, 127; (b) A. P. Combs, R. B. Sparks, T. P. Jr. Maduskuie and J. D. Rodgers, PCT Int. Appl., 2014143768, 2014**;** (c) P. A. Brough, A. Macias, S. D. Roughley and S. Stokes, PCT Int. Appl., 2015040424, 2015.
11. A. S. C. Chan, C.-C. Chen and R. Cao, *Organometallics,* 1997, **16**, 3469.
12. CCDC 1904944 {for [(*S*)-**7g'**]} contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.
13. P. Schnider, G. Koch, R. Prétôt, G. Wang, F. M. Bohnen, C. Krüger and A. Pfaltz, *Chem. Eur. J.,* 1997, **3**, 887.
14. CCDC 1904940 {for [(*S*)-**8f**]} and 1904938 {for [(*S*)-**8g**]} and 1904943 {for [(*S*)-**8m**]} contain the supplementary crystallographic data for this paper. These data can beobtained free of charge from The Cambridge Crystallographic Data Centre
15. (a) S. A. Giacobbe and R. D. Fabio, *Tetrahedron Lett.,* 2001, **42**, 2027; (b) K. Kondo, K. Kan, Y. Tanada, M. Bando, T. Shinohara, M. Kurimura, H. Ogawa, S. Nakamura, T. Hirano, Y. Yamamura, M. Kido, T. Mori and M. Tominaga, *J. Med. Chem.,* 2002, **45**, 3805; (c) A. Palma, A. F. Yépes, S. M. Leal, C. A. Coronado and P. Escobar, *Bioorg. Med. Chem. Lett.,* 2009, **19**, 2360; (d) O. Nyanguile, F. Pauwels, W. Van den Broeck, C. W. Boutton, L. Quirynen, T. Ivens, L. van der Helm, G. Vandercruyssen, W. Mostmans, F. Delouvroy, P. Dehertogh, M. D. Cummings, J.-F. Bonfanti, K. A. Simmen and P. Raboisson, *Antimicrob. Agents Chemother.,* 2008, **52**, 4420; (e) K. Vandyck, M. D. Cummings, O. Nyanguile, C. W. Boutton, S. Vendeville, D. McGowan, B. Devogelaere, K. Amssoms, S. Last, K. Rombauts, A. Tahri, P. Lory, L.-L. Hu, D. A. Beauchamp, K. Simmen and P. Raboisson, *J. Med. Chem.,* 2009, **52**, 4099.
16. For selected examples, see: (a) Z.-Y. Ding, F. Chen, J. Qin, Y.-M. He and Q.-H. Fan, *Angew. Chem., Int. Ed.,* 2012, **51**, 5706; (b) Z. Yang, Z. Ding, F. Chen, Y.-M. He, N. Yang and Q.-H. Fan, *Eur. J. Org. Chem.,* 2017, 1973; (c) K. Gao, B. Wu, C.-B. Yu, Q.-A. Chen, Z.-S. Ye and Y.-G. Zhou, *Org. Lett.,* 2012, **14**, 3890; (d) H.-Q. Shen, X. Gao, C. Liu, S.-B. Hu and Y.-G. Zhou, *Org. Lett.,* 2016, **18**, 5920; (e) B. Ma, Z. Ding, J. Liu, Y.-M. He and Q.-H. Fan, *Chem. Asian J.,* 2013, **8**, 1101; (f) K. Horiguchi, E. Yamamoto, K. Saito, M. Yamanaka and T. Akiyama, *Chem. Eur. J.,* 2016, **22**, 8078; (g) T. Miao, B. Ma, Z. Ding, Y. Liu, Y.-M. He, Q.-H. Fan, *Asian J. Org. Chem.,* 2017, **6**, 1219.
17. CCDC 1904946 {for [(*S*)-**12c**]} contain the supplementary crystallographic data for this paper. These data can be obtained

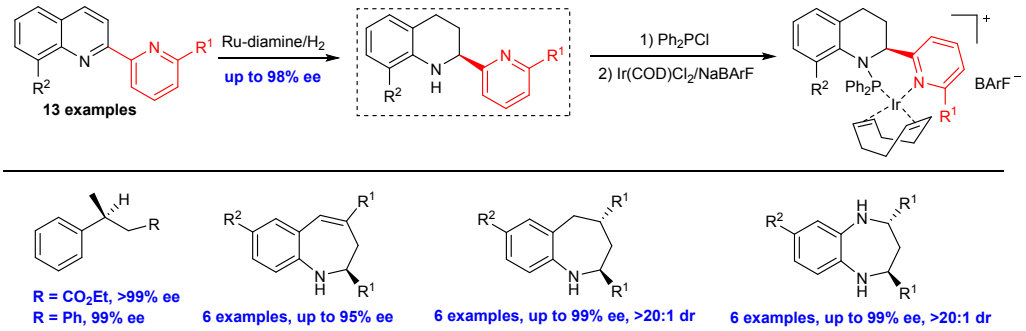
Journal Name ARTICLE

free of charge from The Cambridge Crystallographic Data Centre.

View Article Online
DOI: 10.1039/C9OB00770A

View Article Online
DOI: 10.1039/C9OB00770A

TOC



A small library of tunable chiral pyridine–aminophosphine ligands were synthesized based on chiral tetrahydroquinoline scaffolds, which were obtained *via* Ru-catalyzed asymmetric hydrogenation. The ligands were successfully applied in the Ir-catalyzed asymmetric hydrogenation of olefins and cyclic imines.