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Iridium Catalyzed Asymmetric Hydrogenation of Cyclic Imines of Benzodiazepinones and Benzodiazepines

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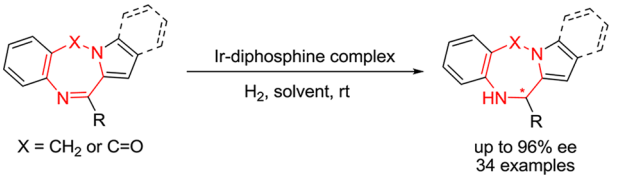
ABSTRACT



Highly enantioselective Ir-catalyzed hydrogenation of seven-membered cyclic imines of benzodiazepinones and benzodiazepines was achieved with up to 96% ee. This method provides a direct access to synthesize a range of chiral cyclic amines existing in numerous important natural products and clinical drugs.

Heterocycles containing a tri- or tetracyclic skeleton are representatives of a major structure type in natural product and medicinal chemistry.[1] Dihydrobenzodiazepinone and -diazepine derivatives containing a pyrrole or an indole moiety are among an important class of heterocyclic compounds with remarkable biological activities.[1] The pyrrolobenzodiazepinone skeleton is present in a family of naturally occurring antitumor antibiotics,[2,3] such as anthramycin and tilivalline, isolated from *Streptomyces*. Aptazepine with a pyrrolobenzodiazepine core is a novel antidepressant agent,[4] which is undergoing clinical trials (Figure 1).

Although a great amount of effort has been made to synthesize the intriguing fused benzodiazepinone and -diazepine heterocycles *via* intramolecular cyclization[5] and transition metal mediated cascade transformation,[6] little attention has been paid to their synthesis through asymmetric catalysis.[7] In this regard, the development of a simple and flexible asymmetric synthetic method is highly desirable. We envisaged that asymmetric hydrogenation of the corresponding cyclic imines would be a convenient and straightforward route to these chiral dihydrobenzodiazepinone and -diazepine derivatives.

During the past two decades, many kinds of catalyst systems for the asymmetric hydrogenation[8] and transfer hydrogenation[9] of cyclic imines have been developed. Recently, Zhang et al. reported the highly efficient asymmetric hydrogenation of a series of cyclic imines using an iridium/f-binaphane complex.[8k] Rueping et al. utilized the organocatalyst for the transfer hydrogenation of heterocyclic imines.[9i] To our knowledge, there are only a few

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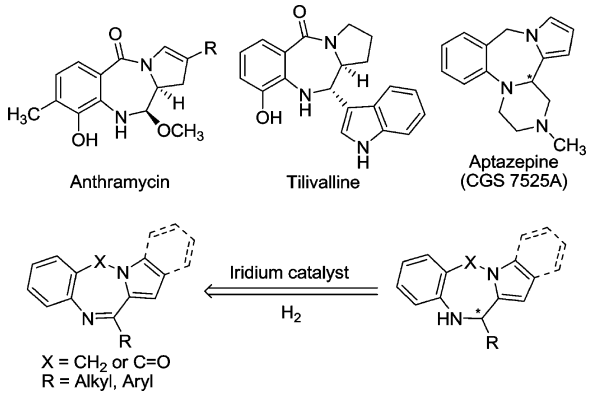
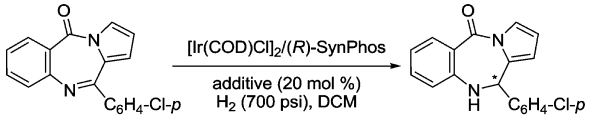


Figure 1. Representative dihydrobenzodiazepinone and dihydrobenzodiazepine derivatives.

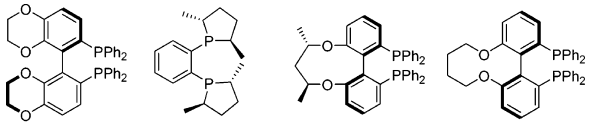
successful examples thus far reported on the asymmetric reduction of seven-membered cyclic imines,[8a,j,9d] probably owing to the relatively rigid and space-demanding features of these imines. Thereby, an efficient catalyst is highly required for the hydrogenation of these seven-membered-ring systems with a unique skeleton. In view of the significance of these intriguing heterocycles, together with our ongoing programs directed to the development of an efficient method for the asymmetric hydrogenation of heteroaromatic compounds[10] and cyclic imines,[11] we disclosed herein the Ir-catalyzed asymmetric hydrogenation of seven-membered cyclic imines of benzodiazepinones and -diazepines (Figure 1).

Table 1. Optimization of Reaction Conditions[a]



entry	additive	ligand	conv (%)[b]	ee (%)[c]
1	–	**L1**	93	73
2	I^2	**L1**	>95	30
3	TFA	**L1**	65	74
4	L-CSA	**L1**	66	72
5	piperidine·HCl	**L1**	93	85
6	morpholine·HCl	**L1**	78	87
7	morpholine·HBr	**L1**	93	71
8	morpholine·TFA	**L1**	>95	88
9[d]	morpholine·TFA	**L1**	>95	87
10[d,e]	morpholine·TFA	**L1**	49	84
11[d,f]	morpholine·TFA	**L1**	54	90
12[d,g]	morpholine·TFA	**L1**	90	93
13[d,h]	morpholine·TFA	**L1**	>95	93
14[d,h]	morpholine·TFA	**L2**	10	85
15[d,h]	morpholine·TFA	**L3**	>95	95
16[d,h]	morpholine·TFA	**L4**	>95	94

[a] Conditions: **1a** (0.125 mmol), $[Ir(COD)Cl]_2$ (2 mol %), (*R*)-SynPhos (4.4 mol %), additive (20 mol %), H_2 (700 psi), DCM (3 mL), rt, 20 h. [b] Determined by ^1H NMR. [c] Determined by HPLC. [d] 10 mol % of morpholine·TFA was used. [e] EtOAc as solvent. [f] THF as solvent. [g] PhMe as solvent. [h] DCM/PhMe (1:2) as solvent.



Initially, catalyst $[Ir(COD)Cl]_2$/(*R*)-SynPhos was chosen to hydrogenate the model substrate 11-(4-chlorophenyl)-5*H*-pyrrolo [2,1-*c*][1,4]benzodiazepin-5-one (**1a**); moderate enantioselectivity was obtained with high conversion (Table 1, entry 1). This preliminary result encouraged us to explore the additive effect on the reactivity and enantioselectivity. With the addition of 20 mol % of I_2,[12] the reaction gave full conversion, but the ee dropped dramatically to 30% (entry 2). Acid additives, such as trifluoroacetic acid, L-camphorsulfonic acid (L-CSA) were also examined,[13] and moderate enantioselectivities were

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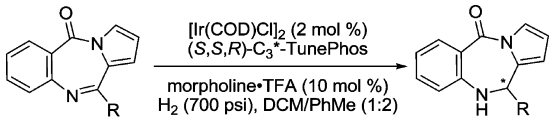
Table 2. Asymmetric Hydrogenation of Pyrrole Fused Benzodiazepinones[a]



1 2

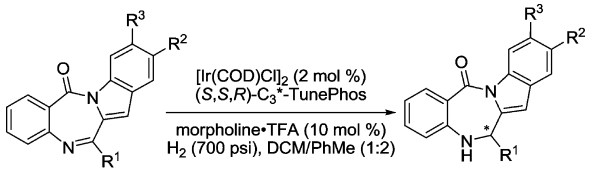
entry	R	yield (%)[b]	ee (%)[c]
1	*p*-ClC_6H_4	95 (**2a**)	95 (+)
2	Ph	97 (**2b**)	95 (+)
3	*m*-MeC_6H_4	97 (**2c**)	94 (+)
4	*p*-MeC_6H_4	92 (**2d**)	95 (+)
5	*p*-FC_6H_4	97 (**2e**)	96 (+)
6	*p*-BrC_6H_4	99 (**2f**)	96 (*R*)[d]
7[e]	Me	96 (**2g**)	91 (+)
8[e]	Et	96 (**2h**)	91 (+)
9[e]	*n*-Pr	97 (**2i**)	93 (+)
10[e]	Bn	92 (**2j**)	90 (+)

[a] Conditions: **1** (0.125 mmol), $[Ir(COD)Cl]_2$ (2 mol %), (*S*,*S*,*R*)-C_3*-TunePhos (4.4 mol %), morpholine·TFA (10 mol %), H_2 (700 psi), DCM/PhMe (1:2, 3 mL), rt, 20 h. [b] Isolated yield. [c] Determined by HPLC. [d] Determined by X-ray diffraction analysis. [e] 10 mol % of piperidine·HCl was used.

achieved yet with limited conversions (entries 3 and 4). Ammonium salts were successfully introduced as effective cocatalysts or additives in organic reactions.[14] Hence the effect of ammonium salt on the reactivity and enantioselectivity was investigated. Delightedly, when piperidinium hydrochloride (piperidine·HCl) was used, the enantiomeric excess was enhanced to 85% (entry 5). Subsequently, several kinds of the salt of morpholine were screened, and morpholinium trifuoroacetate (morpholine·TFA) gave the highest ee (entries 6–8). Lowering the amount of salt resulted in a slight drop in enantioselectivity (entry 9). Further investigation on the solvent effect suggested the combination of dichloromethane and toluene in a ratio of 1:2 was the best choice (entries 10–13). The influence of a chiral ligand was studied through a brief screening of some commercially available diphosphine ligands (entries 14–16). To our delight, C_3*-TunePhos, developed by the Zhang group,[15] showed the highest enantioselectivity.

With the optimized conditions in hand, the scope of the iridium catalyzed asymmetric hydrogenation of pyrrole fused benzodiazepinones **1a**–**j** was explored (Table 2). In general, aryl substituted substrates bearing electron-withdrawing and -donating groups gave high yields and excellent ee's (entries 1–6). Interestingly, for alkyl substituents, the additive should be changed to the piperidinium hydrochloride to maintain high enantioselectivity (entries 7–10). The absolute configuration of **2f** was determined by X-ray diffraction analysis as an *R* isomer.[16]

Table 3. Asymmetric Hydrogenation of Indole Fused Benzodiazepinones[a]



3 4

entry	R^1	R^2	R^3	yield (%)[b]	ee (%)[c]
1	Ph	H	H	98 (**4a**)	95 (−)
2	*m*-MeC_6H_4	H	H	95 (**4b**)	94 (−)
3	*p*-MeC_6H_4	H	H	98 (**4c**)	94 (−)
4	*p*-FC_6H_4	H	H	98 (**4d**)	95 (−)
5	*p*-ClC_6H_4	H	H	96 (**4e**)	94 (−)
6	*p*-BrC_6H_4	H	H	96 (**4f**)	95 (−)
7	Ph	Me	H	98 (**4g**)	96 (−)
8	Ph	H	F	98 (**4h**)	96 (−)
9[d]	*n*-Pr	H	H	97 (**4i**)	90 (−)
10[d]	Phenethyl	H	H	98 (**4j**)	83 (−)

[a] Conditions: **3** (0.125 mmol), $[Ir(COD)Cl]_2$ (2 mol %), (*S*,*S*,*R*)-C_3*-TunePhos (4.4 mol %), morpholine·TFA (10 mol %), H_2 (700 psi), DCM/PhMe (1:2, 3 mL), rt, 20 h. [b] Isolated yield. [c] Determined by HPLC. [d] 10 mol % of piperidine·HCl was used.

Next, we examined the extension of the hydrogenation procedure to indole fused benzodiazepinones **3**. Gratifyingly, the hydrogenation proceeded well with excellent enantioselectivity, as shown in Table 3. When R^1 is an aryl group, 94–96% ee and excellent yields were achieved regardless of the position and electronic effect of substituents on the phenyl ring (entries 1–6); besides, both the methyl and fluoro group on the 5- and 6-position of the indole core were compatible (entries 7 and 8). When R^1 is an alkyl group, high ee's were still obtained by switching the additive to piperidinium hydrochloride (entries 9 and 10).

Having established a general and highly enantioselective hydrogenation of pyrrolobenzodiazepinones **1** and indolobenzodiazepinones **3**, we also decided to apply this efficient catalyst system to hydrogenate pyrrole fused benzodiazepines **5** as this would lead to valuable pharmaceutical intermediates. In complete contrast, when the additive was added in the reaction, the enantioselectivity deteriorated (see the Supporting Information for details). No intermolecular H-bond formed, as that was formed between the additive and carbonyl group in substrate **1** or **3**, which may be responsible for this unexpected

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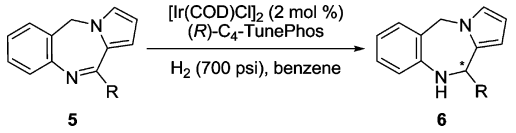
(16) See Supporting Information for details.

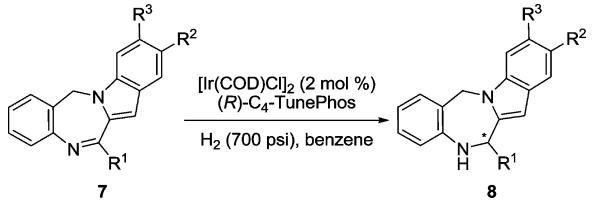
Table 4. Asymmetric Hydrogenation of Pyrrole Fused Benzodiazepines[a]



entry	R	yield (%)[b]	ee (%)[c]
1	Me	98 (**6a**)	96 (−)
2	Et	96 (**6b**)	92 (−)
3	*n*-Pr	96 (**6c**)	91 (−)
4	Phenethyl	97 (**6d**)	93 (−)
5	Bn	97 (**6e**)	87 (−)
6	Ph	96 (**6f**)	92 (−)
7	*p*-MeC_6H_4	97 (**6g**)	82 (−)
8	*p*-FC_6H_4	97 (**6h**)	91 (−)

[a] Conditions: **5** (0.125 mmol), [Ir(COD)Cl]$_2$ (2 mol %), (*R*)-C_4-TunePhos (4.4 mol %), H_2 (700 psi), benzene (3 mL), rt, 20 h. [b] Isolated yield. [c] Determined by HPLC.

Table 5. Asymmetric Hydrogenation of Indole Fused Benzodiazepines[a]



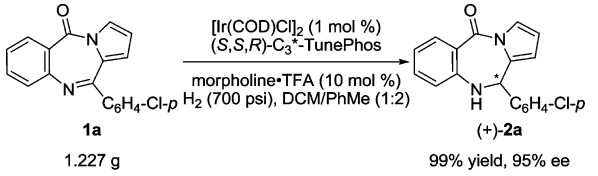
entry	R^1	R^2	R^3	yield (%)[b]	ee (%)[c]
1	Me	H	H	97 (**8a**)	89 (+)
2	Et	H	H	94 (**8b**)	83 (+)
3	*n*-Pr	H	H	97 (**8c**)	85 (+)
4	Bn	H	H	95 (**8d**)	77 (+)
5	Me	Me	H	97 (**8e**)	89 (+)
6	Me	H	F	97 (**8f**)	88 (+)

[a] Conditions: **7** (0.125 mmol), [Ir(COD)Cl]$_2$ (2 mol %), (*R*)-C_4-TunePhos (4.4 mol %), H_2 (700 psi), benzene (3 mL), rt, 20 h. [b] Isolated yield. [c] Determined by HPLC.

phenomenon. After a simple optimization of the reaction, excellent enantioselectivity was recovered with (*R*)-C_4-TunePhos as the ligand and benzene as the solvent (Table 4). Excellent ee's were obtained for substrates bearing alkyl chains (entries 1−5). For aryl substituted compounds, high to excellent enantioselectivities were also achieved under the standard conditions (entries 6−8).

Furthermore, indole fused benzodiazepines **7** could also be hydrogenated with the [Ir(COD)Cl]$_2$/(*R*)-C_4-TunePhos catalyst system (Table 5). The reaction proceeded well with high yields, but slightly lower enantioselectivities were observed (entries 1−6).

Scheme 1. Asymmetric Hydrogenation of **1a** on a Gram Scale



To test the practicality of the current method, the asymmetric hydrogenation of the standard substrate **1a** on a gram scale (1.227 g, 4.0 mmol of **1a**) was carried out with 1 mol % of iridium catalyst [Ir(COD)Cl]$_2$/(*S*,*S*,*R*)-C_3*-TunePhos at room temperature (Scheme 1), giving the chiral product **2a** in 99% yield and 95% ee.

In summary, an efficient iridium catalyst for the highly enantioselective hydrogenation of a series of pyrrole and indole fused benzodiazepinones and -diazepines has been successfully developed with up to 96% ee. Due to the high enantioselectivity and readily available starting materials, this method provides a direct and facile access to a broad scope of corresponding chiral dihydrobenzodiazepinone and -diazepine derivatives existing in numerous important natural products and clinical drugs. Further investigation will be directed toward the extension of this strategy to other synthetically interesting compounds and a mechanism study.

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Supporting Information Available. Experimental, spectroscopic, and crystallographic details. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.