Organic & Biomolecular Chemistry

PAPER

View Article Online
View Journal | View Issue

Cite this: *Org. Biomol. Chem.*, 2019, **17**, 5099

Enantioselective synthesis of tunable chiral pyridine–aminophosphine ligands and their applications in asymmetric hydrogenation†

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

Received 3rd April 2019,
Accepted 30th April 2019

DOI: 10.1039/c9ob00770a

rsc.li/obc

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 with excellent enantioselectivities *via* ruthenium-catalyzed asymmetric hydrogenation of 2-(pyridin-2-yl)quinolines. The protocol features a wide substrate scope and mild reaction conditions, enabling scalable synthesis. These chiral P,N ligands were successfully applied in the Ir-catalyzed asymmetric hydrogenation of benchmark olefins and 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-3*H*-benzo[*b*]azepines and 2,4-diaryl-3*H*-benzo[*b*][1,4]diazepines.

Introduction

Advances in transition-metal catalyzed asymmetric catalysis are closely related to the development of new chiral ligands and 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,c,g] The development of new tunable chiral ligands is still one of the central themes in asymmetric catalysis. On the other hand, the preparation of chiral ligands relies heavily on the 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 the 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 the 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,f,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 (Fig. 1a). All these ligands showed excellent enantioselective control in the iridium-catalyzed asymmetric hydrogenation. Particularly, the iridium complexes of the bicyclic P,N ligand **3** are highly efficient catalysts for the asymmetric hydrogenation of challenging purely alkyl-substituted olefins and furan derivatives.[5c,d] Intrigued by the excel-

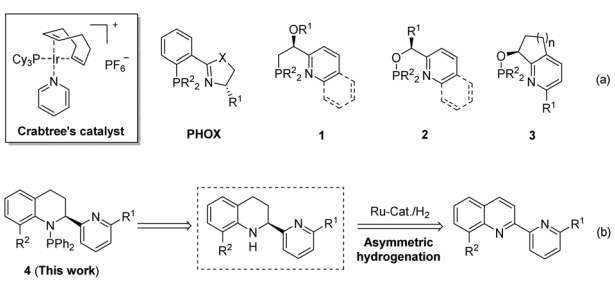


Fig. 1 Representative chiral pyridine-containing P,N ligands (a) and a designed synthetic route to new pyridine-aminophosphine ligands **4** (b).

[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. CCDC 1904938, 1904940, 1904943, 1904944 and 1904946. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c9ob00770a

lent 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 (Fig. 1b).

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

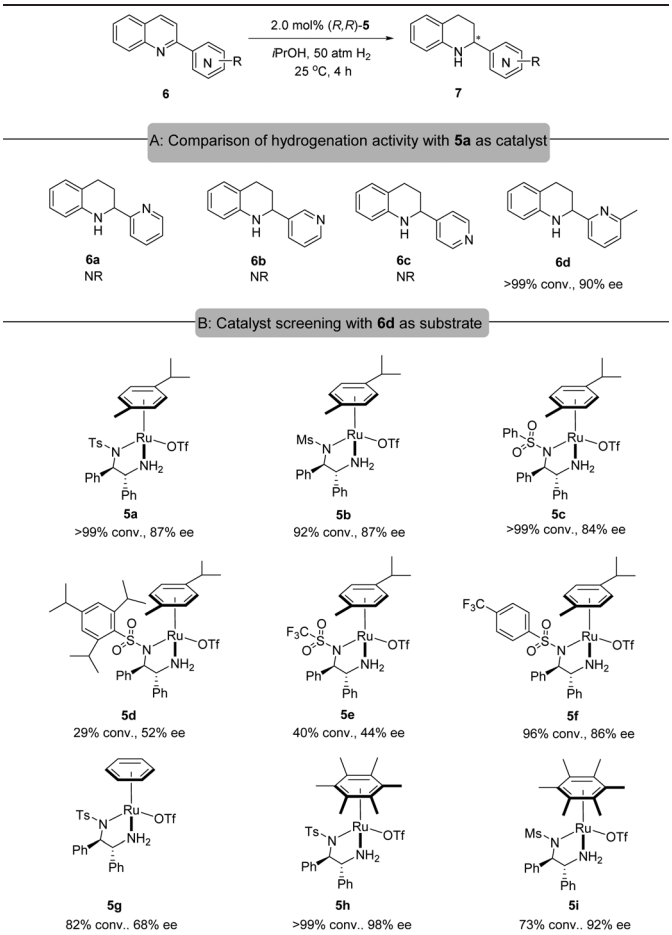
Asymmetric hydrogenation of 2-(pyridin-2-yl)quinoline derivatives

The substrates containing a pyridyl group are difficult to hydrogenate because the pyridyl group has a 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 has not been reported so far, and only a few hydrogenations with the 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 iPrOH under 50 atm H_2. However, the reduced product 2-(pyridin-2-yl)-1,2,3,4-tetrahydroquinoline was not detected. Similarly, the hydrogenation of neither 2-(pyridin-3-yl)quinoline **6b** nor 2-(pyridin-4-yl)quinoline **6c** could take place. Notably, 2-(6-methylpyridin-2-yl)quinoline **6d** was hydrogenated smoothly, and a full conversion 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 the nitrogen atom.[9c,11] In addition, the introduction of a substituent at the *ortho* position of the pyridine ring not only improves the catalytic reactivity but also enables further tuning of the steric effect of the ligand.

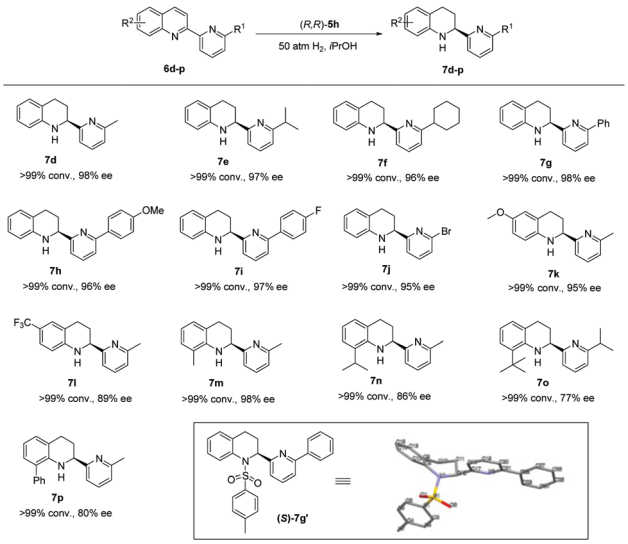
The hydrogenated 2-(6-methylpyridin-2-yl)quinoline (**6d**) was chosen as the model substrate for the optimization of reaction conditions. Firstly, all catalysts described in Table 1 were tested. Generally, the catalytic performance was significantly affected by both the substituents of the η^6-arene ligand and the *N*-sulfonate substituents. Introducing alkyl substituents into the η^6-arene of the Ru catalysts led to a significant increase in enantioselectivity, and the catalyst bearing a hexamethylbenzene ligand (*R*,*R*)-**5h** offered 98% ee and full conversion. In addition, the influence of the solvent was studied and iPrOH was selected as the solvent of choice in terms of both reactivity and enantioselectivity (entries 1–7 in Table S1, ESI†). The influences of temperature and hydrogen pressure were also studied. Reducing the hydrogen pressure or increasing the reaction temperature resulted in a slight decrease in enantioselectivity (entries 8–10 in Table S1†).

Having established the optimal reaction conditions, we 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 alkyl or aryl substituents at the 2-position of the 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 the quinoline

Table 1 Optimization of reaction conditions[a]



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

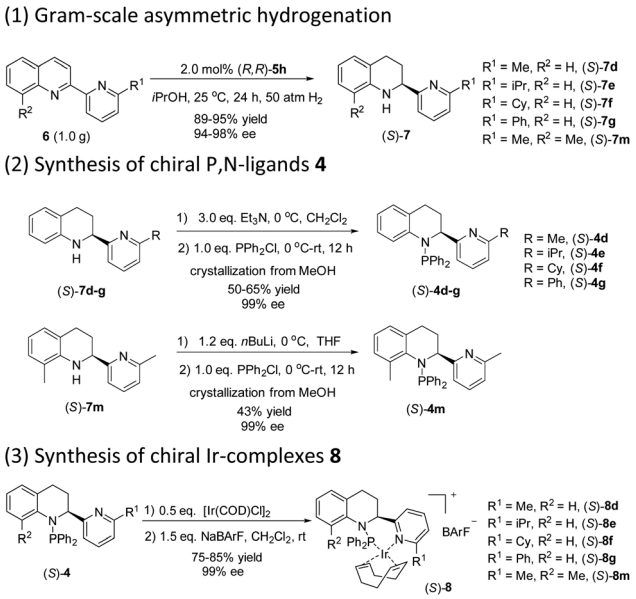


Scheme 1 Asymmetric hydrogenation of 2-(pyridin-2-yl)quinoline derivatives. Reaction conditions: Substrates **6d–i** (0.2 mmol), iPrOH (2 mL), 2.0 mol% of (*R*,*R*)-**5h**, H_2 (50 atm), stirred at 25 °C for 12 h; substrates **6j–p** with 5.0 mol% of (*R*,*R*)-**5h**. The conversions were determined 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]

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 the 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 the 8-phenyl substituted substrate **6p** proceeded smoothly but giving only 80% ee. In addition, the absolute configuration of **7g'** was determined to be *S* based on single-crystal X-ray analysis.

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 is quite simple and straightforward. First, the hydrogenation of 2-(pyridin-2-yl) quinolines **6** on the 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 achieved. After recrystallization from methanol, ligands **4** with 99% ee could be obtained. Finally, the iridium complexes **8** were prepared in very good yields



Scheme 2 Synthesis of P,N-ligands **4** and their Ir-complexes **8**.

(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]

The synthesized iridium complexes **8d–g** and **8m** were characterized by NMR and ESI-MS. Luckily, single crystals of the complexes (*S*)-**8f**, (*S*)-**8g** and (*S*)-**8m** were obtained.[14] As shown in Fig. 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 the alkene substrate bound at the adjacent coordination site. In the case of (*S*)-**8m** bearing another methyl substituent at the 8-position of the tetrahydroquinoline backbone, its structure is somewhat different and the tetrahydroquinoline motif extends towards the coordination sphere. This difference in the structure may have a great impact on their catalytic performance.

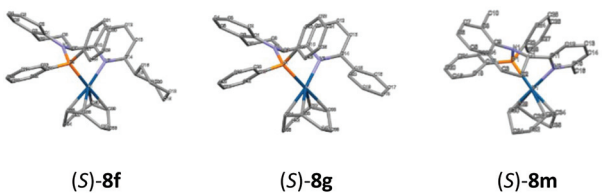


Fig. 2 Crystal structures of (*S*)-**8f**, (*S*)-**8g** and (*S*)-**8m**; the anion $BArF^-$ and hydrogen atoms are omitted for clarity. Selected bond lengths [Å] and angles [°], (*S*)-**8f**: Ir–N 2.142(13), Ir–P 2.303(4), and N–Ir–P 83.8(4). (*S*)-**8g**: Ir–N 2.140(8), Ir–P 2.290(2), and N–Ir–P 84.3(2).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

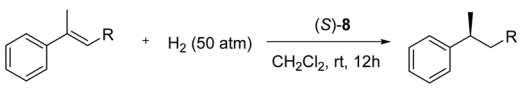
Applications in asymmetric hydrogenation of olefins and cyclic imines

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**, catalysts (*S*)-**8d**, **8e** and **8f** bearing an alkyl group on the pyridine ring gave a 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 the tetrahydroquinoline backbone, led to a remarkable increase in enantioselectivity (90% ee *vs.* 99% ee) but with a 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). These results indicate that the new Ir–P,N-ligand complexes **8** are efficient catalysts for the hydrogenation of trisubstituted olefins.

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 heterocycles such as benzazepines and benzodiazepines are versatile pharmacophores in medicinal chemistry.[15] In sharp contrast to the asymmetric hydrogenation of simple olefins and acyclic imines, the asymmetric hydrogenation of such benzo-fused cyclic imines remains less explored.[16] We first studied the asymmetric hydrogenation of benzazepine derivatives containing both C=C and C=N bonds. Considering the fact that the iridium complexes of P,N-ligands are effective catalysts for both C=C and C=N bonds, it is a challenge to precisely control the chemoselectivity, enantioselectivity and diastereoselectivity.[4]

In our previous study,[16b,g] the asymmetric hydrogenation of 2,4-diaryl-3*H*-benzo[*b*]azepines with chiral Ru- and Ir-catalyst gave only the partially hydrogenated products 2,4-diaryl-2,3-dihydro-1*H*-benzo[*b*]azepines, in which the C=C bond could not be reduced. We firstly examined the asymmetric hydrogenation of 2,4-di-*p*-tolyl-3*H*-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 the 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 a 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** from 1.0 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

Table 2 Asymmetric hydrogenation of ethyl *trans*-beta-methylcinnamate and *E*-methysibene[a]



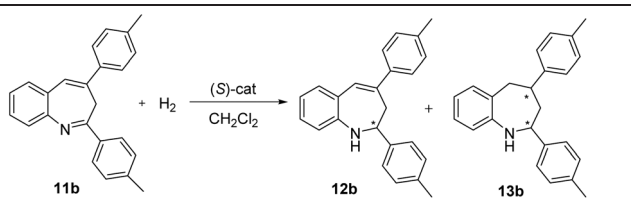
9a: R = CO_2Et
9b: R = Ph

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, and 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 column, and the absolute configuration was determined by comparison of optical rotation with literature data.

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/—	—

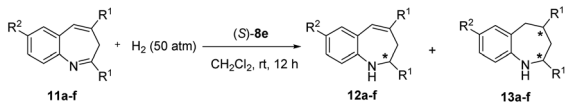
[a] Reaction conditions: Substrate **11b** (0.05 mmol) in CH_2Cl_2 (0.5 mL), Ir-catalyst **8**, and H_2 (50 atm), stirred at rt for 12 h. [b] The conversions were determined by ^{1}H NMR spectroscopy of the crude reaction mixtures. [c] The enantiomeric excesses were determined by HPLC with a chiral OD-H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

enantio- and diastereoselectivity were obtained (90% ee and 12 : 1 dr). In comparison, when 4.0 mol% Ir-PHOX was used as the catalyst under otherwise same conditions, only **12b** was obtained with moderate enantioselectivity (entry 8).

With the optimized 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, the hydrogenation of **11f** bearing a methoxy substituent at the 7-position gave a mixture of both products **12f** and **13f** even under a 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 diastereoselectivity (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 the Ir-PHOX complex was used as the catalyst for substrate **14a**, much lower enantioselectivity and diastereoselectivity were obtained (entry 1 *vs.* 7).

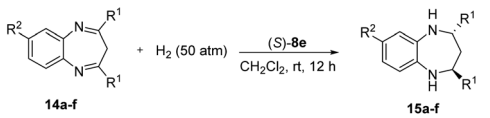
Table 4 Asymmetric hydrogenation of benzazepines catalyzed by (*S*)-**8e**[a]



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
8[f]	H/*p*-tolyl (**11b**)	>99	nd : >99	88 (+)	8 : 1
9[f,g]	H/4-MeO-Ph (**11c**)	>99	nd : >99	99(2*S*,4*S*)	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 the 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 a 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.

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

[a] Reaction conditions: Substrate **14** (0.2 mmol) in CH_2Cl_2 (2 mL), 4.0 mol% (*S*)-**8e**, and 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 the literature data. [d] The dr were determined by ^{1}H NMR. [e] With 4.0 mol% (*S*)-PHOX-Ir catalyst under otherwise 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 catalyst optimization. These iridium catalysts were found to be efficient in the asymmetric hydrogenation of benchmark alkene substrates and 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-3*H*-benzo[*b*]azepines and 2,4-diaryl-3*H*-benzo[*b*][1,4]diazepines. Studies on the further applications of these new ligands in other asymmetric catalysis reactions 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 the CAS (QYZDJSSWSLH023) for the 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 Lett.*, 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. Maduskuie Jr. 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′**]} contains the supplementary crystallographic data for this paper.

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.† .

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 and Q.-H. Fan, *Asian J. Org. Chem.*, 2017, **6**, 1219.

17 CCDC 1904946 {for [(*S*)-**12c**]} contains the supplementary crystallographic data for this paper.†