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Highly Enantioselective Synthesis of Sultams via Pd-Catalyzed Hydrogenation

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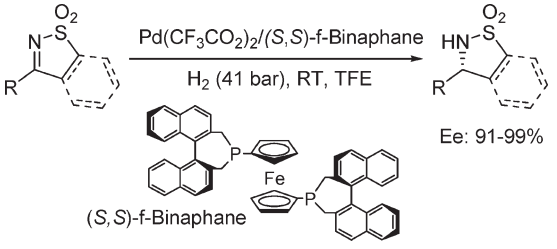
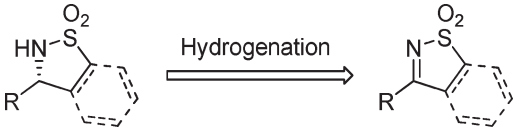


Using pd(cf$_3$co$_2$)$_2$/(*S*,*S*)-f-Binaphane as the catalyst, an efficient enantioselective synthesis of sultams was developed via asymmetric hydrogenation of the corresponding cyclic imines with high enantioselectivities. The hydrogenation products can be conveniently transformed to chiral homoallylic amines without loss of enantioselectivity.

The cyclic sulfonamides, sultams, are of enormous importance as organic synthetic intermediates, chiral auxiliaries with considerable success, and privileged structures in drug discovery due to wide range of biological activities.[1,2] Recently, some efficient methods have been developed for sultams preparation by classical cyclization protocols, including Diels−Alder reactions,[3] [3 + 2] cycloadditions,[4] Friedel−Craft,[5] and a number of transition-metal-catalyzed approaches such as Heck reactions,[6] ring-closing metathesis (RCM),[7] and Rh-, Cu-, and Au-catalyzed selective cyclizations.[8] By retrosynthetic analysis, asymmetric hydrogenation of the easily synthesized cyclic *N*-sulfonylimines is the most convenient approach. Oppolzer[9] reported the asymmetric hydrogenation of cyclic *N*-sulfonylimines with Ru catalyst systems with up to 99% ee. Baker,[10] Ahn,[11] Lennon,[12] and Deng[13] explored Rh- and Ru-catalyzed asymmetric transfer hydrogenation of cyclic *N*-sulfonylimines from saccharin with up to 81%, 93%, 87%, and 98% ee, respectively. Zhang[14] and co-workers described a Pd-catalyzed asymmetric hydrogenation of cyclic *N*-sulfonylimines with 94% ee. However, for the above-reported hydrogenation methods, in general, only a few examples derived from saccharin were reported. So, development of an efficient and general method for synthesis of chiral sultams is highly desirable.



In 2007, we reported an efficient Pd-catalyzed asymmetric hydrogenation of cyclic *N*-sulfonylimines **1** and **3** with 79−93% ee using Pd(CF$_3$CO$_2$)$_2$/(*S*)-SegPhos as catalyst.[15] Only moderate enantioselectivities were obtained for the aryl-substituted substrates **1**. This shortcoming prompted us to seek an efficient asymmetric hydrogenation system for the

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(1) (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) 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.

(2) (a) Wills, M.; Oppolzer, W.; Kelly, M. J.; Signer, M.; Blagg, J. *Tetrahedron Lett.* **1990**, *31*, 5015. (b) Oppolzer, W.; Rodriguez, I.; Starkeman, C.; Walther, E. *Tetrahedron Lett.* **1990**, *31*, 5019. (c) Ahn, K. H.; Kim, S.-K.; Ham, C. *Tetrahedron Lett.* **1998**, *39*, 6321.

(3) (a) Metz, P.; Seng, D.; Frohlich, R. *Synlett.* **1996**, 741. (b) Grieg, I. R.; Tozer, M. J.; Wright, P. T. *Org. Lett.* **2001**, *3*, 369. (c) Rogatchov, V. O.; Bernsmann, H.; Schwab, P.; Frohlich, R.; Wibbeling, B.; Metz, P. *Tetrahedron Lett.* **2002**, *43*, 4753.

(4) Chiacchio, U.; Corsaro, A.; Rescifina, A.; Bkaithan, M.; Grassi, G.; Piperno, A.; Privitera, T.; Romeo, T. G. *Tetrahedron* **2001**, *57*, 3425.

(5) (a) Orazi, O. O.; Corral, R. A.; Bravo, R. *Heteroat. Chem.* **1986**, *23*, 1701. (b) Bravo, R. D.; Canpea, A. A. *Synth. Commun.* **2002**, *32*, 3675.

(6) (a) Merten, S.; Frohlich, R.; Kataeva, O.; Metz, P. *Adv. Synth. Catal.* **2005**, *347*, 754. (b) Vasudevan, A.; Tseng, P. S.; Djuric, S. W. *Tetrahedron Lett.* **2006**, *47*, 8591. (c) Paquette, L. A.; Dura, R. D.; Fosnaugh, N.; Marshall, S. *J. Org. Chem.* **2006**, *71*, 8438.

(7) (a) Moriggi, J. M.; Brown, L. J.; Castro, J. L.; Brown, R. C. D. *Org. Biomol. Chem.* **2004**, *2*, 835. (b) Freitag, D.; Schwab, P.; Metz, P. *Tetrahedron Lett.* **2004**, *45*, 3589. (c) Hopking, M. J.; Hanson, P. R. *Org. Lett.* **2008**, *10*, 2223.

(8) (a) Dieter, E.; Alexanders, M.; Bats, J. W. *Eur. J. Org. Chem.* **2006**, 1271. (b) Fruit, C.; Miiler, P. *Helv. Chim. Acta* **2004**, *87*, 1607. (c) Jaemoon, L.; Zhong, Y. L.; Robert, A.; David, A. *Org. Lett.* **2003**, *5*, 4175. (d) Teeninga, H.; Engberts, J. B. F. *J. Org. Chem.* **1983**, *48*, 537. (e) Zhou, A. H.; Hanson, P. R. *Org. Lett.* **2008**, *10*, 2951. (f) Liu, X.-Y.; Li, C.-H.; Che, C.-M. *Org. Lett.* **2006**, *8*, 2707. (g) Sherman, E. S.; Chemler, S. R.; Tan, T. B.; Gerlits, O. *Org. Lett.* **2004**, *6*, 1573. (h) Zeng, W.; Chemler, S. R. *J. Am. Chem. Soc.* **2007**, *129*, 12948. (i) Liang, J.-L.; Yuan, S.-X.; Chan, P. W. H.; Che, C.-M. *Org. Lett.* **2002**, *4*, 4507.

(9) Oppolzer, W.; Wills, M.; Starkemann, C.; Bernardinelli, G. *Tetrahedron Lett.* **1990**, *31*, 4117.

(10) Mao, J. M.; Baker, D. C. *Org. Lett.* **1999**, *1*, 841.

(11) Ahn, K. H.; Ham, C.; Kim, S. K.; Cho, C. W. *J. Org. Chem.* **1997**, *62*, 7047.

(12) Cobley, C. J.; Foucher, E.; Lecouve, J. P.; Lennon, I. C.; Ramsden, J. A.; Thominot, G. *Tetrahedron: Asymmetry* **2003**, *14*, 3431.

(13) (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.* **2002**, *67*, 5301. (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.-S.; Wang, F.; Ma, Y.-P.; Cui, X.; Cun, L.-F.; Zhu, J.; Deng, J.-G.; Yu, B.-L. *Chem. Commun.* **2006**, 1766.

(14) Yang, Q.; Shang, G.; Gao, W.-Z.; Deng, J.-G.; Zhang, X.-M. *Angew. Chem., Int. Ed.* **2006**, *45*, 3832.

(15) Wang, Y.-Q.; Lu, S.-M.; Zhou, Y.-G. *J. Org. Chem.* **2007**, *72*, 3729.

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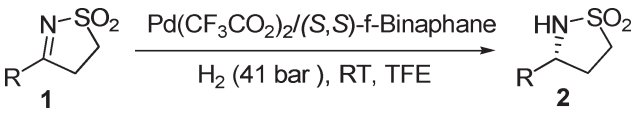
TABLE 1. Pd-Catalyzed Asymmetric Hydrogenation of 1[a]



entry	R of **1**	yield (%)	ee (%)[b]
1	Ph (**1a**)	99 (**2a**)	98 (79)
2	2-MeC_6H_4 (**1b**)	93 (**2b**)	98
3	3-MeC_6H_4 (**1c**)	92 (**2c**)	96
4	4-MeC_6H_4 (**1d**)	92 (**2d**)	97
5	4-FC_6H_4(**1e**))	89 (**2e**)	97
6[c]	Me (**1f**)	98 (**2f**)	94 (88)
7[c]	*n*-C_6H_{13} (**1g**)	98 (**2g**)	95 (90)
8	$C_6H_5CH_2$ (**1h**)	93 (**2h**)	91
9	$C_6H_5OCH_2$ (**1i**)	93 (**2i**)	95 (92)
10	2-Me$C_6H_4OCH_2$ (**1j**)	91 (**2j**)	94 (92)
11	4-Me$C_6H_4OCH_2$ (**1k**)	94 (**2k**)	94 (91)
12	4-$CF_3C_6H_4OCH_2$ (**1*l***)	95 (**2*l***)	95 (93)
13	$C_6H_5CH_2OCH_2$ (**1m**)	90 (**2m**)	91
14	2-nphthylOCH_2 (**1n**)	95 (**2n**)	94 (90)

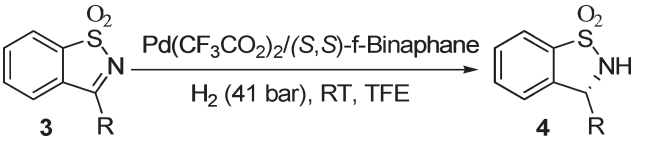
[a] Unless otherwise stated, reactions were performed in TFE on a 0.25 mmol scale: $Pd(CF_3CO_2)_2$ (2 mol %), (*S*,*S*)-f-Binaphane (2.4 mol %), 41 bar of H_2, rt, 14 h. [b] Ee was determined by HPLC analysis; the numbers in parentheses were obtained by using $Pd(CF_3CO_2)_2$/(*S*)-SegPhos under identical conditions. [c] Ee was determined by chiral HPLC analysis of its *N*-cinnamyl derivative.

synthesis of chiral sultams. Very recently, we found that Pd$(CF_3CO_2)_2$/(*S*,*S*)-f-Binaphane is an efficient catalyst for asymmetric hydrogenation of prochiral activated imines.[16] In our ongoing efforts to develop asymmetric hydrogenation, we envisioned that chiral sultams should be synthesized via asymmetric hydrogenation of cyclic *N*-sulfonylimines **1** and **3** by $Pd(CF_3CO_2)_2$/(*S*,*S*)-f-Binaphane. Herein, we report an efficient method for the enantioselective synthesis of chiral sultams by asymmetric hydrogenation of the corresponding cyclic imines using $Pd(CF_3CO_2)_2$/(*S*,*S*)-f-Binaphane as catalyst with up to 99% ee. The hydrogenation products can be conveniently transformed to chiral homoallylic amines without loss of enantioselectivity.

Cyclic imines **1** and **3** can be conveniently prepared from commercially available materials according to the known literature procedure.[17] (*S*,*S*)-f-Binaphane was synthesized according to the literature.[18]

We have previously studied the use of $Pd(CF_3CO_2)_2$/(*S*)-SegPhos in the asymmetric hydrogenation of cyclic imines **1**. To further improve the enantioselectivity, the effects of ligands on the reactivity and enantioselectivity were systematically screened by using imine **1a** as model substrate. Interestingly, when a Pd catalyst containing (*S*,*S*)-f-Binaphane ligand was used in the asymmetric hydrogenation of imines **1a**, a significant increase in the ee value was obtained in comparison with the result of using (*S*)-SegPhos (entry 1 in Table 1, 79% vs. 98% ee). Inspired by the result, a series of cyclic *N*-sulfonylimines **1** were hydrogenated with high enantioselectives and yields; the results are summarized in Table 1. For the aryl-substituted imines, the steric and electronic effects of substituents in aryl have no significant effect on the ee values and the yields (entries 1−5). Simple alkyl-substituted imines (entries 6 and 7), bearing methyl and *n*-hexyl groups, respectively, showed high enantioselectives (94% and 95% ee). Benzyl-substituted imine **1h** gave 91% ee. Various aryloxymethyl- and alkoxylmethyl-substituted imines (entries 8−14) can also be successfully hydrogenated with high enantioselectivity.

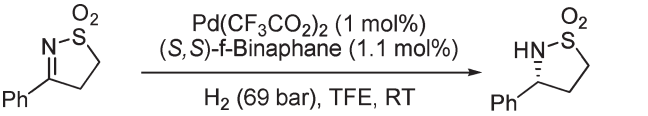
TABLE 2. Pd-Catalyzed Asymmetric Hydrogenation of 3[a]



entry	R of **3**	yield (%)	ee (%)[b]
1	Me (**3a**)	97 (**4a**)	97 (92)
2	*n*-Bu (**3b**)	99 (**4b**)	97 (90)
3	Bn (**3c**)	98 (**4c**)	94 (88)
4	Ph (**3d**)	99 (**4d**)	98
5	2-MeC_6H_4 (**3e**)	99 (**4e**)	98
6	3-MeC_6H_4 (**3f**)	97 (**4f**)	98
7	4-MeC_6H_4 (**3g**)	97 (**4g**)	99
8	4-MeOC_6H_4 (**3h**)	99 (**4h**)	98
9	4-FC_6H_4 (**3i**)	97 (**4i**)	94
10	3-TBSO$CH_2C_6H_4$ (**3j**)	95 (**4j**)	98
11	3-HO$CH_2C_6H_4$ (**3k**)	96 (**4k**)	99

[a] Unless otherwise stated, reactions were performed in TFE on a 0.25 mmol scale: $Pd(CF_3CO_2)_2$ (2 mol %), (*S*,*S*)-f-Binaphane (2.4 mol %), 41 bar of H_2, rt, 14 h. [b] Ee was determined by HPLC analysis; the numbers in parentheses were obtained by using $Pd(CF_3CO_2)_2$/(*S*)-SegPhos under the identical conditions.

SCHEME 1. Pd-Catalyzed Asymmetric Hydrogenation of Imine 1a on a Gram-Scale



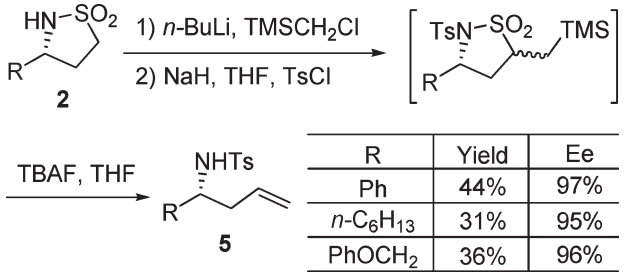
Gratifyingly, the above chiral palladium catalytic system $Pd(CF_3CO_2)_2$/(*S*,*S*)-f-Binaphane can also be extended to asymmetric hydrogenation of assorted benzofused imines **3**. As summarized in Table 2, a variety of aryl- and alkyl-substituted cyclic sultams could be obtained in 94−99% ee values with full conversion. For alkyl-substituted imines, high enantioselectivities and full conversions were also obtained (94−97% ee, entries 1−3, Table 2). The electronic and steric characteristics of substituents in the substrates have no significant influence on the enantioselectivity and reactivity. Substrates with electron-donating or electron-withdrawing aryl substituents can be successfully hydrogenated to give the corresponding cyclic sultams with 94−99% ee (entries 4−11, Table 2). Notably, the palladium catalytic system can tolerate hydroxyl and TBSO groups: for substrates (**3j** and **3k**) bearing a hydroxyl and TBSO, 98% and 99% ee were

(16) (a) Wang, Y.-Q.; Yu, C.-B.; Wang, D.-W.; Wang, X.-B.; Zhou, Y.-G. *Org. Lett.* **2008**, *10*, 2071. For recent examples on Pd-catalyzed asymmetric hydrogenation of imines and ketones, see: (b) Zhou, Y.-G. *Acc. Chem. Res.* **2007**, *40*, 1357. (c) Wang, Y.-Q.; Lu, S.-M.; Zhou, Y.-G. *Org. Lett.* **2005**, *7*, 3235. (d) Wang, Y.-Q.; Zhou, Y.-G. *Synlett.* **2006**, 1189. (e) Rubio-Perez, L.; Perez-Flores, F. J.; Sharm, P.; Velasco, L.; Cabrera, A. *Org. Lett.* **2009**, *11*, 265. (f) Suzuki, A.; Mae, M.; Amii, H.; Uneyama, K. *J. Org. Chem.* **2004**, *69*, 5132.

(17) (a) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, *31*, 2647. (b) Neustadt, B. R. *Tetrahedron Lett.* **1994**, *35*, 379. (c) Freitag, D.; Metz, P. *Tetrahedron* **2006**, *62*, 1799.

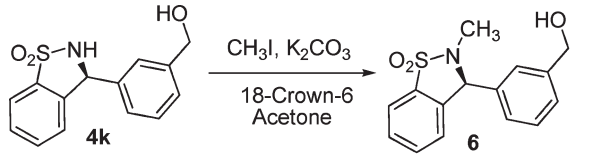
(18) Xiao, D.; Zhang, X.-M. *Angew. Chem., Int. Ed.* **2001**, *40*, 3425.

SCHEME 2. The Synthesis of Chiral Homoallylic Amines from Hydrogenation Products



R	Yield	Ee
Ph	44%	97%
n-C_6H_{13}	31%	95%
$PhOCH_2$	36%	96%

SCHEME 3. The Enantioselective Synthesis of HIV-1



Yield: 97%, Ee: 99%

obtained, respectively (entries 10 and 11, Table 2). It is also noteworthy that $Pd(CF_3CO_2)_2$/(*S*,*S*)-f-Binaphane catalytic system gave higher enantioselecitivity than the Pd $(CF_3CO_2)_2$/(*S*)-SegPhos (entries 1−3, Table 2).

The asymmetric hydrogenation of cyclic *N*-sulfonylimines **1a** on a gram-scale also can be carried out with 1 mol % palladium catalyst $Pd(CF_3CO_2)_2$/(*S*,*S*)-f-Binaphane in TFE at room temperature. As illustrated in Scheme 1, the chiral sultam **2a** was obtained in 99% yield with 98% ee by flash column chromatography.

To explore the potential synthetic utility of this new method, we attempted its application in the synthesis of enantiopure homoallylic amine derivatives. As can be seen in Scheme 2, hydrogenation product **2** reacted with $TMSCH_2Cl$ in the presence of *n*-BuLi to give the intermediates in moderate to good yields,[19] followed by protection of nitrogen with toluenesulfonyl chloride. Tandem desilylation and ring-opening with TBAF in THF afforded chiral homoallylic amine derivatives without the loss of optical purity.[20]

(19) Alonso, D. A.; Najera, C.; Sansano, J. M. *Tetrahedron* **1994**, *50*, 6603.

(20) Hsiao, C. N.; Shechter, H. *J. Org. Chem.* **1988**, *53*, 2688.

The methodology also provides a convenient route to synthesize chiral sultams with biologically activity. Compound **6** (HIV-1), a chiral sultam with anti-HIV activity,[21] can be conveniently synthesized with Pd catalyzed asymmetric hydrogenation as the key step. *N*-Methylation of the **4k** with methyl iodide gave the target **6** HIV-1 (Scheme 3).

In summary, a general method for the synthesis of chiral 3-substituted cyclic sultam derivatives has been effectively developed via asymmetric hydrogenation of the corresponding cyclic imines with $Pd(CF_3CO_2)_2$/(*S*,*S*)-f-Binaphane as catalyst under mild reaction conditions with 91−99% ee. The hydrogenation products can be conveniently transformed to chiral homoallylic amines without loss of enantioselectivity.

Experimental Section

Typical Procedure for the Asymmetric Hydrogenation of Cyclic Imine 1a. (*S*,*S*)-f-Binaphane (4.8 mg, 0.006 mmol) and $Pd(CF_3CO_2)_2$ (1.7 mg, 0.005 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 (3 mL). The imine **1a** (49 mg, 0.25 mmol) was added to the catalyst solution, and then the mixture was transferred to an autoclave. The autoclave was stirred under directed condition for 12 h, then the hydrogen was carefully released, the autoclave was opened, and the reaction mixture was evaporated. Conversion was determined by ^1H NMR analysis. The enantiomeric excess was determined by HPLC after purification on silica gel with hexane and EtOAc. 3-Phenyl-1,2-thiazolidine 1,1-dioxide (**2a**):[15] yield 99%, 98% ee, $[\alpha]_D^{24}$ +39.6 (*c* 1.42, EtOH); ^1H NMR (400 MHz, $CDCl_3$) δ 2.30−2.44 (m, 1H), 2.76−2.79 (m, 1H), 3.19−3.25 (m, 1H), 3.33−3.36 (m, 1H), 4.55 (br, 1H), 4.71−4.76 (m, 1H), 7.26−7.42 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.4, 48.4, 58.4, 126.2, 128.7, 129.2, 140.4. HPLC (OD-H column, ^{i}PrOH/hexane 20/80, 0.8 mL min^{-1}, 254 nm) t_1 = 19.0 min, t_2 = 21.2 min.

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Supporting Information Available: Characterization of products and experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

(21) Rolfe, A.; Young, K.; Hanson, P. R. *Eur. J. Org. Chem.* **2008**, 5254.