Asymmetric Hydrogenation of Cyclic *N*-Sulfonylimines with Phosphine-Free Chiral Cationic Ru-MsDPEN Catalysts†

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Phosphine-free chiral cationic Ru/diamine complexes are effective catalysts for the asymmetric hydrogenation of a range of cyclic *N*-sulfonylimines, affording chiral sultam derivatives with good to excellent enantioselectivity (up to 94% *ee*).

Keywords asymmetric catalysis, hydrogenation, ruthenium, diamine ligand, cyclic *N*-sulfonylimines, sultams

Introduction

The chiral cyclic sulfonamides, sultams, are one type of most practical synthetic intermediates and chiral auxiliaries which have been successfully applied to a number of asymmetric transformations.[1] Among the various methods for sultams preparation, including classical cyclization protocols[2] and metal-catalyzed transfer hydrogenation,[3] asymmetric hydrogenation of the corresponding cyclic *N*-sulfonylimines represents one of the most direct, atom-economic and efficient approaches for attaining optically active sultams. In 1990, Oppolzer *et al*.[1a] first reported the asymmetric hydrogenation of cyclic *N*-sulfonylimines by using Ru catalysts with up to 99% *ee* after crystallization. Recently, Zhang *et al*.[4] described a Pd-catalyzed asymmetric hydrogenation of a cyclic *N*-sulfonylimine with high enantioselectivity. However, for the above-reported catalytic systems, only one substrate derived from saccharin was reported. One of the most notable examples was recently reported by Zhou *et al*.[5] in the hydrogenation of a variety of cyclic *N*-sulfonylimines with up to $>$ 99% *ee* by using Pd/diphosphine catalysts.

Most recently, we have demonstrated the effectiveness of the air-stable Ru and Ir complexes of chiral *N*-sulfonylated diamine,[6] which are powerful catalysts for asymmetric transfer hydrogenation of aromatic ketones and imines,[7] in the asymmetric hydrogenation of quinolines with excellent enantioselectivities and reactivities. At the same time, Xiao *et al*.[8a] demonstrated that a Rh complex of *N*-sulfonylated diamine could efficiently catalyze the asymmetric hydrogenation of cyclic imines in the presence of $AgSbF_6$. Later, they found that a combination of the Ir-diamine complex together with a chiral phosphate anion was an efficient catalyst for the asymmetric hydrogenation of a variety of acyclic *N*-aryl imines with excellent enantioselectivities.[8b,8c] Ikariya *et al*.[8d] also reported that Ir complexes of *N*-sulfonylated diamine could efficiently catalyze asymmetric hydrogenation of acyclic ketimines in the presence of silver salts with up to 78% *ee*. Considering no report on asymmetric hydrogenation of activated imines with such promising catalytic systems and as a continuation of our ongoing endeavor to develop effective catalysts for asymmetric hydrogenation of heteroaromatic compounds and imines,[6,9] we herein report the use of chiral cationic Ru-MsDPEN complexes for asymmetric hydrogenation of cyclic *N*-sulfonylimines, affording chiral sultam derivatives with up to 94% *ee*.

Results and discussion

3-Methyl-1,2-benzisothiazole 1,1-dioxide (**5a**) was selected as the model substrate for the condition optimization. The initial hydrogenation was carried out in methanol in the presence of 1 mol% (*R*,*R*)-**1**.[10] To our delight, the reaction proceeded smoothly, affording (*R*)-3-methyl-1,2-benzisothiazoline 1,1-dioxide (**6a**) in quantatitive yield with 87% *ee* (Table 1, Entry 1). Based on this promising result, the solvent effect was then studied. It was found that alcoholic solvents were suitable for obtaining high enantioselectivities (Table 1, Entries 1—3). In contrast, low reactivities and enantioselectivities were observed in THF and dichloromethane (DCM) (Table 1, Entries 5 and 6). Interestingly, when mixture of MeOH/DCM was used as the solvent, higher enantioselectivity was observed (Table 1, Entries 7—9). In addition, the effect of hydrogen pressure and temperature were also tested. Slightly low enantioselectivities were observed when reaction was performed

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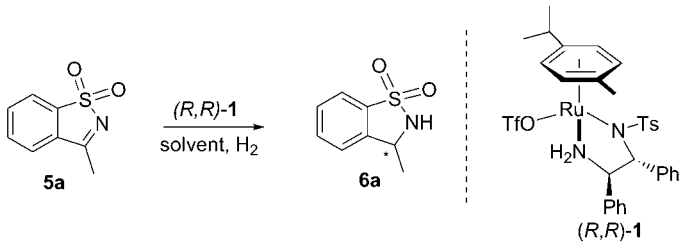
under lower hydrogen pressure or higher temperature (Table 1, Entries 10—13).

Under the optimized reaction conditions, we subsequently investigated the effect of catalysts on this reaction. After a survey of different catalysts in the hydrogenation of **5a** (Table 2, Entries 1—4), catalyst **2** turned out to be optimal in terms of both reactivity and enantioselectivity (Table 2, Entry 2). Notably, both the Ir- and Rh-catalysts showed lower enantioselectivities under otherwise the same reaction conditions (Table 2, Entries 3 and 4).

With the optimal catalyst (*R*,*R*)-**2** in hand, a variety of cyclic *N*-sulfonylimines (**5** and **7**), which can be conveniently prepared from commercially available materials according to the reported procedure,[5] were efficiently hydrogenated to afford the corresponding chiral sultam derivatives with up to 94% *ee* (Table 2). For alkyl-substituted benzofused imines **5a**—**5c**, excellent enantioselectivity and full conversion were observed using mixture of MeOH/DCM as solvent (92%—93% *ee*, Table 2, Entries 2, 5 and 6), which are comparable to those obtained from Pd/(*S*)-SegPhos.[5a] However, for aryl-substituted benzofused imines (**5d**—**5f**), slightly higher enantioselectivities were obtained using neat methanol as solvent (Table 2, Entry 7 vs. Entry 8), which are much lower than those of alkyl-substituted sultams. It was noted that good enantioselectivity was obtained for imine bearing an electron-donating methoxyl group (Table 2, Entry 10). Gratifyingly, this Ru-complex was also found to be an effective catalyst for the asymmetric hydrogenation of cyclic *N*-sulfonylimines **7a**—**7c**. The electronic and steric characteristic of substituents in the substrates has significant influence on the enantioselectivity and reactivity (Table 2, Entries 12—14). Notably, phenyl-substituted imine **7a** gave the highest enantioselectivity (94% *ee*, Table 2, Entry 13). In contrast, hydrogenation of imine with *o*-methylphenyl group (**7c**) offered much lower enantioselectivity and reactivity (Table 2, Entry 13 vs. Entry 14).

On the basis of our successful asymmetric hydrogenation of cyclic *N*-sulfonylimines, some other activated imines were futher hydrogenated under the following conditions: 2 mol% (*R*,*R*)-**2**, 5.05×10^6 Pa of H_2 and 50 ℃ for 24 h (Figure 1). The preliminary results showed that this Ru-catalyst system was not effective for asymmetric hydrogenation of the strong electron-withdrawing *N*-substituent imines. It was found that hydrogenation of acyclic *N*-tosyl ketimine **9** resulted in complete decomposition. Although *N*-diphenylphosphinyl ketimine **11** and exocyclic *N*-tosyl ketimine **10** could be hydrogenated, low conversions and enantioselectivities were observed (Figure 1).

Table 1 Optimization of the reaction conditions for asymmetric hydrogenation of 3-methyl-1,2-benzisothiazole 1,1-dioxide (**5a**)[a]



Entry	$p(H_2)/(10^6$ Pa)	Temp./℃	Solvent	Convn.[b]/%	*ee*[c]/%
1	5.05	25	MeOH	>99	87
2	5.05	25	EtOH	>99	86
3	5.05	25	IPA	>99	86
4	5.05	25	Acetone	>99	80
5	5.05	25	THF	70	34
6	5.05	25	DCM	70	28
7	5.05	25	*V*(MeOH)/*V*(DCM)=1/1	>99	89
8	5.05	25	*V*(MeOH)/*V*(DCM)=1/3	>99	92
9	5.05	25	*V*(MeOH)/*V*(DCM)=1/4	95	91
10	7.58	25	*V*(MeOH)/*V*(DCM)=1/3	>99	92
11	1.01	25	*V*(MeOH)/*V*(DCM)=1/3	>99	85
12	5.05	50	*V*(MeOH)/*V*(DCM)=1/3	>99	88
13	5.05	0	*V*(MeOH)/*V*(DCM)=1/3	95	91

[a] Reaction conditions: 0.2 mmol substrate in 1 mL solvent, 1 mol% catalyst, 24 h. [b] Determined by ^{1}H NMR of the crude reaction mixture. [c] Determined by HPLC with chiral OD-H column.

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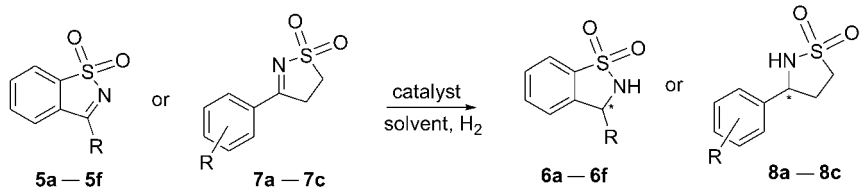
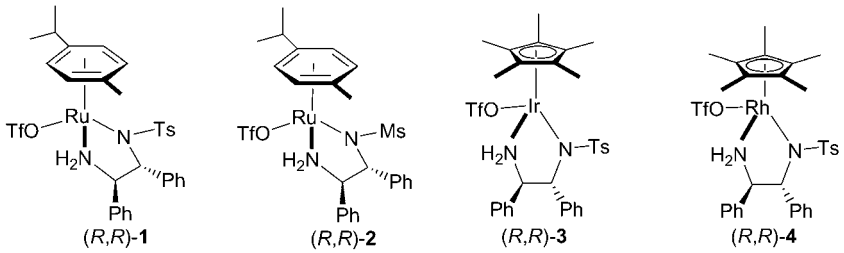
Table 2 Asymmetric hydrogenation of cyclic *N*-sulfonylimines[a]



5a: R = CH_3, **5b**: R = *n*-Bu, **5c**: R = Bn, **5d**: R = C_6H_5, **5e**: R = 4-$CH_3C_6H_5$, **5f**: R = 4-$OCH_3C_6H_5$
7a: R = H, **7b**: R = 4-CH_3, **7c**: R = 2-CH_3



Entry	Substrate	Catalyst	Solvent	Convn.[b]/%	*ee*[c]/%
1	**5a**	(*R*,*R*)-**1**	*V*(MeOH)/*V*(DCM)＝1/3	＞99	92 (*R*)
2	**5a**	(*R*,*R*)-**2**	*V*(MeOH)/*V*(DCM)＝1/3	＞99	93 (*R*)
3	**5a**	(*R*,*R*)-**3**	*V*(MeOH)/*V*(DCM)＝1/3	＞99	83 (*R*)
4	**5a**	(*R*,*R*)-**4**	*V*(MeOH)/*V*(DCM)＝1/3	＞99	58 (*R*)
5	**5b**	(*R*,*R*)-**2**	*V*(MeOH)/*V*(DCM)＝1/3	＞99	93 (*R*)
6	**5c**	(*R*,*R*)-**2**	*V*(MeOH)/*V*(DCM)＝1/3	＞99	92 (*R*)
7	**5e**	(*R*,*R*)-**2**	*V*(MeOH)/*V*(DCM)＝1/3	＞99	44 (*R*)
8	**5e**	(*R*,*R*)-**2**	MeOH	＞99	49 (*R*)
9	**5d**	(*R*,*R*)-**2**	MeOH	＞99	20 (*R*)
10	**5f**	(*R*,*R*)-**2**	MeOH	＞99	78 (*R*)
11[d]	**7b**	(*R*,*R*)-**2**	*V*(MeOH)/*V*(DCM)＝1/3	＞99	62 (*R*)
12[d]	**7b**	(*R*,*R*)-**2**	MeOH	＞99	72 (*R*)
13	**7a**	(*R*,*R*)-**2**	MeOH	＞99	94 (*R*)
14[d,e]	**7c**	(*R*,*R*)-**2**	MeOH	67	76 (*R*)

[a] Reaction conditions: 0.2 mmol substrate in 1 mL solvent, 1 mol% catalyst, 5.05×10^6 Pa of H_2, stirred at 25 ℃ for 24 h. [b] Determined by ^{1}H NMR of the crude reaction mixture. [c] Determined by HPLC with chiral OD-H column, and the configurations were determined by comparison of rotation sign with literature data.[5c] [d] 2 mol% catalyst. [e] Stirred at 40 ℃.

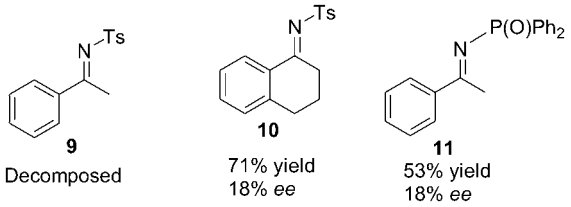


Figure 1 Asymmetric hydrogenation of other activated imines.

Conclusion

In summary, the phosphine-free chiral cationic Ru-MsDPEN catalytic system has been successfully applied in the asymmetric hydrogenation of a range of cyclic *N*-sulfonylimines with good to excellent enantioselectivity. Further work will be directed toward expanding the scope of those cyclic *N*-sulfonylimines and mechanism of the reaction.

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10 Typical procedure for the asymmetric hydrogenation of cyclic *N*-sulfonylimines: A 30 mL glass-lined stainless-steel reactor equipped with a magnetic stirrer bar was charged with (*R*,*R*)-**2** (1.4 mg, 0.002 mmol), imine (0.2 mmol) in methanol (1 mL) under nitrogen atmosphere in a glove box. The autoclave was closed, and the final pressure of the hydrogen gas was adjusted to 5.05×10^6 Pa after purging the autoclave with hydrogen gas several times. The reaction mixture was stirred at 25 ℃ for 24 h. Then the hydrogen gas was carefully released and the conversion was determined by ^{1}H NMR. The reaction mixture was filtered through a short pad of silica and eluted with dichloromethane to give the pure products. The *ee* of the product was determined by HPLC with chiral OD-H column.

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