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Iridium-catalyzed asymmetric hydrogenation of dibenzo[*b,f*][1,4]thiazepines*

Ran-Ning Guo[1,2], Kai Gao[1], Zhi-Shi Ye[1], Lei Shi[1], Yanqin Li[2], and Yong-Gui Zhou[1,‡]

[1]State Key Laboratory of Catalysis, Dalian Institute of Chemical Physics, Chinese Academy of Sciences, 457 Zhongshan Road, Dalian 116023, China; [2]Department of Chemistry, Dalian University of Technology, Dalian 116012, China

Abstract: Highly enantioselective hydrogenation of substituted dibenzo[*b*,*f*][1,4]thiazepines was achieved with up to 96 % ee (enantiomeric excess) using $[Ir(COD)Cl]_2$/(*R*)-SynPhos complex as catalyst in the presence of iodine. This method provides an efficient access to optically active 11-substituted-10,11-dihydrodibenzo[*b*,*f*][1,4]thiazepines.

Keywords: asymmetric hydrogenation; dibenzothiazepines; heterocyclic chemistry; iodine; iridium.

INTRODUCTION

Dihydrodibenzothiazepines are important and widely used scaffolds in medicinal chemistry. Many tricyclic or tetracyclic heterocycles based upon this parent structure exhibit intriguing pharmacological activity [1]. For example (Fig. 1), the conformationally constrained compound **1** is a skeletal thia-analog of the antidepressant nitroxazepine (Sintamil) [2]. Compound **2** is a structure analogue of furosemide—a highly efficient diuretic, whose activity strongly depends on conformational mobility of the 4-substituents in the 3-amino-5-sulfamylbenzoic acid [3], revealing the potential pharmaceutical use of compound **2**. The tetracyclic piperazinothiazepines **3** are useful for the treatment of migraine and neurogenic inflammation [4]. In addition, compound **4** is a nonsteroidal antagonist of the progesterone receptor [5].

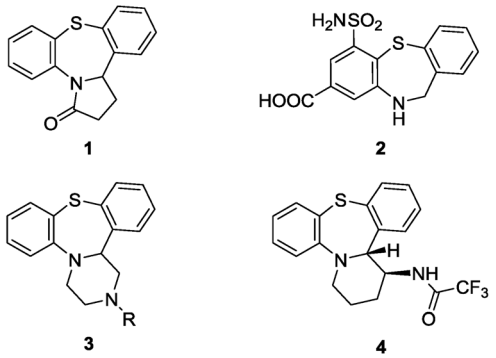

Fig. 1 Representative dihydrodibenzothiazepine derivatives with pharmacological activities.

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‡Corresponding author

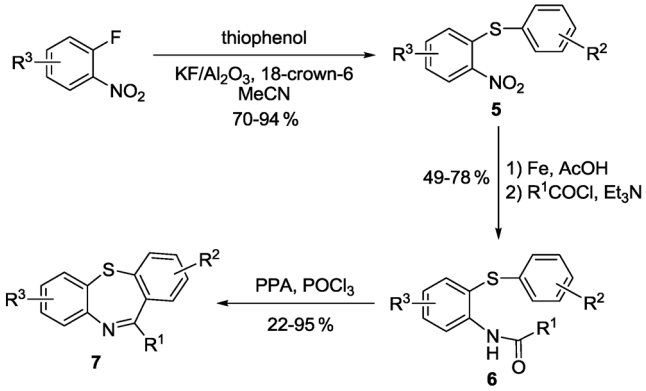
Synthesis of dihydrodibenzothiazepines has attracted much attention, in view of their high potential for discovery of drug candidates. Several synthetic approaches [2–6], including intramolecular cyclization and domino reaction methodology, have been developed. Asymmetric synthesis in this area has received less attention, but strategies for enantioselective synthesis of dihydrodibenzothiazepines are now highly desirable, as a necessary tool to advance the study of structure–activity relationships (SAR) in discrete enantiomers. Asymmetric hydrogenation of prochiral unsaturated compounds is recognized as a particularly efficient and atom-economical method of enantiocontrol, and intensive studies have resulted in successful development of a growing number of novel catalyst formulations [7]. We envisioned asymmetric hydrogenation of dibenzothiazepine imines as a potentially efficient route to the corresponding chiral amines. Hydrogenation of dibenzothiazepine raises questions about a structure-based problem that must be addressed, since catalysts are susceptible to deactivation or poisoning by nitrogen- and sulfur-containing heterocyclic compounds [8]. Therefore, an efficient and high active catalyst system is demanded to solve this problem [9].

Recently, our group developed a highly enantioselective hydrogenation of dibenzo[*b*,*f*][1,4]oxazepines using iridium catalyst in the presence of morpholinium hydrochloride as additive [10a]. Later, asymmetric hydrogenation of a series of pyrrole- and indole-fused benzodiazepines and benzodiazepinones with iridium-diphosphine catalyst system was also developed, up to 96 % ee (enantiomeric excess) was obtained [10b]. In our above work, oxygen and nitrogen atoms in substrates could be tolerated by iridium catalysts. To the best of our knowledge, the asymmetric hydrogenation of imines containing sulfur atoms utilizing transition-metal catalyst has not been reported. As a continuing work on the asymmetric hydrogenation of aromatic compounds and heterocyclic imines [11], herein, we reported the Ir-catalyzed asymmetric hydrogenation of challenging dibenzothiazepines containing sulfur atoms.

RESULTS AND DISCUSSION

Synthesis of dibenzo[*b*,*f*][1,4]thiazepines

According to literature procedures [12], dibenzothiazepines were conveniently synthesized through a slightly modified synthetic approach as shown in Scheme 1. The diphenyl thioether derivatives **5** were obtained by the treatment of *o*-fluoro nitrobenzenes with substituted thiophenols in the presence of KF/Al_2O_3 and 18-crown-6 in acetonitrile. Then the reduction of nitro group with Fe/AcOH followed by acylation with acyl chloride afforded amide derivatives **6**. Subsequently, compounds **6** were transformed to dibenzothiazepines **7** via cyclization with polyphosphoric acid (PPA) and $POCl_3$ at 120 °C.

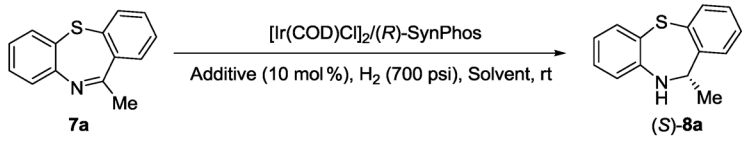


Scheme 1 Synthesis of substituted dibenzo[*b*,*f*][1,4]thiazepines.

Optimization of reaction conditions

In our initial study, the asymmetric hydrogenation of 11-methyldibenzo[*b*,*f*][1,4]thiazepine (**7a**) with $[Ir(COD)Cl]_2$ and (*R*)-SynPhos was chosen as a model reaction. The reaction proceeded smoothly in toluene with 76 % conversion and moderate 52 % enantioselectivity (Table 1, entry 1). Recent results from our group [9a,13] and others [14] have demonstrated that iodine can significantly improve the performance of iridium complex in asymmetric hydrogenation. When iodine was added to the reaction, the ee value was enhanced to 91 % (entry 2). Encouraged by this promising result, the effect of solvents on the reactivity and enantioselectivity was also examined. It was found that enantioselectivity was strongly influenced by the choice of solvent, and that benzene furnished the most favorable outcome at 92 % ee (entries 3–7). Next, the effect of additives was investigated using various halogen sources (entries 8–11). In all cases, the additives were able to efficiently promote this transformation with high yields and ees. Eventually, iodine was still the best additive with respect to reactivity and enantioselectivity. Lowering the amount of iodine, the ee decreased slightly (entry 12).

Table 1 The effect of solvents and additives on the reactivity and enantioselectivity[a].



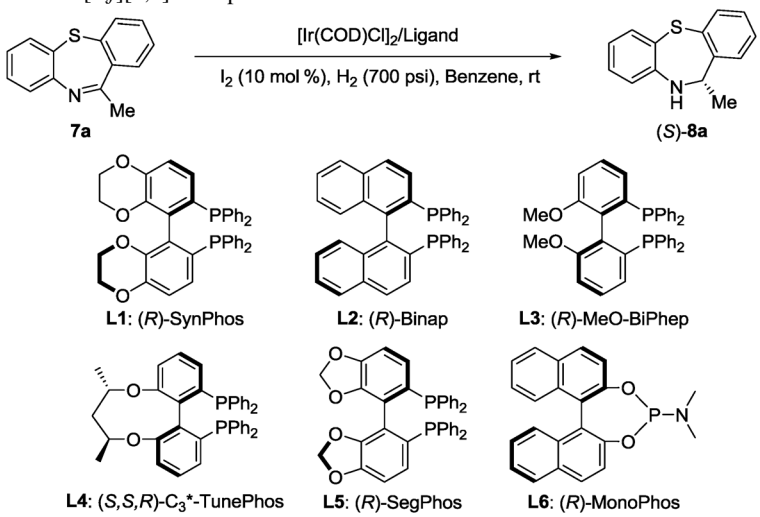
Entry	Additive	Solvent	Yield (%)[b]	Ee (%)[c]
1	None	Toluene	76[d]	52
2	I_2	Toluene	95	91
3	I_2	MeOH	74	17
4	I_2	THF	95	67
5	I_2	1,4-Dioxane	70	74
6	I_2	CH_2Cl_2	95	4
7	I_2	Benzene	84	92
8	NIS	Benzene	81	87
9	DCDMH	Benzene	74	78
10	DBDMH	Benzene	85	86
11	BCDMH	Benzene	92	79
12[e]	I_2	Benzene	95	90

[a]Conditions: **7a** (0.125 mmol), $[Ir(COD)Cl]_2$ (2 mol %), (*R*)-SynPhos (4.4 mol %), additive (10 mol %), 3 mL of solvent, 16 h, rt.
[b]Isolated yield.
[c]Determined by HPLC.
[d]Conversion determined by ^1H NMR.
[e]5 mol % of I_2.

Subsequently, several kinds of commercially available chiral ligands were screened under the above conditions (Table 2). Axially chiral diphosphine ligands provided good to excellent enantioselectivities (entries 1–5). (*R*)-SynPhos ligand **L1** gave the highest enantioselectivity (92 %). Monodentate ligand MonoPhos was also examined, which resulted in full conversion but poor enantio-

selectivity (entry 6). In conclusion, the optimized conditions were established to be $[Ir(COD)Cl]_2$/(*R*)-SynPhos/I_2 (10 mol %)/H_2 (700 psi)/benzene/rt.

Table 2 Ligand screening for the asymmetric hydrogenation of dibenzo[*b*,*f*][1,4]thiazepine **7a**[a].



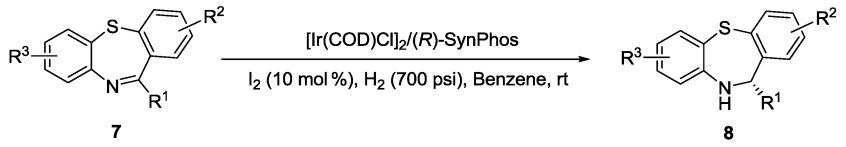
Entry	Ligand	Yield (%)[b]	Ee (%)[c]
1	**L1**	84	92
2	**L2**	84	71
3	**L3**	92	86
4	**L4**	99	84
5	**L5**	95	84
6	**L6**	95	11

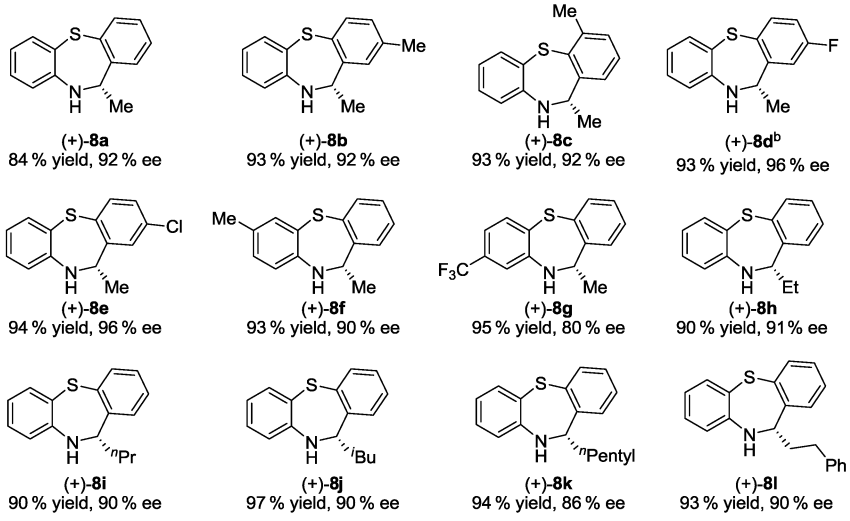
[a]Conditions: **7a** (0.125 mmol), $[Ir(COD)Cl]_2$ (2 mol %), ligand (4.4 mol %), I_2 (10 mol %), 3 mL of benzene, 16 h, rt.
[b]Isolated yield.
[c]Determined by HPLC.

Substrate scope

To demonstrate the substrate generality of this method, a variety of substituted dibenzo[*b*,*f*]-[1,4]thiazepines was subsequently evaluated under the optimized conditions, as shown in Table 3. When R^1 was a methyl group, good yields and excellent enantioselectivities (80–96 % ee) were achieved regardless of position and electronic effect of substituents of phenyl ring (**7b–g**); among them, substrates bearing fluoro- and chloro-substituents on the phenyl ring (**7d,e**) afforded the highest ee values. The enantioselectivity decreased when R^1 was replaced by longer alkyl chains (**7h–k**), such as *iso*-butyl and *n*-pentyl group. Furthermore, the asymmetric hydrogenation of **7l** with phenethyl substituent gave 90 % ee. It is important to stress that this iridium catalyst system can tolerate all the substrates containing sulfur atoms investigated.

Table 3 Ir-catalyzed asymmetric hydrogenation of dibenzo[*b*,*f*][1,4]thiazepines[a].





[a]The reaction was carried out with **7** (0.125 mmol) using $[Ir(COD)Cl]_2$ (2 mol %) and (*R*)-SynPhos (4.4 mol %) in the presence of I_2 (10 mol %) in benzene (3 mL) at room temperature for 16 h. The yields were of the isolated products by column chromatography. The ee values were determined by chiral HPLC analysis.
[b]The absolute configuration of **8d** was determined by X-ray diffraction analysis.

The absolute configuration of the product **8d** was determined to be *S* by X-ray crystallographic analysis after recrystallization from DCM/hexane [15], the absolute configuration of other products was assigned by analogy (Fig. 2).

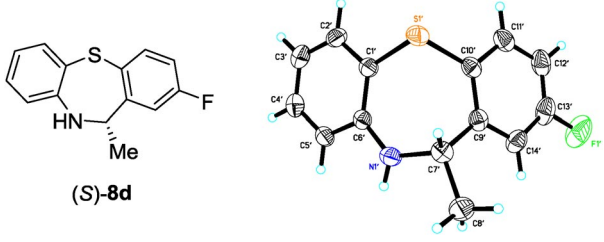


Fig. 2 X-ray crystal structure of (+)-(*S*)-2-fluoro-11-methyl-10,11-dihydrodibenzo[*b*,*f*][1,4]thiazepine **8d**.

CONCLUSION

In summary, we have synthesized a novel type of dibenzothiazepines with *o*-fluoro nitrobenzene derivatives as starting materials, which were hydrogenated by using Ir/(*R*)-SynPhos complex as catalyst in the presence of iodine with up to 96 % ee. As far as we know, this represents the first catalytic asymmetric hydrogenation of heterocyclic imines containing sulfur atoms. The absolute configuration of the

hydrogenation product was also assigned by X-ray crystallographic analysis. Furthermore, this method provides an efficient access to optically active dihydrodibenzothiazepine derivatives.

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15. CCDC 883596 contains the supplementary crystallographic data for this compound. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre at www.ccdc.cam.ac.uk/data_request/cif.

