Organic & Biomolecular Chemistry

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: Y. Zhang, D. Kong, R. Wang and G. Hou, *Org. Biomol. Chem.*, 2017, DOI: 10.1039/C7OB00442G.

ROYAL SOCIETY OF CHEMISTRY

rsc.li/obc

View Article Online
DOI: 10.1039/C7OB00442G

Journal Name

ARTICLE

Synthesis of Chiral Cyclic Amines *via* Ir-Catalyzed Enantioselective Hydrogenation of Cyclic Imines†

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

DOI: 10.1039/x0xx00000x

www.rsc.org/

Ying Zhang, Duanyang Kong, Rui Wang, and Guohua Hou*

A highly enantioselective hydrogenation of cyclic imines for synthesis of chiral cyclic amines has been realized. With the complex of iridium and (*R*,*R*)-f-spiroPhos as the catalyst, a range of cyclic 2-aryl imines were smoothly hydrogenated under mild conditions without any additive to provide the corresponding chiral cyclic amines with excellent enantioselectivities of up to 98% ee. Moreover, this method could be successfully applied to the synthesis of (+)-(6*S*,10b*R*)-McN-4612-Z.

Introduction

Optical cyclic amines are an important class of structural units which are ubiquitous in natural products and pharmaceuticals, for example, nornicotine,[1] McN-4612-Z,[2] PARP-1/2 inhibitor[3] and Bradykinin B1 antagonists[4] (Figure 1). Among various methods for synthesis of optical active cyclic amines,[5] transition-metal-catalyzed asymmetric hydrogenation of cyclic imines has attracted considerable interest from academy and industry, and great efforts have been devoted to this field due to its perfect atom economy, high efficiency, and environmental friendliness.[6]

In the last decades, some efficient transition-metal catalysts including titanium, rhodium, ruthenium and iridium complexes have been developed. Buchwald and co-workers first reported the chiral titanocene-catalyzed asymmetric hydrogenation of cyclic imines with good reactivity and high enantioselectivity in the presence of n-BuLi and silane.[7] Zhang and co-workers found that 2-aryl pyrrolines could be hydrogenated with iridium catalyst albeit a bit lower enantioselectivities of up to 89% ee.[8] Xiao and co-workers applied Rh-TsDPEN to the asymmetric hydrogenation of isoquinoline-type cyclic imines obtaining high enantioselectivity.[9] Fan and co-workers successfully reported the asymmetric hydrogenation of cyclic imines catalyzed by the Ru-MsDPEN complex and also achieved high enantioselectivity with the assistance of Boc_2O which was necessary to eliminate the inhibitory effect on the catalyst by in situ protection of the resulting pyrrolidines.[10] Recently, Zhou and co-workers developed the efficient hydrogenation of 2-pyridyl cyclic imines to provide chiral nicotine derivatives catalyzed by the complex of iridium and chiral spiro phosphine-oxazoline ligands with iodine as the additive.[11] Despite these exciting results and significant achievements, in contrast to the great progress achieved in the asymmetric hydrogenation of olefins, ketones, and acyclic imines,[6c,12] the highly efficient and enantioselective hydrogenation of cyclic imines remains a great challenge due to the inhibitory effect from the resulting free amines with strong coordination to the central metal.[10,13] Therefore, efficient catalysts for the asymmetric hydrogenation of this class of substrates still remain highly desirable.

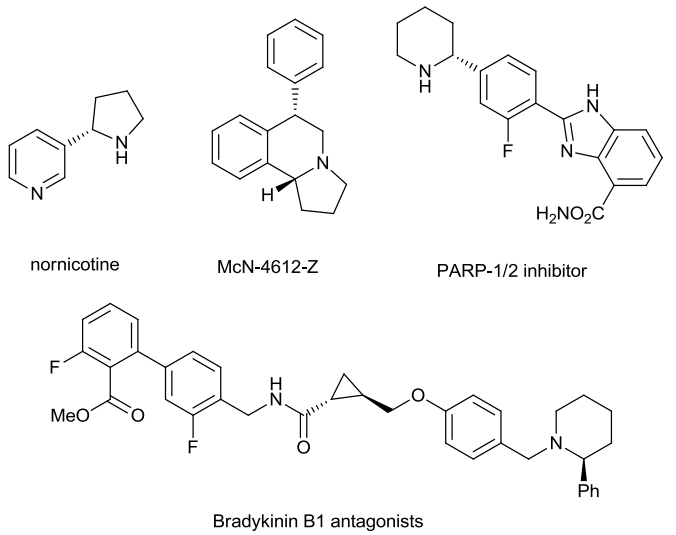


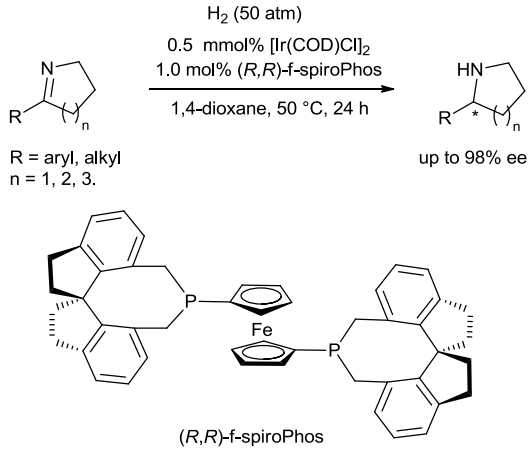
Figure 1. Structures of biologically active compounds and pharmaceutical drugs containing cyclic 2-aryl amine moiety.

Most recently, we demonstrated that the chiral ferrocenyl ligand containing the privileged spirobiindane skeleton developed by Zhou and coworkers,[14] f-spiroPhos was an efficient ligand for asymmetric hydrogenation of various substrates.[15] In particular, the Ir–f-spiroPhos complex exhibited excellent activity and enantioselectivity in the asymmetric hydrogenation of *N*-substituted diarylmethanimines,[15d] which prompted us to envision that the inhibitory effect on the catalyst of hydrogenation products

Key Laboratory of Radiopharmaceuticals, College of Chemistry, Beijing Normal University, No. 19 Xinjiekouwai St., Beijing 100875, China. E-mail: ghhou@bnu.edu.cn

† Electronic Supplementary Information (ESI) available: NMR of hydrogenation products, GC and HPLC spectra of analysis of enantioselectivities of products. See DOI: 10.1039/x0xx00000x

could be avoided by using the bulkier, more rigid and electron-donating ligand in the asymmetric hydrogenation of this class of challenging cyclic imines. Herein, we report the highly enantioselective hydrogenation of a series of cyclic imines using the Ir–f-spiroPhos complex with excellent enantioselectivities, up to 98% ee.

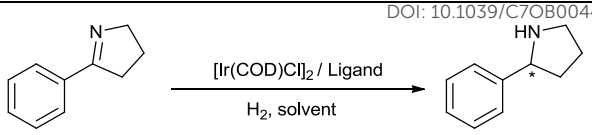


Scheme 1. Ir-Catalyzed Asymmetric Hydrogenation of Cyclic Imines.

Results and discussion

We started our hydrogenation with 2-phenyl-1-pyrroline **1a** as the model substrate, using the complex generated in situ by $[Ir(COD)Cl]_2$ and (*R*,*R*)–f-spiroPhos as the catalyst under 80 atm of H_2 at 40 °C in 1,4-dioxane. Despite the excellent enantioselectivity of 96% ee achieved, an incomplete conversion, 92%, was obtained (Table 1, entry 1). To our delight, a little increase of reaction temperature could make this hydrogenation complete with a slight lower enantioselectivity, 94% ee (Table 1, entry 2). Adjusting the hydrogen pressure and reaction temperature, we found that under 50 °C and 50 atm of H_2 the hydrogenation could provide the corresponding product with both full conversion and excellent ee value (Table 1, entry 2–5). Subsequently, some other bidentate diphosphine ligands including (*R*)-JosiPhos-1, (*S*,*R*)-Duanphos, (*S*)-Binap, (*S*)-DTBM-SegPhos, and chiral ferrocenyl phosphite ligand 1 containing similar spiro-backbone with f-spiroPhos were also evaluated in this hydrogenation. However, poor conversions and moderate enantioselectivities were obtained (Table 1, entry 6–10). These results revealed that both electron-donating and sterically hindered rigid properties of the ligands were presumably critical for the conversion and enantioselectivity in this transformation. Finally, the effect of solvents was investigated. In addition to 1,4-dioxane, most of solvents, such as ethyl acetate (EA), 1,2-dimethoxyethane (DME), tetrahydrofuran (THF) and toluene, could provide good to high conversions (91%–97%) and enantioselectivities (90%–95% ee) (Table 1, entry 11–14), whereas in dichloromethane (DCM) the hydrogenation afforded the product **2a** with only moderate conversion and enantioselectivity (Table 1, entry 15).

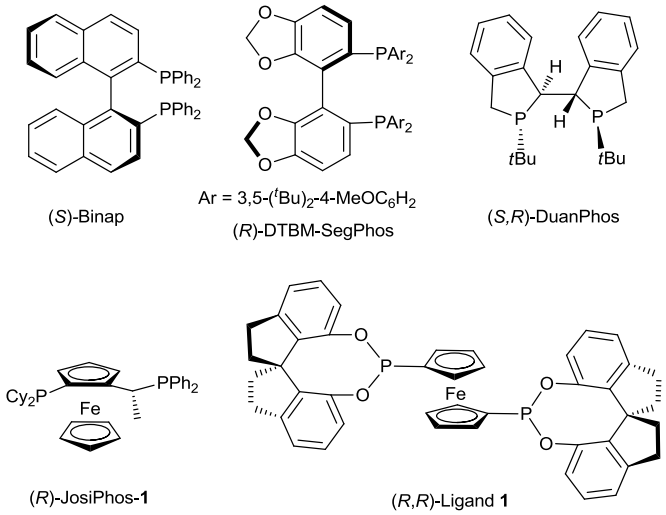
Table1. Optimization of Reaction Conditions. [a]



1a **2a**

entry	ligand	solvent	T(°C)	conv(%)[b]	ee(%)[c]
1[d]	(*R*,*R*)-f-spiroPhos	dioxane	40	92	96
2[d]	(*R*,*R*)-f-spiroPhos	dioxane	60	>99	94
3	(*R*,*R*)-f-spiroPhos	dioxane	60	>99	95
4[e]	(*R*,*R*)-f-spiroPhos	dioxane	60	97	94
5	**(*R*,*R*)-f-spiroPhos**	**dioxane**	**50**	**>99**	**95**
6	(*R*)-Josiphos-1	dioxane	50	20	86
7	(*S*,*R*)-Duanphos	dioxane	50	38	70
8	(*S*)-Binap	dioxane	50	45	88
9	(*S*)-DTBM-segphos	dioxane	50	23	77
10	(*R*,*R*)-Ligand 1	dioxane	50	27	75
11	(*R*,*R*)-f-spiroPhos	EA	50	95	90
12	(*R*,*R*)-f-spiroPhos	DME	50	91	90
13	(*R*,*R*)-f-spiroPhos	THF	50	97	91
14	(*R*,*R*)-f-spiroPhos	toluene	50	91	95
15	(*R*,*R*)-f-spiroPhos	DCM	50	74	85

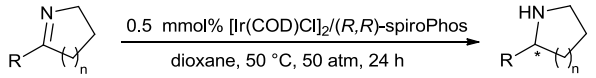
[a] Unless otherwise mentioned, all reactions were carried out with a $[Ir(COD)Cl]_2$/ligand/substrate ratio of 0.5:1.1:100, 50 atm of H_2, 24 h. [b] Determined by ^1H NMR. [c] Determined by GC analysis after the cyclic amine converted into the corresponding trifluoroacetamides. [d] 80 atm of H_2. [e] 30 atm of H_2.



Encouraged by the promising result obtained in the hydrogenation of substrate **1a**, a variety of cyclic imines **1** were prepared and evaluated in the hydrogenation using the Ir/f-spiroPhos catalyst under the optimized reaction conditions (Table 2). It was notable that the ring size of the cyclic imines had no obvious influence on the reactivity and enantioselectivity. All 5-, 6- and 7-membered-ring cyclic imines **1a**, **1k** and **1q** were smoothly hydrogenated to produce the desired chiral amines **2a**, **2k** and **2q** with similar enantioselectivities, 95%–97% ee. Moreover, the electronic properties of the substituents on the phenyl ring also had no obvious effects on the conversion and enantioselectivity. The substrates bearing regardless of the electron-donating

substituents including methyl and methoxyl group or the electron-withdrawing halogen substituents on the phenyl ring could be successfully hydrogenated to afford the corresponding products with full conversion and high enantioselectivities, 90%–98% ee (Table 2, entries 2–8, 11–16, and 18–19). The *ortho*-substituted substrate **1i** could also be applied to this hydrogenation and completely converted to the desired product with comparable enantioselectivity of 92% ee (entry 9). However, the enantioselectivity was dramatically decreased to 77% ee when this catalyst system was used in the asymmetric hydrogenation of alkyl-substituted substrate **1j**, which was possibly attributed to the flexibility of the alkyl group (Table 2, entry 10).

Table 2. Asymmetric Hydrogenation of 2-Substituted Cyclic Imines Catalyzed by Ir/(R,R)-spiroPhos.[a]

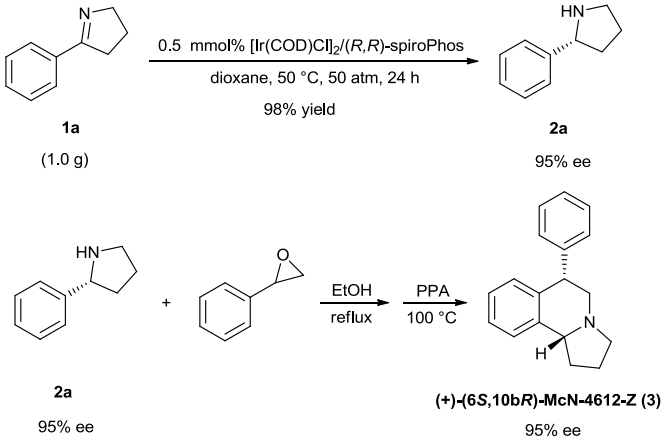


1 2

entry	R	n	product	conv. (%)[b]	ee (%)[c]
1	C_6H_5 (**1a**)	1	**2a**	>99	95(*R*)
2	4-Me-C_6H_5 (**1b**)	1	**2b**	>99	94(+)
3	4-F-C_6H_5 (**1c**)	1	**2c**	>99	93(+)
4	4-Cl-C_6H_5 (**1d**)	1	**2d**	>99	94(+)
5	4-Br-C_6H_5 (**1e**)	1	**2e**	>99	95(+)
6	3-MeO-C_6H_5 (**1f**)	1	**2f**	>99	90(+)
7	3-Me-C_6H_5 (**1g**)	1	**2g**	>99	91(+)
8	3-F-C_6H_5 (**1h**)	1	**2h**	>99	93(+)
9	2-MeO-C_6H_5 (**1i**)	1	**2i**	>99	92(+)
10	*n*-Bu (**1j**)	1	**2j**	>99	77(*R*)
11	C_6H_5 (**1k**)	2	**2k**	>99	97(*R*)
12	4-Me-C_6H_5 (**1l**)	2	**2l**	>99	98(*R*)
13	4-F-C_6H_5 (**1m**)	2	**2m**	>99	97(+)
14	4-Br-C_6H_5 (**1n**)	2	**2n**	>99	98(+)
15	3-Me-C_6H_5 (**1o**)	2	**2o**	>99	97(+)
16	3-F-C_6H_5 (**1p**)	2	**2p**	>99	97(+)
17	C_6H_5 (**1q**)	3	**2q**	>99	96(+)
18	4-Me-C_6H_5 (**1r**)	3	**2r**	>99	93(+)
19	4-F-C_6H_5 (**1s**)	3	**2s**	>99	96(+)

[a] Unless otherwise mentioned, all reactions were carried out with a $[Ir(COD)Cl]_2$/ligand/substrate ratio of 0.5:1.1:100. [b] Determined by ^1H NMR. [c] Determined by HPLC analysis using a chiral stationary phase or chiral GC analysis after the cyclic amine converted into the corresponding trifluoroacetamides or acetamide.

Remarkably, even at the gram scale this catalyst could maintain both the activity and enantioselectivity. For example, the asymmetric hydrogenation of the substrate **1a** (1.0 g) could still be accomplished giving the corresponding product **2a** with high yield and retained enantioselectivity, 95% ee, which showed a good potential for the practical application of this method. To demonstrate the further application of this approach, the catalyst system was evaluated in the synthesis of a biological active molecular skeleton, (+)-(6*S*,10b*R*)-McN-4612-Z, which was one of very potent inhibitors of uptake of the important central neurotransmitters norepinephrine, dopamine and serotonin into nerve cells. The results revealed that the (+)-(6*S*,10b*R*)-McN-4612-Z could be successfully prepared in high yield and maintained ee value from the hydrogenation product **2a** with 95% ee.



Scheme 2. Sythesis of (+)-(6*S*,10b*R*)-McN-4612-Z (**3**) from The Hydrogenation Product **2a**.

Experimental

General Information

All the air- or moisture-sensitive reactions and manipulations were performed by using standard Schlenk techniques and in a nitrogen-filled glovebox. DME, THF, 1,4-dioxane and toluene were distilled from sodium benzophenone ketyl. CH_2Cl_2 and EA were distilled from calcium hydride. ^1H NMR spectra were recorded on Bruker AV (400 MHz) spectrometers. ^{13}C NMR (proton-decoupled) spectra were obtained at 100 MHz. $CDCl_3$ was the solvent used for NMR analysis with TMS as the internal standard. Optical rotation was determined using a polarimeter. Enantiomeric excess values were determined by GC, HPLC or SFC analysis using a chiral stationary phase. Cyclic imines **1a**–**1s** were prepared according to the literature.[10, 16]

General procedure for the asymmetric hydrogenation of cyclic imines: A stock solution was made by mixing $[Ir(COD)Cl]_2$ with (*R,R*)-f-spiroPhos in a 1:2.2 molar ratio in 1,4-dioxane in a nitrogen-filled glovebox. An aliquot of the catalyst solution (1.0 mL, 0.00125 mmol) was transferred by syringe into the vials charged with different substrates (0.125 mmol for each) in anhydrous 1,4-dioxane (2.0 mL). The vials were subsequently transferred into an autoclave which hydrogen gas was charged. The reaction was then stirred under H_2 (50 atm) at 50 °C for 24 h. The hydrogen gas was released slowly and carefully and the conversion was determined by ^1H NMR. The solution was passed through a short column of silica gel to remove the metal complex. The enatiomeric excess of the product was determined by GC or HPLC with a chiral column after converted into the corresponding trifluoroacetamides or acetamides.

(*R*)-2-phenylpyrrolidine (2a): colorless oil; 17.5 mg, 95% yield; 95% ee; $[\alpha]^{20}_D$ = +25.0 (c = 0.5 in CH_2Cl_2); GC condition after converted into the corresponding trifluoroacetamide: Supelco gamma Dex™ 225 column (30 m × 0.25 mm × 0.25 μm), N_2 2.0 mL/min, programmed 100 °C – 3 °C/min – 175 °C – 5 °C/min –

DOI: 10.1039/C7OB00440C

195 °C (hold 15 min); t_{R1} = 20.8 min (minor), t_{R2} = 21.2 min (major); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.37−7.21 (m, 5H), 4.13−4.09 (m, 1H), 3.23−3.18 (m, 1H), 3.04−2.98 (m, 1H), 2.20−2.03 (m, 1H), 1.95 (br, 1H), 1.95−1.83 (m, 2H), 1.70−1.65 (m, 1H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ (ppm) 144.5, 128.2, 126.7, 126.4, 62.4, 46.8, 34.2, 25.4. The analytical data are consistent with the literature.[8] The absolute configuration of (*R*)-**2a** was determined by comparison with optical rotation data for the reported literature.[7b]

(+)-2-(4′-Me-Phenyl)-1-pyrrolidine (2b): colorless oil; 20.1 mg, 99% yield; 94% ee; $[\alpha]^{20}_D$ = +29.6 (c = 0.5 in CH_2Cl_2); GC condition after converted into the corresponding trifluoroacetamide: Supelco gamma Dex™ 225 column (30 m × 0.25 mm × 0.25 μm), N_2 2.0 mL/min, programmed 90 °C − 0.5 °C/min − 175 °C − 5 °C /min − 195 °C (hold 10 min); t_{R1} = 89.0 min (minor), t_{R2} = 90.4 min (major); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.25 (d, *J* = 7.9 Hz, 2H), 7.13 (d, *J* = 7.9 Hz, 2H), 4.08−4.05 (m, 2H), 3.22−3.16 (m, 1H), 3.01−2.95 (m, 1H), 2.60 (br, 1H), 2.33 (s, 3H), 2.19−2.12 (m, 1H), 1.94−1.81(m, 2H), 1.71−1.64 (m, 1H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ (ppm) 140.7, 136.4, 128.9, 126.4, 62.2, 46.6, 33.9, 25.3, 20.9. The analytical data are consistent with the literature.[8]

(+)-2-(4′-F-Phenyl)-1-pyrrolidine (2c): colorless oil; 19.8 mg, 96% yield; 93% ee; $[\alpha]^{20}_D$ = +19.0 (c = 0.5 in CH_2Cl_2); GC condition after converted into the corresponding trifluoroacetamide: Supelco gamma Dex™ 225 column (30 m × 0.25 mm × 0.25 μm), N_2 2.0 mL/min, programmed 100 °C − 3 °C/min − 175 °C − 5 °C /min − 195 °C (hold 10 min); t_{R1} = 21.5 min (minor), t_{R2} = 21.8 min (major); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.31−7.28 (m, 2H), 6.99−6.94 (m, 2H), 4.08−4.04 (m, 1H), 3.18−3.13 (m, 1H), 3.00−2.94 (m, 1H), 2.34 (br. 1H), 2.16−2.11 (m, 1H), 1.91−1.80 (m, 2H), 1.65−1.58 (m, 1H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ (ppm) 161.7 (d, $^1J_{C\text{-}F}$ = 243.0 Hz), 139.7, 128.1, 128.0, 115.1, 114.9, 61.8, 46.7, 34.2, 25.3. The analytical data are consistent with the literature.[8]

(+)-2-(4′-Cl-Phenyl)-1-pyrrolidine (2d): colorless oil; 19.5 mg, 94% yield; 94% ee ; $[\alpha]^{20}_D$ = +31.6 (c = 0.5 in CH_2Cl_2); GC condition after converted into the corresponding trifluoroacetamide: Supelco gamma Dex™ 225 column (30 m × 0.25 mm × 0.25 μm), N_2 1.0 mL/min, programmed 90 °C − 0.8 °C/min − 175 °C − 5 °C /min − 195 °C (hold 10 min); t_{R1} = 94.8 min (minor), t_{R2} = 96.2 min (major); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.31−7.26 (m, 4H), 4.12−4.08 (m, 1H), 3.22−3.16 (m, 1H), 3.05−2.99 (m, 1H), 2.20−2.13 (m, 2H), 1.92−1.82 (m, 2H), 1.77 (br, 1H), 1.66−1.59 (m, 1H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ (ppm) 143.1, 132.2, 128.3, 127.8, 61.8, 41.8, 34.3, 25.4. The analytical data are consistent with the literature.[8]

(+)-2-(4′-Br-Phenyl)-1-pyrrolidine (2e): colorless oil; 26.7 mg, 94% yield; 95% ee; $[\alpha]^{20}_D$ = +30.6 (c = 0.5 in CH_2Cl_2); GC condition after converted into the corresponding trifluoroacetamide: Supelco gamma Dex™ 225 column (30 m × 0.25 mm × 0.25 μm), N_2 2.0 mL/min, programmed 100 °C − 1 °C/min − 175 °C − 5 °C /min − 195 °C (hold 10 min); t_{R1} = 70.5 min (minor), t_{R2} = 71.1 min (major); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.44−7.41 (m, 2H), 7.25−7.23 (m, 2H), 4.10−4.06 (m, 1H), 3.21−3.15 (m, 1H), 3.04−2.98 (m, 1H), 2.02 (br, 1H), 1.93−1.82 (m, 2H), 1.65−1.58 (m, 1H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ (ppm) 143.5, 131.3, 128.4, 128.3, 126.6, 120.4, 61.9, 46.8, 34.3, 25.4. The analytical data are consistent with the literature.[8]

(+)-2-(3′-MeO-Phenyl)-1-pyrrolidine (2f): colorless oil; 21.1 mg, 97% yield; 90% ee; $[\alpha]^{20}_D$ = +35.4 (c = 0.5 in CH_2Cl_2); GC condition after converted into the corresponding acetamide: Supelco gamma Dex™ 225 column (30 m × 0.25 mm × 0.25 μm), N_2 2.0 mL/min, programmed 90 °C − 0.5 °C/min − 195 °C (hold 30 min); t_{R1} = 161.8 min (major), t_{R2} = 163.3 min (minor); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.23−7.19 (m, 1H), 6.93−6.91 (m, 2H), 6.76−6.74 (m, 1H), 4.09−4.05 (m, 1H), 3.78 (s, 3H), 3.20−3.14 (m, 1H), 3.01−2.94 (m, 1H), 2.33 (br, 1H), 2.17−2.13 (m, 1H), 1.89−1.79 (m, 2H), 1.69−1.62 (m, 1H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ (ppm) 159.5, 146.1, 129.2, 118.7, 112.1, 111.9, 62.4, 55.0, 46.7, 34.0, 25.3. The analytical data are consistent with the literature.[8]

(+)-2-(3′-Me-Phenyl)-1-pyrrolidine (2g): colorless oil; 19.8 mg, 98% yield; 91% ee; $[\alpha]^{20}_D$ = +29.2 (c = 0.5 in CH_2Cl_2); GC condition after converted into the corresponding trifluoroacetamide: Supelco gamma Dex™ 225 column (30 m × 0.25 mm × 0.25 μm), N_2 2.0 mL/min, programmed 90 °C − 0.8 °C/min − 175 °C − 5 °C /min − 195 °C (hold 10 min); t_{R1} = 63.8 min (minor), t_{R2} = 65.0 min (major); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.13−7.04 (m, 3H), 6.96−6.94 (m, 1H), 3.99−3.95 (m, 1H), 3.13−3.07 (m, 1H), 2.93−2.87 (m, 1H), 2.43 (br, 1H), 2.25 (s, 3H), 2.09−2.05 (m, 1H), 1.85−1.73 (m, 2H), 1.60−1.55 (m, 1H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ (ppm) 143.9, 137.8, 128.1, 127.5, 127.1, 123.5, 62.4, 46.6, 33.9, 25.3, 21.3. The analytical data are consistent with the literature.[8]

(+)-2-(3′-F-Phenyl)-1-pyrrolidine (2h): colorless oil ; 19.7 mg, 95% yield; 93% ee; $[\alpha]^{20}_D$ = +9.8 (c = 0.5 in CH_2Cl_2) GC condition after converted into the corresponding trifluoroacetamide: Supelco gamma Dex™ 225 column (30 m × 0.25 mm × 0.25 μm), N_2 2.0 mL/min, programmed 100 °C − 1 °C/min − 175 °C − 5 °C /min − 195 °C (hold 10 min); t_{R1} = 42.1 min (minor), t_{R2} = 42.7 min (major); ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 7.28−7.23 (m, 1H), 7.13−7.07 (m, 2H), 6.92−6.88 (m, 1H), 4.14−4.11 (m, 1H), 3.21−3.16 (m, 1H), 3.05−2.98 (m, 1H), 2.22−2.16 (m, 2H), 1.92−1.81 (m, 2H), 1.66−1.61 (m, 1H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ (ppm) 162.7 (d, $^1J_{C\text{-}F}$ = 244.0 Hz), 147.7, 147.6, 129.5, 129.4, 121.88, 121.86, 113.3, 113.2, 113.1, 113.0, 61.7, 46.6, 34.2, 25.2. The analytical data are consistent with the literature.[17]

(+)-2-(2′-MeO-Phenyl)-1-pyrrolidine (2i): colorless oil; 21.6 mg, 97% yield; 92% ee; $[\alpha]^{20}_D$ = +37.2 (c = 0.5 in CH_2Cl_2); GC condition after converted into the corresponding trifluoroacetamide: Supelco gamma Dex™ 225 column (30 m × 0.25 mm × 0.25 μm), N_2 2.0 mL/min, programmed 100 °C − 1 °C/min − 175 °C − 5 °C /min− 195 °C (hold 10 min); t_{R1} = 55.2 min (minor), t_{R2} = 56.6 min (major); ^{1}HNMR (400 MHz, $CDCl_3$): δ (ppm) 7.41−7.38 (m, 1H), 7.23−7.19 (m, 1H), 6.95−6.91 (m, 1H), 6.87−6.85 (m, 1H), 4.39−4.35 (m , 1H), 3.83 (s, 3H), 3.21−3.15 (m, 1H), 3.03−2.98 (m, 1H), 2.51 (br, 1H), 2.20−2.15 (m, 1H), 1.89−1.81 (m, 2H), 1.71−1.64 (m, 1H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ (ppm) 157.0, 129.8, 128.3, 127.2, 120.5, 110.3, 57.8, 55.2, 46.3, 31.6, 25.1. The analytical data are consistent with the literature.[8,18]

View Article Online
DOI: 10.1039/C7OB00412C

(*R*)-2-butyl-1-pyrrolidine (2j): colorless oil; 14.7 mg, 92% yield; 77% ee; $[\alpha]^{20}_D$ = −23.4 (c = 0.53 in dioxane) GC condition after converted into the corresponding trifluoroacetamide: Supelco gamma Dex™ 225 column (30 m × 0.25 mm × 0.25 μm), N_2 2.0 mL/min, programmed 100 °C − 2 °C/min − 195 °C (hold 10 min); t_{R1} = 12.3 min (minor), t_{R2} = 12.6 min (major); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.74 (m, 1H), 2.96−2.80 (m, 3H), 1.81−1.17 (m, 10H), 0.81−0.80 (m, 3H); $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): δ (ppm) 59.2, 46.1, 35.6, 31.5, 29.4, 25.0, 22.6, 13.8. The analytical data are consistent with the literature.[8] The absolute configuration of **(*R*)-2j** was determined by comparison with optical rotation data for the reported literature.[5a]

(*R*)-2-phenyl-1-piperidine (2k): colorless oil; 19.6 mg, 97% yield; 97% ee; $[\alpha]^{20}_D$ = +25.8 (c = 0.5 in CH_2Cl_2); GC condition after converted into the corresponding trifluoroacetamide: Supelco beta Dex™ 120 column (30 m × 0.25 mm × 0.25 μm), N_2 2.0 mL/min, programmed 100 °C − 1 °C/min − 175 °C −5 °C /min − 195 °C (hold 10 min); t_{R1} = 47.3 min (minor), t_{R2} = 48.1 min (major); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.37−7.22 (m, 5H), 3.60−3.57 (m, 1H), 3.20−3.18 (m, 1H), 2.82−2.76 (m, 1H), 1.98 (br , 1H), 1.94−1.78 (m, 2H), 1.67−1.47 (m, 4H); $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): δ (ppm) 145.4, 128.2, 126.8, 126.5, 62.2, 47.6, 34.8, 25.7, 25.3. The analytical data are consistent with the literature.[8] The absolute configuration of **(*R*)-2k** was determined by comparison with optical rotation data for the reported literature.[5a]

(*R*)-2-(4′-Me-Phenyl)-1-piperidine (2l): colorless oil; 20.8 mg, 95% yield; 98% ee; $[\alpha]^{20}_D$ = +22.0 (c = 0.5 in CH_2Cl_2); GC condition after converted into the corresponding trifluoroacetamide: Supelco beta Dex™ 120 column (30 m × 0.25 mm × 0.25 μm), N_2 1.0 mL/min, programmed 90 °C − 0.8 °C/min − 195 °C (hold 20 min); t_{R1} = 89.2 min (minor), t_{R2} = 90.2 min (major); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.26 (d, *J* = 7.9, 2H), 7.12 (d, *J* = 7.9, 2H), 3.57−3.55 (m, 1H), 3.19−3.16 (m, 1H), 2.82−2.81 (m, 1H), 2.33 (s , 3H), 1.90−1.76 (m, 2H), 1.67−1.43 (m, 4H); $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): δ (ppm) 141.8, 136.7, 129.0, 126.6, 61.9, 47.6, 34.5, 25.5, 25.2, 21.0. The analytical data are consistent with the literature.[5d]

(+)-2-(4′-F-Phenyl)-1-piperidine (2m): colorless oil; 21.9 mg, 98% yield; 97% ee; $[\alpha]^{20}_D$ = +38.2 (c = 0.5 in CH_2Cl_2); GC condition after converted into the corresponding trifluoroacetamide: Supelco beta Dex™ 120 column (30 m × 0.25 mm × 0.25 μm), N_2 2.0 mL/min, programmed 100 °C − 2 °C/min − 195 °C (hold 10 min); t_{R1} = 31.1 min (minor), t_{R2} = 31.7 min (major); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.34−7.431 (m, 2H), 7.01−6.96 (m, 2H), 3.59−3.56 (m, 1H), 3.19−3.16 (m, 1H), 2.82−2.75 (m, 1H), 2.48 (br , 1H), 1.90−1.75 (m, 2H), 1.67−1.45 (m, 4H); $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): δ (ppm) 162.0 (d, $^1J_{C-F}$ = 243.0 Hz), 139.4, 128.5, 128.4, 115.3, 115.1, 61.3, 47.2, 33.9, 29.7, 24.9. The analytical data are consistent with the literature.[5d]

(+)-2-(4′-Br-Phenyl)-1-piperidine (2n): colorless oil; 28.8 mg, 96% yield; 98% ee; $[\alpha]^{20}_D$ = +19.6 (c = 0.5 in CH_2Cl_2); GC condition after converted into the corresponding trifluoroacetamide: Supelco beta Dex™ 120 column (30 m × 0.25 mm × 0.25 μm), N_2 1.0 mL/min, programmed 90 °C − 0.8 °C/min − 195 °C (hold 10 min); t_{R1} = 117.4 min (minor), t_{R2} = 118.6 min (major); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.41 (d, *J* = 8.3 Hz, 2H), 7.23 (d, *J* = 8.3, 2H), 3.56−3.53 (m, 1H), 3.19−3.16 (m, 1H), 2.89−2.74 (m, 1H), 2.04 (br , 1H), 1.87−1.73 (m, 2H), 1.67−1.42 (m, 4H); $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): δ (ppm) 144.4, 131.4, 128.3, 120.6, 61.6, 47.6, 34.9, 25.6, 25.2; TOF-HRMS calcd for $C_{11}H_{15}NBr^+$ [M + H^+]: 240.0382, found 240.0384.

(+)-2-(3′-Me-Phenyl)-1-piperidine (2o): colorless oil; 20.9 mg, 95% yield; 97% ee; $[\alpha]_D^{20}$ = +38.6 (c = 0.5 in CH_2Cl_2); GC condition after converted into the corresponding trifluoroacetamide: Supelco beta Dex™ 120 column (30 m × 0.25 mm × 0.25 μm), N_2 1.0 mL/min, programmed 90 °C − 0.8 °C/min − 195 °C (hold 10 min); t_{R1} = 84.8 min (minor), t_{R2} = 86.0 min (major); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.21−7.14 (m, 3H), 7.07−7.05 (m, 1H), 3.58−3.56 (m, 1H), 3.20−3.17 (m, 1H), 2.81−2.76 (m, 1H), 2.50 (br, 1H), 2.34 (s, 3H), 1.91−1.78 (m, 2H), 1.68−1.43 (m, 4H); $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): δ (ppm) 145.0, 137.9, 128.2, 127.8, 127.3, 123.7, 62.2, 47.6, 34.6, 25.6, 25.3, 21.3; TOF-HRMS calcd for $C_{12}H_{18}N^+$ [M + H^+]: 176.1433, found 176.1432.

(+)-2-(3′-F-Phenyl)-1-piperidine (2p): colorless oil; 21.5 mg, 96% yield; 97% ee; $[\alpha]^{20}_D$ = +17.0 (c = 0.5 in CH_2Cl_2); GC condition after converted into the corresponding trifluoroacetamide: Supelco beta Dex™ 120 column (30 m × 0.25 mm × 0.25 μm), N_2 2.0 mL/min, programmed 90 °C − 0.8 °C/min − 195 °C (hold 10 min); t_{R1} = 75.1 min (minor), t_{R2} = 76.8 min (major); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.25−7.20 (m, 1H), 7.10−7.15 (m, 2H)，6.90−6.86 (m, 1H), 3.56−3.54 (m, 2H), 3.16−3.13 (m, 1H), 2.77−2.72 (m, 1H), 1.92−1.74 (m, 3H), 1.63−1.41 (m, 4H); $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): δ (ppm) 162.8 (d, $^1J_{C-F}$ = 244.0 Hz), 148.13, 148.06, 129.63, 129.55, 122.1, 122.0, 113.7, 113.5, 113.4, 113.2, 61.6, 47.5, 34.9, 25.6, 25.1. The analytical data are consistent with the literature.[5e]

(+)-2-phenylazepane (2q): colorless oil; 20.7 mg, 95% yield; 96% ee; $[\alpha]^{20}_D$ = +35.2 (c = 0.5 in CH_2Cl_2); HPLC condition after converted into the corresponding trifluoroacetamide: Lux 5u Cellulose-1 (250 × 4.60 mm), ipa : hex =1:99, 1 mL/min, 230 nm ,t_{R1} = 11.3 min (minor), t_{R2} = 14.0 min (major); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.37−7.28 (m, 4H), 7.23−7.19 (m, 1H), 3.77−3.74 (m, 1H), 3.16−3.11 (m, 1H), 2.88−2.82 (m, 1H), 1.99−1.94 (m, 1H), 1.85−1.62 (m, 8H); $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): δ (ppm) 146.6, 128.1, 126.5, 126.1, 64.7, 47.9, 38.7, 30.5, 26.6, 25.9. The analytical data are consistent with the literature.[8]

(+)-2-(4′-Me-phenyl)-azepane (2r): faint yellow oil; 23.6 mg, 99% yield; 93% ee; $[\alpha]^{20}_D$ = +32.4 (c = 0.5 in CH_2Cl_2); HPLC condition after converted into the corresponding trifluoroacetamide: Lux 5u Cellulose-3 (250 × 4.60 mm), ipa : hex =1:99, 1.0 mL/min, 230 nm; t_{R1} = 6.4 min (major), t_{R2} = 8.2 min (minor); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.23 (d, *J* = 7.9 Hz, 2H), 7.11 (d, *J* = 7.6 Hz , 2H), 3.73−3.70 (m, 1H), 3.16−3.10 (m, 1H), 2.86−2.80 (m, 1H), 2.32 (s, 3H), 1.97−1.91 (m, 1H), 1.84−1.64(m, 8H); $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): δ (ppm) 143.8, 136.0, 128.9, 126.1, 125.7, 64.6, 48.1, 38.9, 30.6, 26.7, 26.0, 20.9; TOF-HRMS calcd for $C_{13}H_{20}N^+$ [M+H^+]: 190.1590, found 190.1592.

(+)-2-(4′-F-phenyl)-azepane (2s): faint yellow oil, 23.1 mg, 95% yield; 96% ee; $[\alpha]^{20}_D$ = +37.0 (c = 0.5 in CH_2Cl_2); HPLC condition

after converted into the corresponding trifluoroacetamide: Lux 5u Cellulose-3 (250 × 4.60 mm), ipa : hex = 1:99, 1.0 mL/min, 230 nm , t_{R1} = 7.6 min (major), t_{R2} = 9.0 min (minor); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.29−7.26 (m, 2H), 6.97−6.90 (m, 2H), 3.73−3.69 (m, 1H), 3.14−3.05 (m, 1H), 2.84−2.78 (m, 1H), 1.93−1.88 (m, 1H), 1.80−1.54 (m, 7H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ (ppm) 161.6 (d, $^1J_{C\text{-}F}$ = 243.0 Hz), 142.5, 127.9, 127.8, 115.2, 115.0, 64.1, 48.0, 40.0, 30.6, 26.8, 26.0; TOF-HRMS calcd for $C_{12}H_{15}NF^+$ [M+H$^+$]: 194.1339, found 194.1342.

Procedure for Synthesis of (+)-(6*S*,10b*R*)-McN-4612-Z (3): (*R*)-2-phenylpyrrolidine **2a (**150 mg, 1.02 mmol, 95% ee), and styrene oxide (122.6 mg, 1.02 mmol) were combined in 2 mL of absolute ethanol in 25 mL single port flask and refluxed. After 19 hours, **2a** reacted completed with TLC monitored. Then the solution was evaporated to yellow oil, which was combined with PPA (2.0 g), 2 mL toluene and heated at 100 °C for 4 hours. The reaction was cooled, diluted with ice water, basified with 40% aqueous potassium hydroxide (PH >11) under cooling, and extracted with methylene chloride. The organic layers was washed with water, dried with potassium carbonate, and evaporated to brown oil. The mixture was separated by column chromatography (silica gel, acetate/petroleum ether = 1:5−1:0) to give the (+)-(6*S*, 10b*R*)-McN-4612-Z (**3**) (195 mg, 60%) as yellow oil. 95% ee, $[\alpha]^{20}_D$ = +18.8 (c = 0.5 in CH_3OH) ; SFC conditions: Lux 5u Cellulose-3 (250 × 4.60 mm), CH_3OH : CO_2 = 10:90, 2.5 mL/min, 230 nm , t_{R1} = 2.2 min (minor), t_{R2} = 2.34 min (major); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.35−7.28 (m, 3H), 7.24−7.14 (m, 4H), 7.10−7.07 (m, 1H), 6.88−6.86 (m, 1H), 4.47−4.41 (t, *J* = 7.6 Hz, 1H), 3.60−3.56 (m, 1H), 3.51−3.47 (m, 1H), 3.20−3.16 (m, 1H), 2.72−2.67 (m, 1H), 2.54−2.46 (m, 2H), 2.00−1.79 (m, 4H). ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ (ppm) 144.26, 139.27, 137.64, 129.13, 129.09, 128.38, 126.44, 126.22, 126.12, 125.10, 63.89, 58.15, 52.98, 45.27, 30.42, 21.95. The analytical data are consistent with the literature.[19, 20]

Conclusions

In conclusion, a highly enantioselective Ir−(*R*,*R*)-spiroPhos catalyzed asymmetric hydrogenation of 2-aryl cyclic imines in absence of any additives has been developed. Under mild reaction conditions a variety of 2-aryl cyclic imines were smoothly hydrogenated to afford the corresponding chiral free cyclic amines in high yields and excellent enantioselectivities (up to 98%). This approach provided a straightforward access to chiral free cyclic amines and could be successfully applied to the synthesis of a biological active molecular skeleton, (+)-(6*S*,10b*R*)-McN-4612-Z.

Acknowledgements

We are grateful for the financial support from the National Natural Science Foundation of China (grant nos. 21672024, 21272026, and 21472013), Program for Changjiang Scholars and Innovative Research Team in University, and Beijing Municipal Commission of Education.

Notes and references

View Article Online
DOI: 10.1039/C7OB00442G

1 J. I. Seeman, C. G. Chavdarian and H. V. Secor, *J. Org. Chem.*, 1985, **50**, 5419.

2 (a) B. E. Maryanoff, D. F. McComsey, M. J. Costanzo, P. E. Setler, J. F. Gardocki, R. P. Shank and C. R. Schneider, *J. Med. Chem.*, 1984, **27**, 943; (b) B. E. Maryanoff, D. F. McComsey, R. R. Inners, M. S. Mutter, G. P. Wooden, S. L. Mayo and R. A. Olofson, *J. Am. Chem. Soc.*, 1989, **111**, 2487.

3 (a) T. D. Penning, G.-D. Zhu, J. Gong, S. Thomas, V. B. Gandhi, X. Liu, Y. Shi, V. Klinghofer, E. F. Johnson, C. H. Park, E. H. Fry, C. K. Donawho, D. J. Frost, F. G. Buchanan, G. T. Bukofzer, L. E. Rodriguez, V. Bontcheva-Diaz, J. J. Bouska, D. J. Osterling, A. M. Olson, K. C. Marsh, Y. Luo and V. L. Giranda, *J. Med. Chem.*, 2010, **53**, 3142; (b) L. Wang, K. A. Mason, K. K. Ang, T. Buchholz, D. Valdecanas, A. Mathur, C. Buser-Doepner, C. Toniatti and L. Milas, *Invest. New Drugs*, 2012, **30**, 2113.

4 M. C. Bryan, K. Biswas, T. A. N. Peterkin, R. M. Rzasa, L. Arik, S. G. Lehto, H. Sun, F.-Y. Hsieh, C. Xu, R. T. Fremeau and J. R. Allen, *Bioorg. Med. Chem. Lett.*, 2012, **22**, 619.

5 (a) L. E. Burgess and A. I. Meyers, *J. Org. Chem.*, 1992, **57**, 1656; (b) C. J. Dunsmore, R.Carr, T. Fleming and N. J. Turner, *J. Am. Chem. Soc.*, 2006, **128**, 2224; (c) E. J. Cochrane, D. Leonori, L. A. Hassall and I. Coldham, *Chem. Commun.*, 2014, **50**, 9910; (d) S. Hussain, F. Leipold, H. Man, E. Wells, S. P. France, K. R. Mulholland, G. Grogan and N. J. Turner, *ChemCatChem*, 2015, **7**, 579; (e) G. A. Aleku, H. Man, S. P. France, F. Leipold, S. Hussain, L. Toca-Gonzalez, R. Marchington, S. Hart, J. P. Turkenburg, G. Grogan and N. J. Turner, *ACS Catalysis*, 2016, **6**, 3880; (f) C. Ge, R.-X. Liang, R.-R. Liu, B. Xiang and Y.-X. Jia, *Tetrahedron Lett.*, 2017, **58**, 142.

6 (a) T. C. Nugent and M. El-Shazly, *Adv. Synth. Catal.*, 2010, **352**, 753; (b) W. Tang and X. Zhang, *Chem. Rev.*, 2003, **103**, 3029; (c) J.-H. Xie, S.-F. Zhu and Q.-L. Zhou, *Chem. Rev.*, 2011, **111**, 1713.

7 (a) C. A. Willoughby and S. L. Buchwald, *J. Am. Chem. Soc.*, 1992, **114**, 7562; (b) C. A. Willoughby and S. L. Buchwald, *J. Org. Chem.*, 1993, **58**, 7627; (c) C. A. Willoughby and S. L. Buchwald, *J. Am. Chem. Soc.*, 1994, **116**, 11703.

8 M. Chang, W. Li, G. Hou and X. Zhang, *Adv. Synth. Catal.*, 2010, **352**, 3121.

9 C. Li and J. Xiao, *J. Am. Chem. Soc.*, 2008, **130**, 13208.

10 F. Chen, Z. Ding, J. Qin, T. Wang, Y. He and Q.-H. Fan, *Org. Lett.*, 2011, **13**, 4348.

11 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.

12 (a) *Chiral Amine Synthesis*, ed. P. G. Andersson, Wiley-VCH Weinheim 2010, pp. 179-223; (b) S. J. Roseblade and A. Pfaltz, *Acc. Chem. Res.*, 2007, **40**, 1402; (c) D.-S. Wang, Q.-A. Chen, S.-M. Lu and Y.-G. Zhou, *Chem. Rev.*, 2012, **112**, 2557; (d) J. J. Verendel, O. Pàmies, M. Diéguez and P. G. Andersson, *Chem. Rev.*, 2014, **114**, 2130.

13 (a) T. Yamagata, H. Tadaoka, M. Nagata, T. Hirao, Y. Kataoka, V. Ratovelomanana-Vidal, J. P. Genet and K. Mashima, *Organometallics*, 2006, **25**, 2505; (b) G. Zhu and X. Zhang, *Tetrahedron: Asymmetry*, 1998, **9**, 2415.

14 (a) *Privileged Chiral Ligands and Catalysts*, ed. Q.-L. Zhou, Wiley-VCH, Weinheim, 2011; pp. 137-170; (b) J.-H. Xie and Q.-L. Zhou, *Acc. Chem. Res.*, 2008, **41**, 581; (c) K. Ding, Z. Han and Z. Wang, *Chem. –Asian J.*, 2009, **4**, 32; (d) J.-H. Xie and Q.-L. Zhou, *Acta Chim. Sinica*, 2014, **72**, 778.

15 (a) Q. Yan, D. Kong, M. Li, G. Hou and G. Zi, *J. Am. Chem. Soc.*, 2015, **137**, 10177; (b) D. Kong, M. Li, R. Wang, G. Zi and G. Hou, *Org. Biomol. Chem.*, 2016, **14**, 1216; (c) D. Kong, M. Li, G. Zi and G. Hou, *Org. Biomol. Chem.*, 2016, **14**, 4046; (d) D. Kong, M. Li, G. Zi, G. Hou and Y. He, *J. Org. Chem.*, 2016, **81**, 6640; (e) Q. Yan, D. Kong, W. Zhao, G. Zi and G. Hou, *J. Org. Chem.*, 2016, **81**, 2070.

View Article Online
DOI: 10.1039/C7OB00442G

16 (a) D. H. Hua, S. W. Miao, S. N. Bharathi, T. Katsuhira and A. A. Bravo, *J. Org. Chem.*, 1990, **55**, 3682; (b) C. Matera, M. Quadri, M. Sciaccaluga, D. Y. Pomè, F. Fasoli, M. De Amici, S. Fucile, C. Gotti, C. Dallanoce and G. Grazioso, *Eur. J. Med. Chem.*, 2016, **108**, 392; (c) J. Bielawski, S. Brandänge and L. Lindblom, *J. Heterocyclic Chem.*, 1978, **15**, 97.
17 J. Loren, V. Molteni, Y. Fan, G. Chopiuk, P. A. Albaugh, B. T. Flatt and J. M. Smith, WO 2012034095 A1.
18 H. Nate, Y. Sekine, K. Oda, K. Aoe, H. Nakai, H. Wada, M. Takeda, H. Yabana and T. Nagao, *Chem. Pharm. Bull.*, 1987, **35**, 3253.
19 B. E. Maryanoff and D. F. McComsey, *J. Heterocyclic Chem.*, 1985, **22**, 911.
20 T. Ayako, H. Naoya, Y. Yoshitaka and A. Masatoshi, *Bull. Chem. Soc. Japn.*, 2007, **80**, 2418.