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Ir-Catalyzed Enantioselective Hydrogenation of 2*H*-1,4-Benzoxazines with a Chiral 1,2,3,4-Tetrahydro-1-naphthylamine Derived Phosphine-aminophosphine Ligand

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Unsymmetrical hybrid chiral phosphine-aminophosphine ligand derived from 1,2,3,4-tetrahydro-1-naphthylamine has been found to be highly efficient in the Ir-catalyzed asymmetric hydrogenation of various 3-aryl-2*H*-1,4-benzoxazines, providing good enantioselectivities (up to 95% *ee*) and high catalytic activity (S/C up to 5000).

Keywords asymmetric catalysis, hydrogenation, iridium, 2*H*-1,4-benzoxazine, phosphine-aminophosphine ligand

Introduction

Although great progress has been achieved in the highly enantioselective hydrogenation of various prochiral C=N double bonds in the past few decades,[1] very limited success was obtained in the catalytic asymmetric hydrogenation of 2*H*-1,4-benzoxazines, a type of cyclic imines in nature. In 1998, Kanai *et al*.[2] described the asymmetric hydrogenation of 7,8-difluoro-3-methyl-2*H*-1,4-benzoxazine with a catalytic system composed of iridium(I), (2*S*,4*S*)-BPPM and bismuth(III) iodides. However, the result for this hydrogenation is not so satisfactory since good enantioselectivity (90% *ee*) was achieved only when the hydrogenation was performed at −10 ℃ under a catalyst loading of 5 mol%. Very recently, Zhou *et al*.[3] have reported that up to 92% *ee* could be obtained in the hydrogenation of 3-aryl-2*H*-1,4-benzoxazines by use of a $[Ir(COD)Cl]_2$/(*S*)-SegPhos/I_2 catalytic system. However, 2 mol% of Ir-catalyst was required for completing this hydrogenation. Since chiral 3,4-dihydro-2*H*-benzoxazines are valuable building blocks in the synthesis of many pharmaceuticals as well as the structural motif of various natural products with interesting biological activities,[4] the development of highly enantioselective and reactive catalysts that could successfully address the challenges of low reactivity and narrow substrate scope in the hydrogenation of 2*H*-1,4-benzoxazines is therefore of great interest. Herein we report an enantioselective hydrogenation of 2*H*-1,4-benzoxazines catalyzed by Ir complexes with a chiral phosphine-aminophosphine ligand.

In the past few years, we and some other groups have demonstrated the efficiency of unsymmetrical hybrid chiral phosphine-aminophosphine ligands in the Rh-catalyzed asymmetric hydrogenation of various functionalized olefins.[5] This ligand type has advantages of being highly modular, stable toward air and moisture, and easily tuning the electronic and steric properties, which make it very suitable as ligand motif for asymmetric catalysis. However, the use of this ligand type in other metal-mediated catalytic reactions has been seldom explored. With the aim of expanding the application of this ligand type in asymmetric catalysis, in this research, we have demonstrated for the first time that chiral phosphine-aminophosphine ligands were efficient for the Ir-catalyzed asymmetric hydrogenation of 3-aryl-2*H*-1,4-benzoxazines, in which good enantioselectivity (up to 95% *ee*) and high catalytic activity (S/C up to 5000) were achieved.

Results and Discussion

In a first attempt to induce enantioselectivity in the hydrogenation of 3-phenyl-2*H*-1,4-benzoxazine (**4a**), we screened a series of Ir/phosphine-aminophosphine complexes, and the results are summarized in Table 1. We decided to focus on the Ir-catalytic system in this study because of its demonstrated track record at effecting catalytic asymmetric hydrogenation of various

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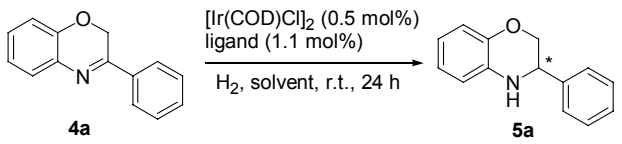
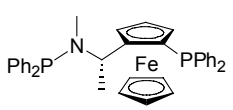
cyclic and acyclic imines.[1]

Table 1 Survey of ligands for Ir-catalyzed asymmetric hydrogenation of 3-phenyl-2*H*-1,4-benzoxazine (**4a**)[a]

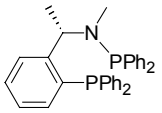


4a **5a**

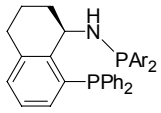
Ligand:



(S_c,R_p)-BoPhoz (**1**)



(S_c)-HHPhos (**2**)



(R_c)-HWPhos (**3**)

3a: Ar = Ph
3b: Ar = 4-$CF_3C_6H_4$
3c: Ar = 3,5-$(CF_3)_2C_6H_3$
3d: Ar = 3,5-$F_2C_6H_3$

Entry	Ligand	H_2/(10^6 Pa)	Solvent	Additive	S/C	Convn.[b]/%	*ee*[c]/%
1	**1**	1	CH_2Cl_2	None	100	>95	38[d]
2	**2**	1	CH_2Cl_2	None	100	>95	81
3	**3a**	1	CH_2Cl_2	None	100	81	92
4	**3b**	1	CH_2Cl_2	None	100	31	84
5	**3c**	1	CH_2Cl_2	None	100	93	77
6	**3d**	1	CH_2Cl_2	None	100	95	86
7	**3a**	3	CH_2Cl_2	None	100	>95	92
8	**3a**	3	MeOH	None	100	>95	20
9	**3a**	3	THF	None	100	<10	—[e]
10	**3a**	3	$PhCH_3$	None	100	18	—[e]
11	**3a**	3	CH_2Cl_2	I_2	100	>95	89
12	**3a**	3	CH_2Cl_2	KI	100	>95	91
13	**3a**	3	CH_2Cl_2	AcOH	100	93	91
14	**3a**	3	CH_2Cl_2	NBS	100	>95	21
15	**3a**	3	CH_2Cl_2	Phthalimide	100	95	92
16	**3a**	4	CH_2Cl_2	None	100	>95	92
17	**3a**	4	CH_2Cl_2	None	1000	>95	88
18	**3a**	4	CH_2Cl_2	None	5000	>95	89

[a] The reactions were carried out with 0.5 mmol of **4a** in 2 mL of solvent at room temperature for 24 h in the presence of 1 mol% of Ir-catalyst *in situ* prepared from $[Ir(COD)Cl]_2$ and 1.1 equiv. of ligand. [b] Degrees of conversion were determined by ^{1}H NMR spectroscopy or GC. [c] The *ee* values were determined by HPLC on chiralcel OD-H column. [d] 0.25 mmol of **4a** and 1 mol% of $[Ir(COD)_2]BF_4$ were used. [e] Not determined due to low conversion.

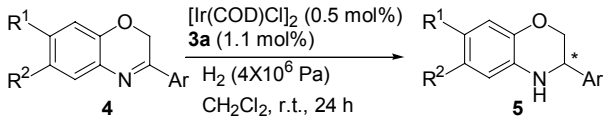
Initial experiments were examined with some known phosphine-aminophosphine ligands which are commercially available or developed within our group. The results in Table 1 disclosed that ligand backbone has significant effect on the reactivity and enantioselectivity (Entries 1—3). Thus, both ferrocene- and benzene-based phosphine-aminophosphine ligands **1**[5a] and **2**[5k] gave full conversions but with very different enantioselectivities (38% *ee* for **1** and 81% *ee* for **2**) (Entries 1 and 2). Remarkably, chiral 1,2,3,4-tetrahydro-1-naphthylamine derived phosphine-aminophosphine ligand **3a**[5m] showed good enantioselectivity of up to 92% *ee*, although incomplete conversion (81% conversion) was obtained (Entry 3). A careful survey of ligands **3** with varying aminophosphino moieties was then carried out (Entries 3—6). However, none of modified ligands **3b**—**3d** was superior to **3a** in term of the enantioselectivity, and **3a** was therefore identified as the best ligand. Following optimization with ligand **3a** disclosed that the increase of H_2 pressure to 3×10^6 Pa significantly promoted the hydrogenation, leading to full conversions with the same high enantioselectivity as that obtained under 1×10^6 Pa of H_2 pressure (Entry 7). A solvent screening experiment revealed that the catalytic activity and enantioselectivity are highly depended on the nature of the solvent used, and CH_2Cl_2 proved to be the best hydrogenation media (Entries 7—10). The additive effect was subsequently investigated. The results indicated that the additive displayed significant influence on the enantioselectivity. However, no positive effect on this hydrogenation was observed in all cases (Entries 11—15). To our delight, the present Ir/**3a** catalytic system gave full conversion and good enantioselectivity (89% *ee*) in the hydrogenation of 3-phenyl-2*H*-1,4-benzoxazines even at a catalyst loading of as low as 0.02 mol% (S/C=5000), representing the most efficient catalytic system in this hydrogenation reported so far (Entry 18).

Having established the optimized hydrogenation conditions, we then examined the scope of this Ir/(R_c)-**3a** catalytic system by employing a range of 2*H*-1,4-benzoxazine derivatives. The results in Table 2 indicated that this catalytic system was efficient to the hydrogenation of various 2*H*-1,4-benzoxazines, affording good to excellent enantioselectivities. The electronic property of the substituent on the phenyl ring showed a limited influence on the enantioselectivity (Entries 1—6). Excellent selectivity of up to 95% *ee* was achieved in the hydrogenation of 3-(4-methoxyphenyl)-2*H*-1,4-benzoxazine (**4f**, Entry 6). Under the optimized hydrogenation condition, however, the present catalytic system showed very low reactivity for the hydrogenation of 3-(2-thienyl)-2*H*-1,4-benzoxazine (**4g**, Entry 7). By introducing I_2 as the additive, excellent performance (98% yield and 94% *ee*) could be achieved (Entry 8). 3-(1-Naphthyl)-2*H*-1,4-benzoxazine (**4h**) and 3-(2-naphthyl)-2*H*-1,4-benzoxazine (**4i**) were also proved to be suitable substrates for this hydrogenation, both giving 98% yields and 85% *ee* (Entries 9 and 10). The substituent on the phenyl ring of 2*H*-1,4-benzoxazine backbone has some influence on the enantioselectivity, normally resulting in reduced enantioselectivities (Entries 11—14).

In summary, we have demonstrated that unsymme-

trical hybrid chiral phosphine-aminophosphine ligands derived from 1,2,3,4-tetrahydro-1-naphthylamine were highly efficient for the Ir-catalyzed asymmetric hydrogenation of 3-aryl-2*H*-1,4-benzoxazine derivatives. Good enantioselectivity (up to 95% *ee*) and high catalytic reactivity (S/C up to 5000) have been achieved, which represent the best result reported so far. The present research also suggested that the additives showed no positive effect on the enantioselectivity and reactivity, different with those reports on the Ir-catalyzed asymmetric hydrogenation of 2*H*-1,4-benzoxazines.

Table 2 Ir-catalyzed asymmetric hydrogenation of 2*H*-1,4-benzoxazine derivatives (**4**): substrate scope[a]



Entry	Substrate	R^2	R^2	R^3	Convn.[b]/%	Yield[c]/%	*ee*[d]/%
1	**4a**	H	H	Ph	>95	99	92
2	**4b**	H	H	4-FC_6H_4	>95	97	93
3	**4c**	H	H	4-ClC_6H_4	>95	98	90
4	**4d**	H	H	4-BrC_6H_4	>95	97	89
5	**4e**	H	H	4-MeC_6H_4	>95	99	92
6	**4f**	H	H	4-$MeOC_6H_4$	>95	97	95
7	**4g**	H	H	2-Thienyl	30	—	—[e]
8	**4g**	H	H	2-Thienyl	>95	98	94[f]
9	**4h**	H	H	1-Naphthyl	>95	98	85
10	**4i**	H	H	2-Naphthyl	>95	98	85
11	**4j**	H	Cl	Ph	>95	96	82
12	**4k**	Cl	H	Ph	>95	97	86
13	**4l**	H	Me	Ph	>95	94	75
14	**4m**	Me	H	Ph	>95	97	84

[a] The reactions were carried out with 0.5 mmol of substrate in 2 mL of CH_2Cl_2 at room temperature for 24 h in the presence of 1 mol% of Ir-catalyst *in situ* prepared from $[Ir(COD)Cl]_2$ and 1.1 equiv. of ligand. [b] Degrees of conversion were determined by ^1H NMR spectroscopy. [c] Isolated yields. [d] The *ee* values were determined by HPLC on Chiralcel OD-H column. [e] Not determined due to low conversion. [f] The reaction was carried out under 1×10^6 Pa of H_2 using 5 mol% of I_2 as additive.

Experimental

All reactions were conducted under a nitrogen or argon atmosphere unless otherwise noted. Anhydrous procedures were conducted using oven-dried or flame-dried glassware and standard syringe and cannula transfer techniques. Hydrogenation was performed in a stainless steel autoclave. Solvents were of reagent grade, dried and distilled before use following standard procedures. 3-Aryl-2*H*-1,4-benzoxazines (**4a** — **4m**) were prepared according to literature.[6] All other chemicals were obtained commercially. ^1H, ^{13}C and ^{31}P NMR spectra were recorded on a Bruker DRX 400 spectrometers using $CDCl_3$ as the solvent. HPLC analyses were performed with an Agilent 1100 series instrument.

General hydrogenation procedure

To a solution of $[Ir(COD)Cl]_2$ (1.7 mg, 0.0025 mmol) in anhydrous and degassed CH_2Cl_2 (1 mL), which was placed in a nitrogen-filled glovebox, was added phosphine-aminophosphine ligand (0.0055 mmol). The reaction mixture was stirred at room temperature for 30 min, and then a solution of 2*H*-1,4-benzoxazine (0.5 mmol) in 1 mL of CH_2Cl_2 was added. The mixture was transferred to a Par stainless autoclave. The autoclave was purged three times with hydrogen, and maintained a hydrogen pressure of 4×10^6 Pa. The hydrogenation was performed at room temperature for 24 h. After carefully releasing the hydrogen gas, the solvent was removed. Conversion was directly determined by GC or ^1H NMR spectroscopy. The enantiomeric excess was determined by HPLC after the purification on silica gel eluting with petroleum ether, EtOAc, and CH_2Cl_2 (10∶1∶1 with R_f at 0.35—0.5).

3-Phenyl-3,4-dihydro-2*H*-1,4-benzoxazine (**5a**):[3,7-9] Viscous oil, 99% yield; 92% *ee*, HPLC conditions for *ee*-analysis: chiralcel OD-H, 40 ℃, 254 nm, *n*-hexane/2-propanol (*V*∶*V*=80∶20), flow rate=0.6 mL/min; $[\alpha]_{20}^{D}$ −141.6 (0.7, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 3.90—3.95 (m, 2H), 4.21 (dd, *J*=10.6, 2.8 Hz, 1H), 4.39 (dd, *J*=8.6, 2.7 Hz, 1H), 6.59 (d, *J*=7.8 Hz, 1H), 6.66 (t, *J*=7.7 Hz, 1H), 6.77 (t, *J*=7.5 Hz, 1H), 6.81 (d, *J*=7.9 Hz, 1H), 7.28—7.34 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 54.3, 71.0, 115.5, 116.7, 119.0, 121.6, 127.3, 128.4, 128.9, 134.1, 139.3, 143.6.

3-(4-Fluorophenyl)-3,4-dihydro-2*H*-1,4-benzoxazine (**5b**):[8] Light yellow crystal, 97% yield, m.p. 83—85 ℃; 93% *ee*, HPLC conditions for *ee*-analysis: chiralcel OD-H, 40 ℃, 254 nm, *n*-hexane/2-propanol (*V*∶*V*=80∶20), flow rate=0.6 mL/min; $[\alpha]_{20}^{D}$ −129.4 (1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 3.87—3.92 (m, 2H), 4.19 (dd, *J*=10.6, 3.0 Hz, 1H), 4.40 (dd, *J*=8.5, 2.9 Hz, 1H), 6.62 (dd, *J*=7.8, 0.9 Hz, 1H), 6.67 (t, *J*=7.6 Hz, 1H), 6.78 (t, *J*=7.5 Hz, 1H), 6.82 (d, *J*=7.9 Hz, 1H), 7.03 (t, 8.6 Hz, 2H), 7.29—7.33 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 53.6, 70.9, 115.5 (d, *J*=13 Hz), 115.9, 116.7, 119.2, 121.6, 128.9 (d, *J*=8 Hz), 133.8, 135.1, 143.6, 162.7 (d, *J*=245 Hz).

3-(4-Chlorophenyl)-3,4-dihydro-2*H*-1,4-benzoxazine (**5c**):[8] Light yellow crystal, 98% yield, m.p. 108—110 ℃; 90% *ee*, HPLC conditions for *ee*-analysis: chiralcel OD-H, 40 ℃, 254 nm, *n*-hexane/2-propanol (*V*∶*V*=80∶20), flow rate=1.0 mL/min; $[\alpha]_{20}^{D}$ −128.6 (0.9, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 3.92—3.97 (m, 2H), 4.24 (dd, *J*=10.6, 3.0 Hz, 1H), 4.48 (dd, *J*=8.4, 2.9 Hz, 1H), 6.66—6.72 (m, 2H), 6.80—6.85 (m, 2H), 7.32—7.37 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 53.6, 70.8, 115.5, 116.7, 119.2, 121.6, 128.6, 129.0, 133.6, 134.1, 137.8, 143.5.

3-(4-Bromophenyl)-3,4-dihydro-2*H*-1,4-benzoxazine (**5d**):[7] Light yellow solid, 97% yield, m.p. 84—86 ℃; 89 % *ee*, HPLC conditions for *ee*-analysis: chiralcel OD-H, 40 ℃, 254 nm, *n*-hexane/2-propanol (*V*∶*V*=80∶20), flow rate=1.0 mL/min; $[\alpha]_{20}^{D}$ −86.2 (1.22, $CHCl_3$); ^{1}H NMR (400 MHz, DMSO) *δ*: 3.87—3.91 (m, 2H), 4.19 (dd, *J*=10.3, 2.1 Hz, 1H), 4.44—4.48 (m, 1H), 6.51—6.54 (m, 1H), 6.69—6.72 (m, 3H), 7.37 (d, *J*=8.0 Hz, 2H), 7.56 (d, *J*=8.1 Hz, 2H); ^{13}C NMR (100 MHz, DMSO) *δ*: 52.5 (d, *J*=11 Hz), 70.0, 115.4, 116.3, 117.5, 121.1, 121.8, 129.8, 131.7, 135.0, 140.2, 143.2.

3-(4-Methylphenyl)-3,4-dihydro-2*H*-1,4-benzoxazine (**5e**):[7] Light yellow crystal, 99% yield, m.p. 57—59 ℃; 92% *ee*, HPLC conditions for *ee*-analysis: chiralcel OD-H, 40 ℃, 254 nm, *n*-hexane/2-propanol (*V*∶*V*=80∶20), flow rate=1.0 mL/min; $[\alpha]_{20}^{D}$ −127.2 (1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 2.24 (s, 3H), 3.80—3.85 (m, 2H), 4.11 (dd, *J*=10.6, 3.0 Hz, 1H), 4.28 (dd, *J*=8.6, 2.9 Hz, 1H), 6.51 (d, *J*=7.7 Hz, 1H), 6.57 (t, *J*=7.5 Hz, 1H), 6.68 (t, *J*=7.3 Hz, 1H), 6.73 (d, *J*=7.8 Hz, 1H), 7.07 (d, *J*=7.7 Hz, 2H), 7.15 (d, *J*=7.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 21.3, 54.0, 71.1, 115.5, 116.7, 119.0, 121.5, 127.2, 129.6, 134.1, 136.2, 138.2, 143.6.

3-(4-Methoxylphenyl)-3,4-dihydro-2*H*-1,4-benzoxazine (**5f**):[7] Light yellow crystal, 97% yield, m.p. 123—125 ℃; 95% *ee*, HPLC conditions for *ee*-analysis: chiralcel OD-H, 40 ℃, 254 nm, *n*-hexane/2-propanol (*V*∶*V*=80∶20), flow rate=1.0 mL/min; $[\alpha]_{20}^{D}$ −127.0 (0.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 3.77 (s, 3H), 3.89—3.94 (m, 2H), 4.20 (dd, *J*=10.6, 2.2 Hz, 1H), 4.38 (d, *J*=8.5 Hz, 1H), 6.61 (d, *J*=7.8 Hz, 1H), 6.67 (t, *J*=7.6 Hz, 1H), 6.77 (t, *J*=7.5 Hz, 1H), 6.82 (d, *J*=7.9 Hz, 1H), 6.88 (d, *J*=8.2 Hz, 2H), 7.27 (d, *J*=8.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 53.6, 55.4, 71.1, 114.3, 115.5, 116.6, 119.0, 121.5, 128.4, 131.2, 134.1, 143.6, 159.7.

3-Thienyl-3,4-dihydro-2*H*-1,4-benzoxazine (**5g**):[7-9] Viscous oil, 98% yield; 94% *ee*, HPLC conditions for *ee*-analysis: chiralcel OD-H, 40 ℃, 254 nm, *n*-hexane/2-propanol (*V*∶*V*=80∶20), flow rate=1.0 mL/min; $[\alpha]_{20}^{D}$ −120.5 (0.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 3.85 (br, 1H), 4.03—4.08 (m, 1H), 4.30 (dd, *J*=10.6, 2.5 Hz, 1H), 4.79 (dd, *J*=8.0, 2.4 Hz, 1H), 6.62 (d, *J*=7.6 Hz, 1H), 6.69 (t, *J*=7.4 Hz, 1H), 6.77—6.84 (m, 2H), 6.98—7.00 (m, 1H), 7.04 (s, 1H), 7.26—7.27 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 50.2, 71.1, 115.7, 116.7, 119.5, 121.7, 124.9, 125.4, 127.0, 133.1, 142.8, 143.6.

3-(1-Naphthyl)-3,4-dihydro-2*H*-1,4-benzoxazine (**5h**):[7-9] Viscous oil, 98% yield; 85% *ee*, HPLC conditions for *ee*-analysis: chiralcel OD-H, 40 ℃, 254 nm, *n*-hexane/2-propanol (*V*∶*V*=80∶20), flow rate=1.0 mL/min; $[\alpha]_{20}^{D}$ −126.8 (0.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 3.98—4.03 (m, 2H), 4.27 (dd, *J*=10.6, 2.3 Hz, 1H), 4.53 (d, *J*=8.5 Hz, 1H), 6.63 (d, *J*=7.7 Hz, 1H), 6.69 (t, *J*=7.6 Hz, 1H), 6.79 (t, *J*=7.5 Hz, 1H), 6.86 (d, *J*=7.9 Hz, 1H), 7.39—7.46 (m, 3H), 7.78—7.80 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 50.2, 71.1, 115.7, 116.7, 119.5, 121.7, 124.9, 125.4, 127.0, 133.1, 142.8, 143.6.

3-(2-Naphthyl)-3,4-dihydro-2*H*-1,4-benzoxazine (**5i**):[8] Viscous oil, 98% yield; 85% *ee*, HPLC conditions for *ee*-analysis: chiralcel OD-H, 40 ℃, 254 nm, *n*-hexane/2-propanol (*V*∶*V*=80∶20), flow rate=1.0 mL/min; $[\alpha]_{20}^{D}$ −119.6 (1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 3.96—4.01 (m, 2H), 4.27 (dd, *J*=10.6, 2.3 Hz, 1H), 4.53 (d, *J*=8.5 Hz, 1H), 6.63 (d, *J*=7.7 Hz, 1H), 6.69 (t, *J*=7.6 Hz, 1H), 6.79 (t, *J*=7.5 Hz, 1H), 6.86 (d, *J*=7.9 Hz, 1H), 7.39—7.46 (m, 3H), 7.78—7.80 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 54.4, 71.0, 115.6, 116.8, 119.1, 121.7, 125.1, 126.3, 126.5, 127.9, 128.0, 128.7, 133.4, 133.5, 134.0, 136.6, 143.7.

3-Phenyl-6-chloro-3,4-dihydro-2*H*-1,4-benzoxazine (**5j**):[9] Light yellow crystal, 96% yield, m.p. 92—94 ℃; 82% *ee*, HPLC conditions for *ee*-analysis: chiralcel OD-H, 40 ℃, 254 nm, *n*-hexane/2-propanol (*V*∶*V*=80∶20), flow rate=1.0 mL/min; $[\alpha]_{20}^{D}$ −91.1 (1.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 3.91—3.95 (m, 2H), 4.25 (dd, *J*=10.4, 2.8 Hz, 1H), 4.45 (dd, *J*=8.0, 2.4 Hz, 1H), 6.61—6.62 (m, 2H), 6.72—6.74 (m, 1H), 7.36—7.38 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 54.0, 70.8, 114.8, 117.5, 118.4, 126.2, 127.2, 128.6, 128.9, 134.9, 138.7, 142.1.

3-Phenyl-7-chloro-3,4-dihydro-2*H*-1,4-benzoxazine (**5k**):[9] Viscous oil, 97% yield; 86% *ee*, HPLC conditions for *ee*-analysis: chiralcel OD-H, 40 ℃, 254 nm, *n*-hexane/2-propanol (*V*∶*V*=80∶20), flow rate=1.0 mL/min; $[\alpha]_{20}^{D}$ −81.3 (1.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 3.93—3.98 (m, 2H), 4.26 (dd, *J*=10.8, 3.0 Hz, 1H), 4.45 (dd, *J*=8.4, 2.9 Hz, 1H), 6.55—6.57 (m, 1H), 6.74—6.77 (m, 1H), 6.83—6.84 (m, 1H), 7.33—7.37 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 54.1, 70.9, 115.9, 116.8, 121.3, 123.1, 127.2, 128.5, 128.9, 132.6, 138.7, 144.0.

3-Phenyl-6-methyl-3,4-dihydro-2*H*-1,4-benzoxazine (**5l**):[10] Viscous oil, 94% yield; 75% *ee*, HPLC conditions for *ee*-analysis: chiralcel OD-H, 40 ℃, 254 nm, *n*-hexane/2-propanol (*V*∶*V*=80∶20), flow rate=1.0 mL/min; $[\alpha]_{20}^{D}$ −109.2 (0.9, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 2.22 (s, 3H), 3.91—3.96 (m, 2H), 4.23 (dd, *J*=10.6, 2.2 Hz, 1H), 4.45 (dd, *J*=8.6, 2.7 Hz, 1H), 6.46—6.50 (m, 2H), 6.72—6.74 (m, 1H), 7.31—7.37 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 20.8, 54.4, 71.1, 116.0, 116.4, 119.5, 127.2, 128.3, 128.9, 131.0, 133.6, 139.4, 141.4.

3-Phenyl-7-methyl-3,4-dihydro-2*H*-1,4-benzoxazine (**5m**):[10] Viscous oil, 97% yield; 84% *ee*, HPLC conditions for *ee*-analysis: chiralcel OD-H, 40 ℃, 254 nm, *n*-hexane/2-propanol (*V*∶*V*=80∶20), flow rate=1.0 mL/min; $[\alpha]_{20}^{D}$ −115.1 (0.9, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 2.23 (s, 3H), 3.93—3.98 (m, 2H), 4.24 (dd, *J*=10.6, 2.8 Hz, 1H), 4.43 (dd, *J*=8.6, 2.7 Hz, 1H), 6.54—6.56 (m, 1H), 6.60—6.62 (m, 1H), 6.67 (s, 1H), 7.31—7.39 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 20.7, 54.4, 71.1, 115.5, 117.2, 119.0, 122.0, 127.3,

128.3, 128.8, 131.3, 139.3, 143.5.

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