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Enantioselective Pd-catalyzed hydrogenation of enesulfonamides†

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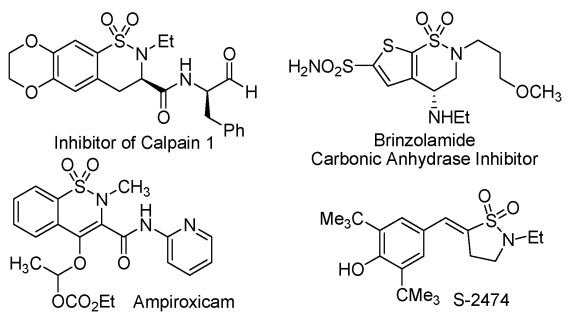
Asymmetric hydrogenation of cyclic enesulfonamides affords chiral cyclic sulfonamides using $Pd(OCOCF_3)_2$/diphosphine complexes as catalysts with up to 98% ee.

Chiral amines are important structure motifs in synthetic chemistry, medicinal chemistry, and materials industries.[1] Compounds containing the sulfonamide skeleton have gained wide attention.[2] Cyclic sulfonamide (sultams) analogs are useful structures in drug active compounds due to their wide chemical and biological activities including anti-HIV, anti-inflammatory, anti-malarial, and so on (Scheme 1).[3]

In the past decades, numerous strategies[4] have been developed to synthesize sultams, they are generally obtained by Friedel–Craft reactions, [3 + 2] cycloadditions, dianion reactions, and Diels–Alder reactions, ring-closing metathesis (RCM), Heck reactions, as well as Rh-, Au- and Cu-catalyzed cyclizations.[5] However, to date only a few examples of the asymmetric catalytic versions have been reported despite its synthetic significance. Toward further investigation of new biological activities of sulfonamides, a more practical and general route to sultams, particularly for their optically pure enantiomers, is highly attractive. According to the retro-synthetic analysis, we envisioned that asymmetric hydrogenation of the corresponding cyclic *N*-sulfonylimines or enesulfonamides is also the convenient and efficient route to obtain chiral cyclic sulfonamides in terms of simplicity and



Scheme 1 Biologically active sultams.

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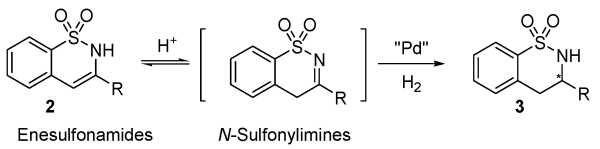


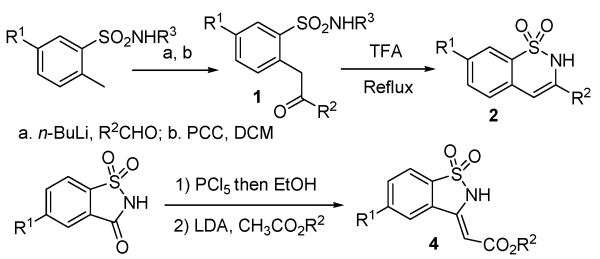
Scheme 2 Synthesis of chiral sulfonamides.

atom efficiency (Scheme 2). In the past few years, cyclic *N*-sulfonylimines have been hydrogenated successfully by us[6] and other groups.[7] However, to the best of our knowledge, the asymmetric hydrogenation of cyclic enesulfonamides **2** and **4** has not been reported.

Recently, chiral palladium complexes have been successfully applied to asymmetric hydrogenation of activated imines (especially for the activated *N*-sulfonylimines), functionalized ketones and unprotected indoles.[6,8,9] Considering enesulfonamide could tautomerize to the corresponding *N*-sulfonylimines under the acidic conditions (Scheme 2), this instance inspired us to conjecture that enesulfonamides would be good substrates for palladium-catalyzed asymmetric hydrogenation. Herein, we present our results on the Pd-catalyzed hydrogenation of enesulfonamides, up to 98% ee was obtained.

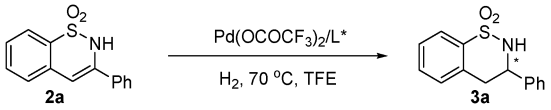
Enesulfonamides (**2** and **4**) can be conveniently synthesized from 2-methyl substituted arylsulfonamides and saccharins by slightly modified literature procedures (Scheme 3).[10]

Asymmetric hydrogenation of enesulfonamide **2a** was chosen as the model reaction and initial hydrogenation experiment was performed in trifluoroethanol (TFE) using $Pd(OCOCF_3)_2$/(*S*,*S*)-f-Binaphane at room temperature. However, no product was obtained (entry 1, Table 1). When the reaction temperature was elevated to 70 °C, 96% yield and moderate 82% ee were obtained (entry 2, Table 1). Next, the ligand effect was screened (entries 3–6, Table 1). Fortunately, up to 97% ee was achieved using (R,S_p)-JosiPhos (entry 6, Table 1). Slightly low enantioselectivities were obtained under the low hydrogen pressure (entries 7–9, Table 1).

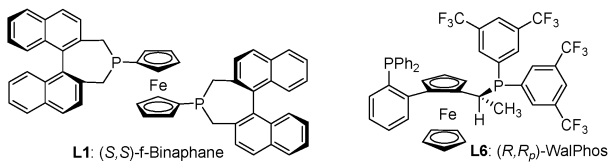


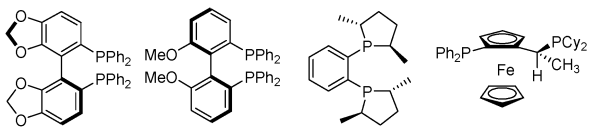
Scheme 3 Synthesis of cyclic enesulfonamides **2** and **4**.

Table 1 Pd-catalyzed asymmetric hydrogenation of **2a**[a]



Entry	L*	H_2 (atm)	Yield[b] (%)	ee[c] (%)
1[d]	**L1**	42	—	—
2	**L1**	42	96	82
3	**L2**	42	86	79
4	**L3**	42	96	67
5	**L4**	42	93	49
6	**L5**	42	98	97
7	**L5**	28	98	98
8	**L5**	14	94	96
9	**L5**	1	99	93

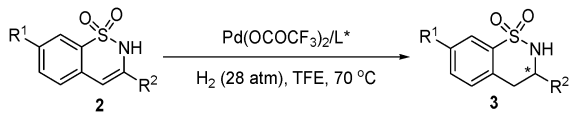




[a] The reaction was carried out with **2a** (0.125 mmol), $Pd(OCOCF_3)_2$ (0.0025 mmol), ligand (0.003 mmol), and 3 mL TFE under 70 °C for 16 h. [b] Isolated yield. [c] ee was determined by HPLC analysis. [d] The reaction was run at room temperature.

Under the optimal reaction conditions, a variety of enesulfonamides **2** was explored to examine the substrates scope. As shown in Table 2, substrates with steric difference in aryl resulted in similar enantioselectivities (97–98% ee, entries 1–4, Table 2).

Table 2 Pd-catalyzed asymmetric hydrogenation of **2**[a]



Entry	R^1 of **2**	R^2 of **2**	L*	Yield[b] (%)	ee[c,d] (%)
1	H	Ph	**L5**	96 (**3a**)	98 (+)
2	H	2-Me-C_6H_4	**L5**	97 (**3b**)	98 (+)
3	H	3-Me-C_6H_4	**L5**	97 (**3c**)	97 (*R*)
4	H	4-Me-C_6H_4	**L5**	99 (**3d**)	97 (+)
5	H	4-MeO-C_6H_4	**L5**	97 (**3e**)	95 (+)
6	H	4-F-C_6H_4	**L5**	99 (**3f**)	98 (+)
7	H	4-Cl-C_6H_4	**L5**	97 (**3g**)	98 (+)
8	Me	Ph	**L5**	97 (**3h**)	96 (+)
9	H	2-Furyl	**L5**	99 (**3i**)	81 (+)
10	H	Me	**L6**	99 (**3j**)	98 (−)
11[e]	H	*n*-C_3H_7	**L6**	92 (**3k**)	96 (−)
12[e]	H	*n*-C_5H_{11}	**L6**	90 (**3l**)	90 (−)
13[e]	H	$C_6H_5CH_2CH_2$	**L6**	75 (**3m**)	96 (−)

[a] The reaction was carried out with **2** (0.125 mmol), $Pd(OCOCF_3)_2$ (0.0025 mmol), ligand (0.003 mmol), and 3 mL TFE under directed conditions for 16 h. [b] Isolated yield. [c] ee was determined by HPLC analysis. [d] The absolute configuration of the major enantiomer of **3c** was determined by X-ray analysis. Other products' absolute configurations were assigned by analogy to **3c**. [e] Determined by ^1H NMR.

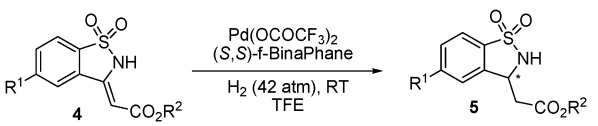
When an electron-donating or electron-withdrawing group is present on the aromatic ring of substrates, the corresponding cyclic sulfonamides can be achieved successfully in high ees (95–98% ee, entries 5–7, Table 2). Substrate **2h** with a substituent at the 7-position could also be hydrogenated smoothly, and 96% ee was observed (entry 8, Table 2). In the case of the R^2 group being 2-furyl, full conversion and 81% ee were obtained (entry 9, Table 2). However, for **2k** containing the *n*-propyl group, only moderate 69% ee was obtained under the above standard conditions. Fortunately, when ligand (R,S_p)-JosiPhos was replaced by (R,R_P)-WalPhos, a significant increase in the ee value was observed (96% ee, entry 11, Table 2). Under the optimum conditions, for substrates with a variety of alkyl substituents, there was no remarkable influence on reactivity and enantioselectivity regardless of the chain length (90–98% ee, entries 10–13, Table 2).

A single crystal of sulfonamides **3c** (>99% ee) was obtained by recrystallization from DCM/hexane, and its absolute configuration was unambiguously assigned as (*R*)-**3c** by X-ray diffraction analysis (see ESI†).[11]

In addition to *endo*-cyclic-enesulfonamides **2**, we also explored the asymmetric hydrogenation of *exo*-cyclic-enesulfonamides **4** with the above Pd catalyst system. Interestingly, when the Pd catalyst containing the (*S*,*S*)-f-Binaphane ligand was used in the asymmetric hydrogenation of **4a** full conversion and 92% ee value were obtained. Inspired by the result, a series of *exo*-enesulfonamides **4** were synthesized from the saccharin. Fortunately, all substrates were transformed completely and good to excellent ee values were obtained. The results are summarized in Table 3. High enantioselectivities were obtained for alkyl ester bearing ethyl and *tert*-butyl groups (92% and 96%, entries 2–3, Table 3). Albeit methyl and benzyl ester (**4a** and **4d**) gave slightly lower ee values (86% and 87%, entries 1 and 4, Table 3). Substrate **4e** with a substituent at the 5-position could also be smoothly hydrogenated with 87% ee (entry 5, Table 3).

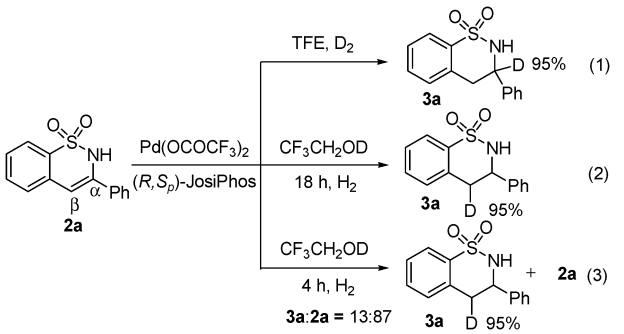
To investigate the process of the hydrogenation reaction, three isotopic labeling experiments were carried out. When **2a** was subjected to hydrogenation with D_2, one deuterium atom was incorporated to the α-position, and deuterium at the β-position was not observed (eqn (1), Scheme 4). When the hydrogenation was carried out in CF_3CH_2OD with full

Table 3 Pd-catalyzed asymmetric hydrogenation of **4**[a]



Entry	R^1 of **4**	R^2 of **4**	Yield[b] (%)	ee[c] (%)
1	H	Me	97 (**5a**)	86 (−)
2	H	Et	97 (**5b**)	92 (−)
3	H	*t*-Bu	97 (**5c**)	96 (+)
4[d]	H	Bn	97 (**5d**)	87 (−)
5[e]	Me	Et	99 (**5e**)	87 (−)

[a] The reaction was carried out with **4** (0.125 mmol), $Pd(OCOCF_3)_2$ (0.0025 mmol), (*S*,*S*)-f-Binaphane (0.003 mmol), and 3 mL TFE under directed conditions for 16 h. [b] Isolated yield. [c] ee was determined by HPLC. [d] The reaction was conducted under 70 °C. [e] The reaction was run at 60 °C.



Scheme 4 Isotopic labeling experiments using D_2 and CF_3CH_2OD.

conversion of substrate, (eqn (2), Scheme 4), ^{1}H NMR analysis of the hydrogenated product showed that one deuterium atom was incorporated to the β-position. However, when incomplete conversion was carried out, ^{1}H NMR analysis of the crude hydrogenated product showed that one deuterium atom was incorporated to the β-position, while no deuterium atom was observed in the recovered starting material **2a** (eqn (3), Scheme 4). The above experiments confirmed that the hydrogenation of enesulfonamides was conducted *via* *N*-sulfonylimine intermediates, and the tautomerization process of enesulfonamides to *N*-sulfonylimine intermediates was slower than the hydrogenation.

In conclusion, we have developed an efficient and highly enantioselective Pd-catalyzed hydrogenation of enesulfonamides, which led to the facile synthesis of chiral cyclic sultams in good to excellent enantioselectivities. Further exploring the applications of this method in asymmetric synthesis of some biologically active compounds is currently underway.

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11 Selected bond lengths [Å] and angles [°]: C8–N1, 1.497(4); C8–C9, 1.520(5); C9–C10, C7–C8, 1.521(4); 1.370(5); N1–S1, 1.598(3); C6–C7–C8, 114.3(3); N1–C8–C9, 109.1(3); N1–C8–C7, 110.0(3); C9–C8–C7, 114.6(3); N1–C8–H8,107.6; C9–C8–H8, 107.6; C7–C8–H8,107.6.

