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Synthesis and enantioselective hydrogenation of seven-membered cyclic imines: substituted dibenzo[*b*,*f*][1,4]oxazepines†

Kai Gao,[a] Chang-Bin Yu,[a] Wei Li,[b] Yong-Gui Zhou*[a] and Xumu Zhang*[b]

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Highly enantioselective hydrogenation of seven-membered cyclic imines, substituted dibenzo[*b*,*f*][1,4]oxazepines, was achieved, with up to 94% ee, by using the [Ir(COD)Cl]$_2$/(*S*)-Xyl-C$_3$*-TunePhos complex as the catalyst in the presence of morpholine-HCl.

The chemistry of dibenzo[*b*,*f*][1,4]oxazepine derivatives has attracted much attention from many research groups due to their significance in many physiologically active compounds. Among the compounds containing the scaffold (Fig. 1, compounds **1–4**) are important non-nucleoside HIV-1 reverse transcriptase inhibitors,[1] efficient antidepressants and anti-psychotics,[2] as well as progesterone receptor agonists.[3,4]

Efforts have been made to synthesise 11-substituted-10,11-dihydrodibenzo[*b*,*f*][1,4]oxazepine derivatives, *via* methods including microwave-assisted one-pot U-4CR and intramolecular O-arylation,[5a] domino elimination–rearrangement–addition reactions,[5b] intramolecular π-cationic cyclization[5c] and 1,3-dipolar cycloaddition reactions.[5d] However, no example of a catalytic asymmetric version was reported. To further the investigation of the bioactive properties of these compounds, optically pure enantiomers are required. According to the retrosynthetic analysis (Fig. 1), direct asymmetric hydrogenation of the corresponding imines would be an efficient and atom-economical approach to the synthesis of these chiral amines.

Despite the great success in the hydrogenation of imines,[6] especially using the iridium catalyst system,[7] the hydrogenation of seven-membered cyclic imines remains less explored.[8] In our studies of the asymmetric hydrogenation of heteroaromatic compounds,[9] we conjectured that hydrogenation of seven-membered cyclic imines would be an appropriate route to chiral dibenzo[*b*,*f*][1,4]oxazepine derivatives with iridium complexes. Herein, we delivered our results on iridium-catalyzed hydrogenation of cyclic imines, for which high yields and up to 94% ee were obtained.

Cyclic imines were conveniently synthesized according to the modified literature procedures[10] shown in Scheme 1. The treatment of *o*-fluoro nitrobenzene derivatives **5** with substituted phenols in the presence of NaH in DMF afforded compounds **6**, then **6** were reduced with Pd/C to give 2′-phenoxylaniline derivatives followed by acylation. The obtained amide derivatives **7** were then transformed to the hydrogenation substrates **8** through cyclization with PPA and $POCl_3$ at 120 °C with good yields.

With the imine substrates in hand, we began our study with cyclic imine **8a** as a model substrate and [Ir(COD)Cl]$_2$/(*S*)-SegPhos as the catalyst under 700 psi of hydrogen pressure in CH_2Cl_2. The hydrogenation proceeded smoothly, but with only 36% ee (Table 1, entry 1). Recently, the superiority of a Brønsted acid or the corresponding salt as an additive has been demonstrated in asymmetric hydrogenation.[11] 10 mol% of morpholine-TFA was added as an additive, and pleasingly, 74% ee was obtained (Table 1, entry 2). Solvent screening revealed that CH_2Cl_2 was the best solvent (Table 1, entries 2–7). Then, several other additives were tested in CH_2Cl_2. Better results were found when the salts of morpholine were used as additives than when those of piperidine were used (Table 1, entries 2 *vs.* 8 and 12 *vs.* 9). Eventually, morpholine-HCl was found to be the optimal choice, as full conversion and 78% ee were obtained (Table 1, entry 12). Furthermore, the amount of additive was also tested (Table 1, entries 13–15),

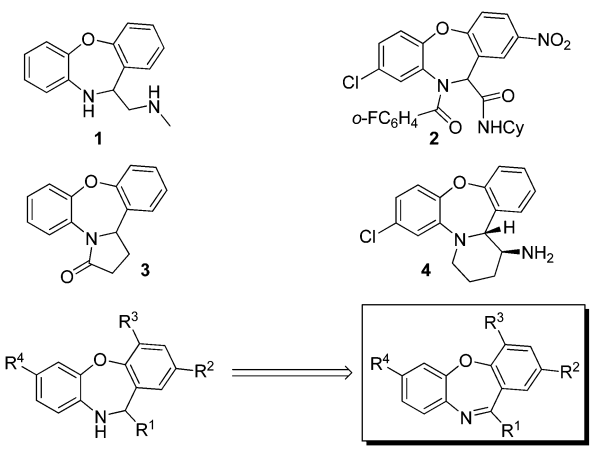

Fig. 1 Derivatives of cyclic amines containing dibenzo[*b*,*f*][1,4]oxazepine.

[a] *State Key Laboratory of Catalysis, Dalian Institute of Chemical Physics, Chinese Academy of Sciences, 457 Zhongshan Road, Dalian 116023, P. R. China. E-mail: ygzhou@dicp.ac.cn*
[b] *Department of Chemistry, Rutgers, The State University of New Jersey, Piscataway, New Jersey 08854, United States. E-mail: xumu@rutgers.edu*

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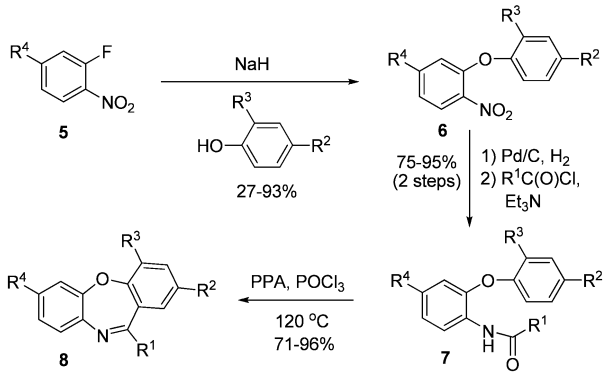
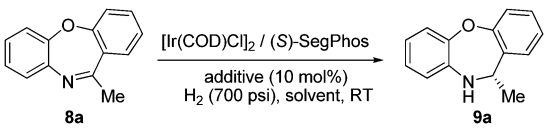


Scheme 1 The synthesis of seven-membered cyclic imines **8**.

Table 1 The effect of solvents and additives on the reaction[a]



Entry	Additive	Solvent	Conv. (%)[b]	ee (%)[c]
1	—	CH_2Cl_2	>95	36
2	morpholine-TFA	CH_2Cl_2	>95	74
3	morpholine-TFA	EtOAc	>95	67
4	morpholine-TFA	THF	>95	67
5	morpholine-TFA	MeOH	84	45
6	morpholine-TFA	Toluene	>95	65
7	morpholine-TFA	$ClCH_2CH_2Cl$	>95	62
8	piperidine-TFA	CH_2Cl_2	>95	65
9	piperidine-HCl	CH_2Cl_2	>95	68
10	morpholine-HF	CH_2Cl_2	24	48
11	morpholine-HBr	CH_2Cl_2	>95	72
12	morpholine-HCl	CH_2Cl_2	>95	78
13[d]	morpholine-HCl	CH_2Cl_2	>95	82
14[e]	morpholine-HCl	CH_2Cl_2	>95	83
15[f]	morpholine-HCl	CH_2Cl_2	>95	83

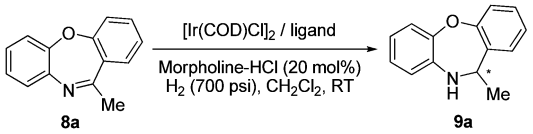
[a] Conditions: 0.25 mmol of **8a**, $[Ir(COD)Cl]_2$ (1 mol%), (*S*)-SegPhos (2.2 mol%), additive (10 mol%), 3 mL of solvent, 20 h, RT. [b] Determined by ^1H NMR. [c] Determined by HPLC. [d] 20 mol% of morpholine-HCl. [e] 50 mol% of morpholine-HCl. [f] 100 mol% of morpholine-HCl.

revealing that 20 mol% of morpholine-HCl was appropriate considering its solubility (Table 1, entry 13).

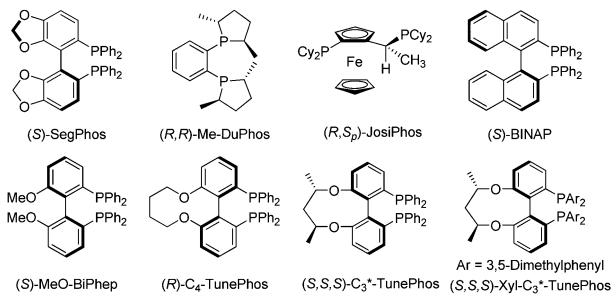
Subsequently, some commercially available bisphosphine ligands were examined. Initially, electron-sufficient (*R*,*R*)-Me-DuPhos gave poor conversion and enantioselectivity (Table 2, entry 2). Lower enantioselectivities were also observed with JosiPhos and BINAP ligands (Table 2, entries 3–4). When MeO-BiPhep, C_4-TunePhos and C_3*-TunePhos were employed, full conversions and high enantioselectivities were achieved (Table 2, entries 5–7). The sterically hindered (*S*)-Xyl-C_3*-TunePhos gave the highest enantioselectivity (94% ee, Table 2, entry 8). Therefore, the optimized conditions were: $[Ir(COD)Cl]_2$/(*S*)-Xyl-C_3*-TunePhos/morpholine-HCl/H_2 (700 psi)/CH_2Cl_2.

Under the optimal conditions, a variety of substituted dibenzo[*b*,*f*][1,4]oxazepines were subjected to asymmetric hydrogenation, as shown in Table 3. When R^1 was a methyl group, excellent enantioselectivities (86–94% ee) were

Table 2 Ligand screening for asymmetric hydrogenation of **8a**[a]



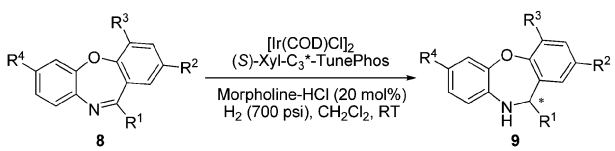
Entry	Ligand	Conv. (%)[b]	ee (%)[c]
1	(*S*)-SegPhos	>95	82
2	(*R*,*R*)-Me-DuPhos	17	12
3	(*R*,S_p)-JosiPhos	>95	21
4	(*S*)-BINAP	>95	34
5	(*S*)-MeO-BiPhep	>95	75
6	(*R*)-C_4-TunePhos	>95	81
7	(*S*)-C_3*-TunePhos	>95	87
8	(*S*)-Xyl-C_3*-TunePhos	>95	94



[a] Conditions: 0.25 mmol of **8a**, $[Ir(COD)Cl]_2$ (1 mol%), ligand (2.2 mol%), morpholine-HCl (20 mol%), 3 mL of CH_2Cl_2, 20 h, RT. [b] Determined by ^1H NMR. [c] Determined by HPLC.

achieved, regardless of the position and electronic effect of the substituents of the phenyl ring (Table 3, entries 1–10). When a substrate with a longer ethyl or propyl chain in the position of R^1 was used, the ee value decreased slightly, but the yield remained high (Table 3, entries 11–12). For the substrates with

Table 3 Ir-catalyzed asymmetric hydrogenation of **8**[a]



Entry	$R^1/R^2/R^3/R^4$ in **8**	Yield (%)[b]	ee (%)[c]
1	Me/H/H/H (**8a**)	98	94 (−)
2	Me/Me/H/H (**8b**)	96	90 (−)
3	Me/H /Me/H (**8c**)	98	91 (−)
4	Me /H/*i*Pr/H (**8d**)	97	93 (−)
5	Me/Ph/H/H (**8e**)	94	86 (−)
6	Me/H/Ph/H (**8f**)	98	90 (+)
7	Me/H/H/Me (**8g**)	93	92 (−)
8	Me/F/H/H (**8h**)	98	90 (−)
9	Me/H/Cl/H (**8i**)	95	90 (+)
10	Me/H/Br/H (**8j**)	97	87 (*S*)
11	Et/H/H/H (**8k**)	98	83 (−)
12	*n*Pr/H/H/H (**8l**)	97	81 (−)
13	Bn/H/H/H (**8m**)	85	52 (−)
14	Ph/H/H/H (**8n**)	12[d]	78 (−)

[a] Conditions: 0.25 mmol of **8**, $[Ir(COD)Cl]_2$ (1 mol%), (*S*)-Xyl-C_3*-TunePhos (2.2 mol%), morpholine-HCl (20 mol%), 3 mL of CH_2Cl_2, 20 h, RT. [b] Isolated yield. [c] Determined by HPLC. [d] Determined by ^1H NMR.

R^1 bearing benzyl or phenyl groups, a lower reactivity and moderate enantioselectivity were obtained (Table 3, entries 13–14).

To determine the absolute configuration, chiral amine **9j** was acylated with benzoyl chloride and then recrystallized from DCM/hexane to give amide **10** (> 99% ee) as a colorless crystal, and its configuration was assigned as (*S*)-**10** by X-ray diffraction analysis (see ESI†).[12] The other products' absolute configurations were assigned by analogy with **9j**.

In summary, we have synthesized a novel type of cyclic imine using *o*-fluoro nitrobenzene derivatives as the starting materials, which were hydrogenated by using the Ir/(*S*)-Xyl-C_3*-TunePhos catalyst system in the presence of morpholine-HCl with up to 94% ee. This method provides an efficient route to optically active 11-substituted-10,11-dihydrodibenzo[*b*,*f*][1,4]oxazepines.

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12 Selected bond lengths [Å] and angles [°]: N1–C7, 1.458(5); C6–C7, 1.518(5); C7–C8, 1.537(6); N1–C9, 1.369(5); C9–N1–C7, 118.4(3); N1–C7–C6, 114.4(3); N1–C7–C8, 110.9(3); C6–C7–C8, 112.0(3); N1–C7–H7, 106.3; C6–C7–H7, 106.3, C8–C7–H7, 106.3.