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Highly Enantioselective Pd-Catalyzed Asymmetric Hydrogenation of Activated Imines

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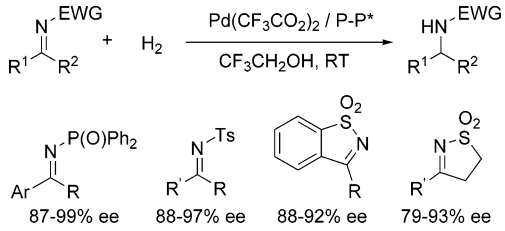

Pd/bisphosphines complexes are highly effective catalysts for asymmetric hydrogenation of activated imines in trifluoroethanol. The asymmetric hydrogenation of *N*-diphenylphosphinyl ketimines **3** with $Pd(CF_3CO_2)$/(*S*)-SegPhos indicated 87−99% ee, and *N*-tosylimines **5** could gave 88−97% ee with Pd-(CF_3CO_2)/(*S*)-SynPhos as a catalyst. Cyclic *N*-sulfonylimines **7** and **11** were hydrogenated to afford the useful chiral sultam derivatives in 79−93% ee, which are important organic synthetic intermediates and structural units of agricultural and pharmaceutical agents.

Introduction

Catalytic asymmetric synthesis presents one of most powerful methods for accessing a wide range of enantiomerically enriched compounds. Among various catalysts, complexes of transition metals and chiral ligands as chiral homogeneous (pre)catalysis represent a convenient methodology for the synthesis of chiral molecules.[1] The asymmetric hydrogenation reaction utilizing cheap molecular hydrogen to reduce prochiral substrates is widely applied even on the industrial scale.[2,3] Ru and Rh complexes have been used as catalysts to obtain excellent results, and other transition metals such as Ir, Ti, and so on are also effective.[1−3] In the periodic table, Pd, Ru, and Rh are all elements in the fifth period and group VIII. The Pd catalyst system has been applied to promote a wide range of useful synthetic organic reactions.[4] In addition, Pd/C is the most popular heterogeneous hydrogenation catalyst, and some successful examples of heterogeneous asymmetric hydrogenation reactions catalyzed by Pd(0) have been well documented in the literature,[3b,5] but very little attention has been paid to the homogeneous asymmetric hydrogenation reactions with Pd complexes. Pioneering work by Amii and co-workers established the use of $Pd(CF_3CO_2)_2$/BINAP as a catalyst for asymmetric

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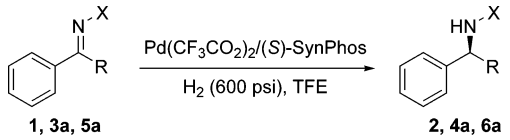
hydrogenation of α-fluorinated iminoesters with up to 91% ee;[6] however, this method is successful for a limited range of substrates. Alper and his co-workers reported Pd-catalyzed asymmetric double carbohydroamination of iodobenzene for the synthesis of chiral α-aminoamides,[7] the catalytic cycle they suggested involved Pd-catalyzed asymmetric hydrogenation of α-iminoamide intermediates; however, no evidence was given. Very recently, Zhang's group also reported asymmetric hydrogenation of *N*-tosylimines using a $Pd(CF_3CO_2)_2$-TangPhos complex at 40 °C in methlyene chloride with up to 99% ee.[8] In the course of our research on asymmetric hydrogenation of heteroaromatic compounds,[9] we became interested in exploring Pd-catalyzed asymmetric hydrogenation. In 2005, we reported the first highly enantioselective Pd-catalyzed asymmetric hydrogenation of functionalized ketones.[10] As an extension of Pd-catalyzed asymmetric hydrogenation, in a preliminary communication,[11] enantioselective hydrogenation of *N*-diphenylphosphinyl imines was reported with a $Pd(CF_3CO_2)_2$/SegPhos system with up to 99% ee. Herein, we report the detailed studies on Pd-catalyzed asymmetric hydrogenation of four kinds of activated imines. A series of chiral 3-substituted sultams were obtained conveniently by asymmetric hydrogenation of their corresponding cyclic *N*-sulfonylimines, which are very stable and can be conveniently synthesized from the substituted oxiranes.

Results and Discussion

Chiral amines are important intermediates for biologically active compounds and chiral auxiliaries for asymmetric synthesis, therefore, the development of an efficient method for their synthesis is one of the most challenging tasks for organic chemists. Among many methods for preparing them,[12,13] the asymmetric hydrogenation of the C═N bond is considered to be the most convenient and efficient route. Recently, enantioselective reduction of the C═N bond and reductive amination with organocatalyts have been reported with excellent enantioselectivity,[14] and a number of transition metal-based catalysts, such as those containing Rh, Ru, Ti, Zr, and Ir, have been applied to asymmetric hydrogenation of imines.[1,13,15] However, this method has been less successful than hydrogenation of ketones and alkenes because of relatively poor reactivity of imines toward hydrogenation. There are some difficulties in obtaining excellent results on asymmetric hydrogenation of imines. For example, *E* and *Z* isomers of acyclic imines give different enantioselectivity,[16] some imines are difficult to prepare and very sensitive to moisture, and hydrogenation product amines usually partially poison the metal catalysts through coordination with the transition metal. Therefore, the search for a new catalytic system for asymmetric hydrogenation of the C═N bond is still a challenge.

On the basis of our previous successful asymmetric hydrogenation for functionalized ketones with Pd complexes,[10] using the $Pd(OCOCF_3)_2$/SynPhos system as a hydrogenation catalyst, the effect of different substituents of imines on reactivity and enantioselectivity was investigated in 2,2,2-trifluoroethanol (TFE) as the solvent (Table 1). The preliminary investigations of the asymmetric hydrogenation of imines with Pd complex catalysts suggested that the suitable *N*-substituent is crucial in achieving good reactivity. For example, high enantioselectivity (94% ee) was obtained in the asymmetric hydrogenation of simple *N*-*p*-methoxyphenyl ketimine, but the conversion was only 26% (Table 1, entry 1). An addition of 4Å molecular sieves,

TABLE 1. Effects of the Various *N*-Substituents of Imines[a]



1, 3a, 5a 2, 4a, 6a

entry	R/X	temp (°C)	conv[b] (%)	ee[c] (%)
1	Me/4-MeOC$_6$H$_4$ (**1a**)	rt	26	94
2[d]	Me/4-MeOC$_6$H$_4$ (**1a**)	rt	25	95
3	Me/4-MeOC$_6$H$_4$ (**1a**)	60	9[e]	77
4	Me/4-FC$_6$H$_4$ (**1b**)	rt	15	N/D
5	Me/2-MeOC$_6$H$_4$ (**1c**)	rt	24	N/D
6	Me/AcO (**1d**)	rt	<5	N/A
7	Me/BzNH (**1e**)	rt	44	58
8[f]	CO_2Et/PMP (**1f**)	rt	>95	33
9[g]	Me/P(O)Ph$_2$ (**3a**)	rt	85	95
10	Me/Ts (**5a**)	rt	>95	97

[a] Unless otherwise stated, reactions were performed in TFE on a 0.20−0.25 mmol scale: Pd precursor 2 mol %, (*S*)-SynPhos 2.4−3.0 mol %, 600 psi of H_2. [b] Determined by ^{1}H NMR analysis of the crude product.[c] Ee was determined by HPLC analysis, and the absolute configuration was determined by comparison of rotation sign with literature data. [d] 4Å MS was added. [e] Isolated yields. [f] (*R*)-BINAP was used. [g] (*R*)-SynPhos was used; the configuration of product is *R*.

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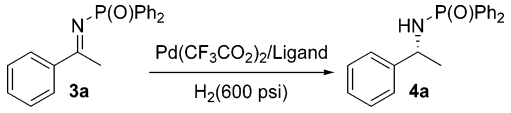
which can stablize ketimine, has no clear effect on the conversion (entry 2). Furthermore, when the temperature was increased to 60 °C, a lower isolated yield (9%) was obtained (entry 3). The reactivity was also low when an electron-donating methoxy group (**1a**) was replaced by an electron-withdrawing fluoro group (**1b**) (entry 4). Imines **1c** and **1d** bearing weak coordinating groups, 2-MeOPh and OAc, respectively, which might cause chelation with the central metal,[17] also gave very low activities (entries 5 and 6). An increasing conversion (44%) was observed with imine **1e** bearing a NHBz group (entry 7). Gratifyingly, the asymmetric hydrogenation of *N*-diphenylphosphinylimine **3a**[18] and *N*-tosylimine **5a**[19] with strong electron-withdrawing Ts and $Ph_2P(O)$ groups, respectively, afforded their corresponding products in high conversions and enantioselectivities (entries 9 and 10), and the reason may be that the strong electron-withdrawing character of tosyl and diphenylphosphinyl reduces the inhibitory effect of the starting material and product on the catalyst, and activated imines exist exclusively as the *E* isomer. So, for Pd-catalyzed asymmetric hydrogenation of imines, activated imines are good substrates in view of reactivity and enantioselectivity.

It should be noted that the asymmetric induction sense of the asymmetric hydrogenation of the ketimines (Table 1, entries 9 and 10) is the same as that of the unfunctionalized ketones such as acetophenone[10] with the same Pd catalyst ($Pd(OCOCF_3)_2$/SynPhos).

The Asymmetric Hydrogenation of *N*-Diphenylphosphinyl Ketimines (3). With use of *N*-diphenylphosphinyl ketimine (**3a**) as the model substrate,[20] the effect of solvents, reaction temperature, Pd precursors, hydrogen pressure, and ligands on reactivity and enantioselectivity was screened, and the result is shown in Table 2. A strongly solvent-dependent effect was observed (entries 1−7); TFE is the only effective solvent. Then the effect of Pd precursors was also tested (entries 1 and 9−11). The Pd precursors with weakly coordinating anions such as $CF_3CO_2^-$ and $CH_3CO_2^-$ provided similar good results. Pleasingly, an increase in the hydrogen pressure led to complete conversion with the same enantioselectivity (entry 12). Some commercially available chiral bisphosphine ligands were also tested under the same conditions, and the best result (96% ee) was achieved with (*S*)-SegPhos (entry 17). The optimized reaction[21] conditions are the following: $Pd(OCOCF_3)_2$/(*S*)-SegPhos, TFE, 1000 psi of H_2.

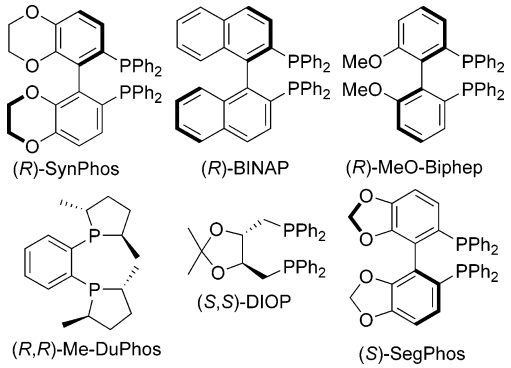
The results for asymmetric hydrogenation of various *N*-diphenylphosphinyl ketimines **3a**−**j**, prepared conveniently from their corresponding ketones in two steps according to the known procedures,[18] are presented in Table 3. The imines were converted into their corresponding amines with excellent enantioselectivities (87−99% ee) and in good yields under optimized conditions. The activities of the reaction could be improved in the presence of 4Å molecular sieves (entry 2 vs entry 3),[22] which might remove traces of water to make the substrate and catalyst more stable. The highest enantioselectivity was achieved for *o*-methoxy-substituted aryl imine **3g** (99% ee, entry 8). For substrate **3h** derived from 1-acetylnaphthalene, a low conversion was observed (entry 9). The resulting *N*-phosphinyl amines[18,20,23] can be readily converted to the free amine salts under mild acidic conditions (HCl/MeOH) with retention of the ee values.

TABLE 2. Optimization of Reaction Conditions for Pd-Catalyzed Asymmetric Hydrogenation of *N*-Diphenylphosphinyl Ketimine 3a[a]



entry	Pd precursor	ligand[g]	solvent	yield[b] (%)	ee[c] (%)
1	$Pd(CF_3CO_2)_2$	(*R*)-SynPhos	TFE	80 (85)	95 (*R*)
2	$Pd(CF_3CO_2)_2$	(*R*)-SynPhos	*i*-PrOH	<5	N/A
3	$Pd(CF_3CO_2)_2$	(*R*)-SynPhos	EtOH	<5	N/A
4	$Pd(CF_3CO_2)_2$	(*R*)-SynPhos	MeOH	<5	N/A
5	$Pd(CF_3CO_2)_2$	(*R*)-SynPhos	THF	<5	N/A
6	$Pd(CF_3CO_2)_2$	(*R*)-SynPhos	CH_2Cl_2	<5	N/A
7	$Pd(CF_3CO_2)_2$	(*R*)-SynPhos	Toluene	<5	N/A
8[d]	$Pd(CF_3CO_2)_2$	(*R*)-SynPhos	TFE	79	93 (*R*)
9	$Pd(CH_3CO_2)_2$	(*R*)-SynPhos	TFE	82	95 (*R*)
10[e]	$Pd(OTf)_2$	(*R*)-SynPhos	TFE	37	92 (*R*)
11[e]	$PdCl_2$	(*R*)-SynPhos	TFE	7	N/D
12[f]	$Pd(CF_3CO_2)_2$	(*R*)-SynPhos	TFE	85 (>95)	94 (*R*)
13[f]	$Pd(CF_3CO_2)_2$	(*R*)-BINAP	TFE	54	96 (*R*)
14[f]	$Pd(CF_3CO_2)_2$	(*R*)-MeO-Biphep	TFE	96	95 (*R*)
15[f]	$Pd(CF_3CO_2)_2$	(*R*,*R*)-Me-DuPhos	TFE	93	28 (*R*)
16[f]	$Pd(CF_3CO_2)_2$	(*S*,*S*)-DIOP	TFE	<5	N/A
17[f]	$Pd(CF_3CO_2)_2$	(*S*)-SegPhos	TFE	98	96 (*S*)

[a] Unless otherwise stated, reactions were performed on a 0.2 mmol scale: Pd precursor 2 mol %, ligand 2.4 mol %, 600 psi of H_2, rt, 8 h. [b] Isolated yields. Conversions determined by ^1H NMR analysis are shown in parentheses. [c] Ee was determined by HPLC analysis, and the absolute configuration was determined by comparison of rotation sign with literature data. [d] The reaction was carried out in an oil bath of 50 °C. [e] Pure complex (2 mol %) was used and no extra ligand added. [f] 1000 psi of H_2. [g] Ligands:



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(21) The $Pd(CH_3CO_2)_2$ works as well as the $Pd(CF_3CO_2)_2$ for imines **3a**, but not in the case of bulky imines such as **3h**. The hydrogenation of **3h** was conducted under the following two conditions: $Pd(CF_3CO_2)_2$/(*S*)-SegPhos (conversion >95%, 87% ee), $Pd(CH_3CO_2)_2$/(*S*)-SegPhos (conversion 89%, 85% ee). Therefore, $Pd(CF_3CO_2)_2$ was employed as a metal precursor in the optimized conditions.

(22) Several additives were tested for **3b**: 3Å MS (conversion >95%, 96.4% ee), 5Å MS (conversion 72%, 96.4% ee), and Na_2SO_4 (conversion 64%, 96.4% ee).

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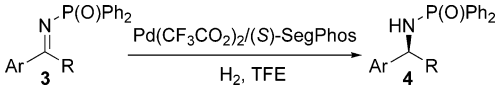
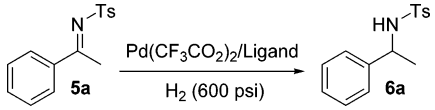
TABLE 3. Asymmetric Hydrogenation of *N*-Diphenylphosphinyl Ketimines 3 Catalyzed by a Pd(OCOCF$_3$)$_2$/(*S*)-SegPhos System[a]



entry	Ar/R (**3**)	conv[b] (%)	ee[c] (%)
1[d]	C_6H_5/Me (**3a**)	>95 (98)	96
2[d]	4-MeC_6H_4/Me (**3b**)	45 (35)	95
3	4-MeC_6H_4/Me (**3b**)	>95 (93)	97
4	4-MeOC_6H_4/Me (**3c**)	>95 (96)	96
5	4-FC_6H_4/Me (**3d**)	>95 (87)	94
6	4-ClC_6H_4/Me (**3e**)	94 (90)	94
7	3-MeOC_6H_4/Me (**3f**)	>95 (97)	96
8[e]	2-MeOC_6H_4/Me (**3g**)	91 (80)	99
9	1-Naphthyl/Me (**3h**)	9	N/D
10[e]	2-Naphthyl/Me (**3i**)	77 (70)	93
11[e]	2-Furyl/Me (**3j**)	62 (29)	87
12[e]	C_6H_5/Et (**3k**)	>95 (93)	87

[a] Unless otherwise stated, reactions were performed in TFE on a 0.2 mmol scale: Pd(CF$_3$CO$_2$)$_2$ 2 mol %, (*S*)-SegPhos 2.4 mol %, 4Å MS, 1000 psi of H_2, rt, 8 h. [b] Conversions were determined by ^{1}H NMR; isolated yields are shown in parentheses. [c]Determined by chiral HPLC analysis.[d] No 4Å MS was added. [e] 4 mol % Pd catalyst was used.

TABLE 4. Optimizaion of Reaction Conditions for Pd-Catalyzed Asymmetric Hydrogenation of *N*-Tosyl Ketimine 5a[a]

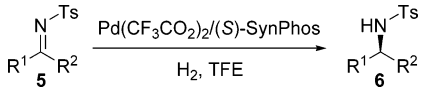


entry	Pd precursor	ligand	conv[b] (%)	ee[c] (%)
1	Pd(CF$_3$CO$_2$)$_2$	(*S*)-SynPhos	>95	97 (*S*)
2[d]	Pd(CF$_3$CO$_2$)$_2$	(*S*)-SynPhos	63	97 (*S*)
3	$PdCl_2$	(*S*)-SynPhos	<5	
4	Pd(CH$_3$CO$_2$)$_2$	(*S*)-SynPhos	>95	90 (*S*)
5	Pd(CF$_3$CO$_2$)$_2$	(*S*)-BINAP	>95	97 (*S*)
6	Pd(CF$_3$CO$_2$)$_2$	(*S*)-MeO-Biphep	>95	97 (*S*)
7	Pd(CF$_3$CO$_2$)$_2$	(*R*,*R*)-Me-DuPhos	>95	60 (*R*)
8	Pd(CF$_3$CO$_2$)$_2$	(*S*,*S*)-DIOP	38	18 (*S*)
9	Pd(CF$_3$CO$_2$)$_2$	(*S*)-SegPhos	>95	96 (*S*)

[a] Unless otherwise stated, reactions were performed in TFE on a 0.25 mmol scale: Pd precursor 2 mol %, ligand 2.4 mol %, rt, 12 h. [b] Conversions were determined by ^{1}H NMR. [c] Determined by HPLC analysis. [d] 200 psi of H_2.

The Asymmetric Hydrogenation of *N*-Tosyl Ketimines (5). The enantioselective hydrogenation with Pd complex as the catalyst was also successfully applied to the reduction of *N*-tosyl ketimines.[24,25] Initial experiments conducted in TFE at room temperature under 600 psi of H_2 by using a Pd(OCOCF$_3$)$_2$/(*S*)-SynPhos system led to an excellent result with conversion >95% and 97% ee (Table 4, entry 1). A decrease in hydrogen pressure (200 psi) results in incomplete consumption of *N*-tosylimines **5a** and does not enhance the enantioselectivity of product (entry 2 vs entry 1). The effect of solvents on the catalytic activity is remarkable; only TFE leads to high conversion and enantioselectivity while other solvents, such as CH_2Cl_2, THF, and EtOH, lead to very low conversions. Next, Pd precursors were also tested in the reaction (entries 1 and 3−4). The complex of neutral $PdCl_2$ as the catalyst is rendered inoperative. Pd(CH$_3$CO$_2$)$_2$ provided slightly lower ee values in spite of the full conversion. Finally, the effect of some commercially available chiral bidentate phosphine ligands was tested for this reaction (entries 1 and 5−9). Similar results were obtained by using bisphosphine ligands with biphenyl or binaphthyl motif (>95% conversion and 96−97% ee).

TABLE 5. Asymmetric Hydrogenation of *N*-Tosyl Ketimines 5 Catalyzed by a Pd(OCOCF$_3$)$_2$/(*S*)-SynPhos System[a]



entry	R^1/R^2 (**5**)	yield[b] (%)	ee[c] (%)
1	C_6H_5/Me (**5a**)	84	96
2	4-FC_6H_4/Me (**5b**)	98	96
3	4-MeOC_6H_4/Me (**5c**)	98	97
4	3-MeOC_6H_4/Me (**5d**)	86	93
5	2-MeOC_6H_4/Me (**5e**)	84	94
6	2-Naphthyl/Me (**5f**)	95	95
7	C_6H_5/Et (**5g**)	90	88
8	*t*-Bu/Me (**5h**)	94	91

[a] Unless otherwise stated, reactions were performed in TFE on a 0.25 mmol scale: Pd(CF$_3$CO$_2$)$_2$ 2 mol %, (*S*)-SynPhos 2.4 mol %, 4Å MS, 600 psi of H_2, rt, 12 h. [b] Determined by ^{1}H NMR analysis of the crude products. [c] ee was determined by HPLC analysis, and the absolute configuration was determined by comparison of rotation sign with literature data or by analogy.

Under the optimized reaction conditions (Pd(OCOCF$_3$)$_2$/(*S*)-SynPhos, TFE as a solvent, 600 psi of H_2, 4Å MS, rt), a variety of *N*-tosyl ketimines (**5**), prepared from their corresponding ketones according to known procedures,[19] can be successfully hydrogenated to afford their corresponding amide derivatives (**6**). As illustrated in Table 5, both aryl and alkyl *N*-tosyl ketimines can be hydrogenated with good reactivity and high enantioselectivity. The imines with an electron-withdrawing F substituent (**5b**), a methoxy group at the para, meta, or ortho position on the phenyl ring (**5c**, **5d**, **5e**), and the bulkier naphthyl group provided high enantioselectivities in 94−96% ee (entries 2−6). Imine **5g** derived from the propiophenone gave a lower enantioselectivity than that of imine **5a** from acetophenone. Aliphatic ketimine **5h** was also applied to this reaction to give the hydrogenated product in 94% isolated yield with 91% ee (entry 8).

The Asymmetric Hydrogenation of Cyclic *N*-Sulfonylimines (7). The sultam compounds **8** are an important class of chiral auxiliaries which have been successfully applied to a number of asymmetric reactions.[26,27] They can be synthesized through asymmetric reduction of the corresponding imines **7**[27,28]

Eur. J. **2003**, *9*, 4485. (d) Lipshutz, B. H.; Shimizu, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 2228. (e) Nolin, K. A.; Ahn, R. W.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 12462. (f) Graves, C. R.; Scheidt, K. A.; Nguyen, S. T. *Org. Lett.* **2006**, *6*, 1229.

(24) Ru-catalyzed asymmetric hydrogenation of *N*-tosylimines **5**: Charette, A. B.; Giroux, A. *Tetrahedron Lett.* **1996**, *37*, 6669.

(25) Asymmetric reduction of *N*-tosylimines **5** with trimethoxyhydrosilane: Nishikori, H.; Yoshihara, R.; Hosomi, A. *Synlett* **2003**, 561.

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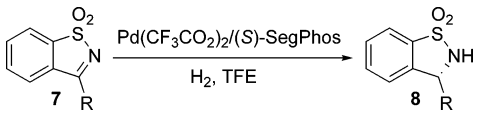
(28) Asymmetric reduction of **7** without hydrogen: (a) Chen, Y.-C.; Wu, T.-F.; Deng, J.-G.; Liu, H.; Cui, X.; Zhu, J.; Jiang, Y.-Z.; Choi, M. C. K.; Chan, A. S. C. *J. Org. Chem.* **2000**, *65*, 1399. (b) Liu, P.-N.; Gu, P.-M.; Deng, J.-G.; Tu, Y.-Q.; Ma, Y.-P. *Eur. J. Org. Chem.* **2005**, 3221. (c) Wu, J.; Wang, F.; Ma, Y.; Cui, X.; Cun, L.; Zhu, J.; Deng, J.; Yu, B. *Chem. Commun.* **2006**, 1766. (d) Mao, J. M.; Baker, D. C. *Org. Lett.* **1999**, *1*, 841−843. (e) Reference 27b

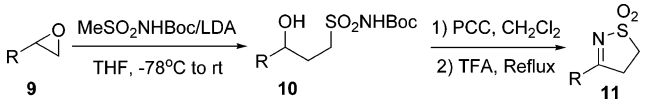
TABLE 6. Asymmetric Hydrogenation of Cyclic *N*-Sulfonylimines 7[a]



entry	R of SM	ligand	conv[b] (%)	ee[c] (%)
1	Me (**1a**)	(*S*)-SynPhos	>95	82 (*R*)
2	Me (**1a**)	(*S*)-MeO-Biphep	>95	81 (*R*)
3	Me (**1a**)	(*R*,*R*)-Me-DuPhos	>95	82 (*S*)
4	Me (**1a**)	(*S*)-SegPhos	>95 (98)	92 (*R*)
5	*n*-Bu (**1b**)	(*S*)-SegPhos	>95 (98)	90 (*R*)
6	Bn (**1c**)	(*S*)-SegPhos	>95 (93)	88 (*R*)

[a] Unless otherwise stated, reactions were performed in TFE on a 0.25 mmol scale: $Pd(CF_3CO_2)_2$ 2 mol %, ligand 2.4 mol %, 4Å MS, H_2 600 psi, rt, 12 h. [b] Conversions were determined by ^1H NMR, and isolated yields are shown in parentheses. [c] Ee was determined by HPLC analysis, and the absolute configuration was determined by comparison of rotation sign with literature data.

SCHEME 1. Preparation of *N*-Sulfonylimines 11

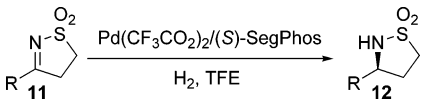


which can be prepared from commercially available saccharin material according to procedures reported in the literature.[27]

First, the asymmetric hydrogenation of **7a** (R = Me) was performed with the following conditions: $Pd(OCOCF_3)_2$/(*S*)-SynPhos, TFE as a solvent, 600 psi of H_2, 4Å MS, room temperature (Table 6, entry 1), which had been successfully applied to the asymmetric hydrogenation of *N*-tosyl ketimines **5**. The enantioselectivity was moderate (82% ee), then the ligand effect was evaluated (entries 1−4). Gratifyingly, (*S*)-SegPhos gave the product with 92% ee. Under this conditions, other substrates such as **7b** (R = Bu) and **7c** (R = Bn) also gave excellent enantioselectivity (entries 5 and 6).

The Asymmetric Hydrogenation of Cyclic *N*-Sulfonylimines (11). For Pd-catalyzed asymmetric hydrogenation of imines, only activated imines gave good reactivity and enantioseletivity. As a consequence, design and synthesis of new activated imines is also a challenging and imperative task. The cyclic forms of sulfonamides, the sultams derivatives, are important organic synthetic intermediates and structural units of agricultural and pharmaceutical agents.[29] Many different methods have been developed for their preparation in the past few years, and only a few allow the synthesis of optically active 3-substituted sultams.[30] Although the hydrogen pressure is required, asymmetric hydrogenation of cyclic imines **11** is the ideal reaction for preparing 3-substituted γ-sultams **12** in terms of ecology and atom economy. In 2006, Freitag and Metz reported the synthesis of cyclic imines **11** from the corresponding substituted oxiranes **9** in the course of the preparation of *N*-sulfonylated β-amino acids[31c] (Scheme 1). By following their modified procedure, we synthesized a series of cyclic imines **11**.[31] It should be noted that cyclic imines **11** were very stable to moisture and oxygen.

TABLE 7. Asymmetric Hydrogenation of Cyclic *N*-Sulfonylimines 11[a]



entry	R	yield[b] (%)	ee[c] (%)
1	Ph (**11a**)	93	79
2[d]	Me (**11b**)	91	88
3[d]	n-C_6H_{13} (**11c**)	99	90
4	$C_6H_5OCH_2$ (**11d**)	99	92
5	4-$CF_3C_6H_4OCH_2$ (**11e**)	99	93
6	4-$MeC_6H_4OCH_2$ (**11f**)	93	91
7	2-$MeC_6H_4OCH_2$ (**11g**)	95	92
8	2-naphthylOCH_2 (**11h**)	97	90

[a] Unless otherwise stated, reactions were performed in TFE on a 0.25 mmol scale: $Pd(CF_3CO_2)_2$ 2 mol %, (*S*)-SegPhos 2.4 mol %, 600 psi of H_2, rt, 12 h. [b] Isolated yields. [c] Ee was determined by HPLC analysis, and the absolute configuration was determined by comparison of rotation sign with literature data or by analogy. [d] Ee was determined by chiral HPLC analysis of its *N*-cinnamyl derivative.

Under the previous optimized condition ($Pd(OCOCF_3)_2$/(*S*)-SegPhos, TFE, 600 psi of H_2, rt), a series of cyclic *N*-sulfonylimines **11** were hydrogenated to afford their corresponding 3-substituted sultams **12** in high isolated yields and enantioselectivities (Table 7). It was found that alkyl substituted imines **11b**,**c** bearing methyl and hexyl groups, respectively, show a better enantioselectivity than imine **11a** with a phenyl group (entries 2 and 3 vs entry 1). For various aryloxymethyl-substituted imines **11d**−**h**, high enantioselectivities (91−93% ee) were also obtained (entries 4−8). The absolute configuration of the sultams **12a** and **12c** was determined by comparison of the rotation sign with the literature data, and other products were determined by chemical interrelation, comparing them with the asymmetric sense of the product. It is noteworthy that this is the first example to provide optically active 3-substituted sultams **12** by means of the asymmetric hydrogenation of cyclic *N*-sulfonylimines with high enantioselectivity.

The asymmetric hydrogenation of cyclic *N*-sulfonylimine can be run on a gram-scale providing a potential synthetic application.[32] As illustrated in Scheme 2, the chiral sultam **12d** was obtained in 99% isolated yield with 93% ee by flash column chromatography, and 72% isolated yield with >99% ee after single recrystallization from ethanol/water (3/2 v/v).

Cyclic *N*-sulfonylimine **11i** bearing the BnO group was also hydrogenated to afford the product **12i** with 86% ee in the presence of 4Å MS. **12i** can be transformed to chiral 3-hydroxymethyl sultam **13** by removing the Bn group (Scheme 3), which may be a good ligand for asymmetric catalysis and a useful chiral auxiliary in organic synthesis.

(29) (a) Katritzky, A. R.; Wu, J.; Rachwal, S.; Rachwal, B.; Macomber, D. W.; Smith, T. P. *Org. Prep. Proced. Int.* **1992**, *24*, 463. (b) Miller, R. A.; Humphrey, G. R.; Lieberman, D. R.; Celiga, S. S.; Kennedy, D. J.; Grabowski, E. J. J.; Reider, P. J. *J. Org. Chem.* **2000**, *65*, 1399. (c) Inagaki, M.; Tsuri, T.; Jyoyama, H.; Ono, T.; Yamada, K.; Kobayashi, M.; Hori, Y.; Arimura, A.; Yasui, K.; Ohno, K.; Kakudo, S.; Koizumi, K.; Suzuki, R.; Kawai, S.; Kato, M.; Matsumoto, S. *J. Med. Chem.* **2000**, *43*, 2040. (d) Brunetti, L.; Cacciatore, I.; Di Stefano, A.; Duprè, S.; Giorgi, A.; Luisi, G.; Michelotto, B.; Orlando, G.; Pinnen, F.; Recinella, L.; Sozio, P.; Spirito, A. *Farmaco* **2002**, *57*, 479. (e) Cherney, R. J.; Mo, R.; Meyer, D. T.; Hardman, K. D.; Liu, R.-Q.; Covington, M. B.; Qian, M.; Wasserman, Z. R.; Christ, D. D.; Trzaskos, J. M.; Newton, R. C.; Decicco, C. P. *J. Med. Chem.* **2004**, *47*, 2981.

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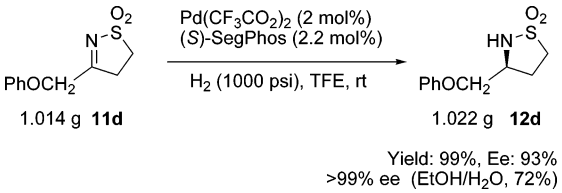
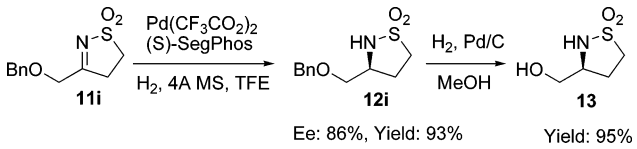
(32) The experimental detail is given in the Supporting Information, S5.

SCHEME 2. Asymmetric Hydrogenation of 11d at a Gram-Scale



SCHEME 3. Asymmetric Hydrogenation of the BnO-Substituted Imine 11i



Conclusions

In summary, the Pd/bisphosphines complexes were found to be the effective catalysts for the asymmetric hydrogenation of a series of activated imines, such as *N*-diphenylphosphinyl ketimines, acyclic *N*-tosylimines, and cyclic *N*-sulfonylimines. The synthesis of chiral 3-substituted sultams **12** was achieved for the first time through the asymmetric hydrogenation of their corresponding cyclic *N*-sulfonylimines. Our ongoing experiments are focused on asymmetric hydrogenation of other substrates and investigation of the reaction mechanism.[33]

(33) Our measurements on the nonlinear effect using ligands of different ee (see the Supporting Information for experimental details) reveal the relationship is near linear between the ee of the product and the ee of the ligand. It is suggested that the active species is the Pd complex with one ligand.

Experimental Section

Typical procedure for the asymmetric hydrogenation of imines: (*S*)-SegPhos (2.9 mg, 0.0048 mmol) and $Pd(CF_3CO_2)_2$ (1.3 mg, 0.004 mmol) were placed in a dried Schlenk tube under nitrogen atmosphere, and degassed anhydrous acetone was added. The mixture was stirred at room temperature for 1 h. The solvent was removed under vacuum to give the catalyst. This catalyst was taken into a glovebox filled with nitrogen and dissolved in dry TFE. To the mixture of imine (0.2 mmol) and 4Å MS (50 mg) was added this catalyst solution, and then the mixture was transferred to an autoclave. The autoclave was stirred under directed condition (oil bath temperature was shown if it was heated). After release of the hydrogen, the autoclave was opened and the reaction mixture was evaporated. Conversion was directly determined by ^1H NMR spectroscopy. The enantiomeric excess was determined by HPLC after purification on silica gel with petroleum ether and EtOAc in the presence of 1% Et_3N. The absolute configuration was determined by comparison of rotation sign with literature data or by analogy.

Acknowledgment. We are grateful to the financial support from National Science Foundation of China (20532050) and State Key Laboratory of Organometallic Chemistry (06-24).

Supporting Information Available: Spectroscopic date, GC, HPLC spectra, and experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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