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Rh/DuanPhos-Catalyzed Asymmetric Hydrogenation of β-Acetylamino Vinylsulfides: An Approach to Chiral β-Acetylamino Sulfides

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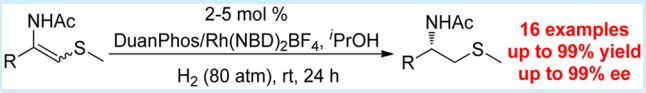
Supporting Information

ABSTRACT: Rh/DuanPhos-catalyzed asymmetric hydrogenation of challenging β-acetylamino vinylsulfides has been developed, affording chiral β-acetylamino sulfides with high yields and excellent ee's (up to 99% ee). This novel methodology provides an efficient and concise synthetic route to chiral β-acetylamino sulfides. The potential utility of this protocol in the synthesis of Apremilast has also been disclosed.



Chiral organosulfur compounds play important roles in organic chemistry and medicinal chemistry because of their inherent biological values and potential pharmaceutical applications (Figure 1).[1] Particularly, about 20% of marketed

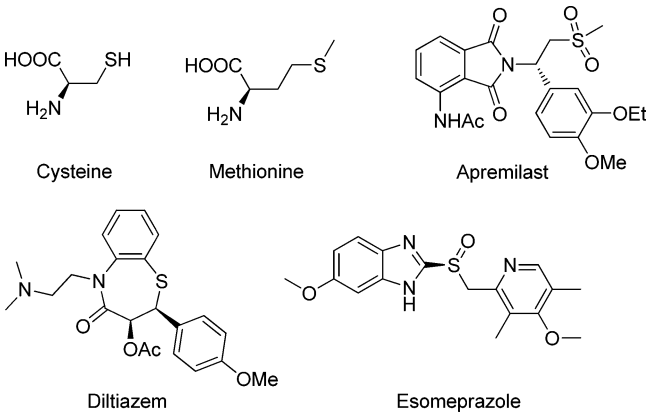
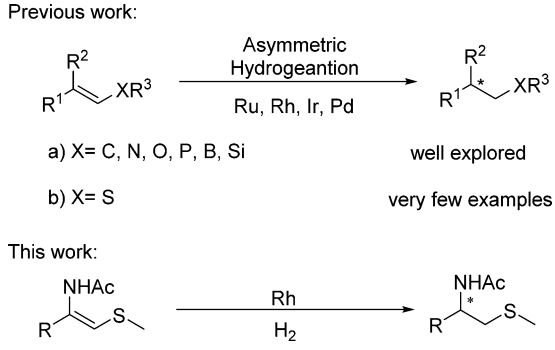


Figure 1. Chiral pharmaceuticals containing C−S bonds.

pharmaceuticals are organosulfur compounds, with many of the top selling drugs in 2012 containing at least one C−S bond.[2] Therefore, C−S bond formations hold a prominent position in organic synthesis and have attracted extreme enthusiasm from organic chemists. To date, significant advancement has been achieved for the establishment of the C−S bond, which mainly refers to addition, substitution, and other strategies.[3] However, there are relatively few methods for the synthesis of chiral organosulfur compounds. Therefore, developing convenient and efficient methodology for chiral organosulfur compounds is still in great demand.

In recent decades, transition-metal-catalyzed asymmetric hydrogenation has been extensively applied in both academic study and practical production, which has been developed as one of the most powerful and environmentally friendly methodology to obtain chiral compounds.[4] In this context, the asymmetric hydrogenation of functionalized alkenes bearing C, N, O, P, B, or Si substituents have been well explored (Scheme 1).[5] However, the asymmetric hydrogenation of

Scheme 1. Asymmetric Hydrogenation of β-Acetylamino Vinylsulfides



alkenes bearing a sulfur substituent is rare.[6] The main challenge lies in the fact that the S atom extremely tends to coordinate with the transition metal which results in the catalyst deactivation.[6] Our group has been devoted to developing rigid and electron-rich chiral phosphine ligands which have been applied in asymmetric hydrogenation to synthesize chiral amines and chiral alcohols.[7] Based on our previous work in asymmetric hydrogenation, we envisioned that the electron-rich S atom could be easily solvated by protic solvent. Meanwhile, the formation of a hydrogen bond between the S atom and protic solvent would weaken the coordination ability of sulfur.[8] With this idea in mind, we wish to solve the issue of asymmetric hydrogenation of sulfur-functionalized alkenes. Herein, we

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disclosed a new strategy to generate chiral β-acetylamino sulfides in high yields and excellent enantioselectivities via Rh-catalyzed asymmetric hydrogenation of β-acetylamino vinylsulfides.

Initially, *N*-(2-(methylthio)-1-phenylvinyl)acetamide **1a** was prepared from the 2-bromo-1-phenylethan-1-one according to the literature (see Supporting Information for details), and Rh-catalyzed asymmetric hydrogenation of the mixture of *Z*/*E* isomers of **1a** was chosen as the model reaction to optimize the reaction conditions. The reaction was initially conducted in MeOH under 80 atm of H_2 at room temperature for 24 h in the presence of 2 mol % $Rh(NBD)_2BF_4$, evaluating a variety of diphosphine ligands developed in our group and some commercial available chiral ligands (Figure 2). As shown in

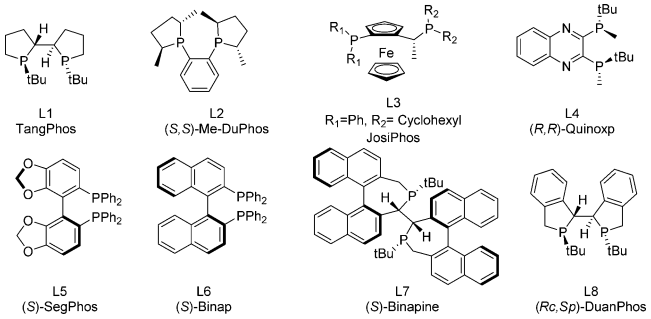
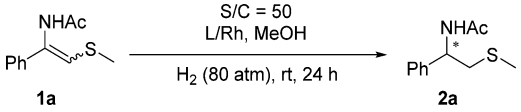


Figure 2. Structures of the phosphine ligands for hydrogenation of **1a**.

Table 1. Ligand and Rh Precursor Screening For Asymmetric Hydrogenation of 1a[a]



1a **2a**

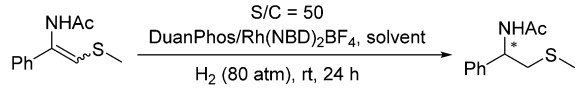
entry	L	Rh	conv (%)[b]	ee (%)[c]
1	L1	$Rh(NBD)_2BF_4$	–	–
2	L2	$Rh(NBD)_2BF_4$	–	–
3	L3	$Rh(NBD)_2BF_4$	trace	–
4	L4	$Rh(NBD)_2BF_4$	–	–
5	L5	$Rh(NBD)_2BF_4$	–	–
6	L6	$Rh(NBD)_2BF_4$	27	45
7	L7	$Rh(NBD)_2BF_4$	14	20
8	L8	$Rh(NBD)_2BF_4$	30	95
9	L8	$Rh(COD)_2BF_4$	4	94
10	L8	$[Rh(COD)Cl]_2$	15	95
11	L8	$Rh(COD)_2SO_3CF_3$	10	94

[a]Unless otherwise mentioned, **1a** was hydrogenated with the conditions: Rh/ligand/substrate ratio of 1:1.1:50, in 1 mL of MeOH under 80 atm of H_2 at room temperature for 24 h. **1a** is the mixture of *Z*/*E* isomers, and the ratio is 2:1. [b]Determined by ^1H NMR spectroscopy. [c]Determined by HPLC analysis using a chiral stationary phase.

Table 1, no matter if P-chiral diphosphine ligands, axially chiral biarylbisphosphorus ligands, or chiral ferrocenyldiphosphine ligands were employed for this reaction, all of them exhibited poor activity (Table 1, entries 1−8). To our delight, the desired product **2a** was obtained with excellent enantioselectivity when (*Sc*,*Rp*)-DuanPhos was employed, although the conversion is low (Table 1, entry 8). Subsequently, several rhodium precursors were tested; the high enantioselectivities were maintained, but the conversion dropped dramatically (Table 1, entries 9−11).

Encouraged by the promising results, further optimization of reaction conditions were conducted to improve the conversion of **1a**. As shown in Table 2, the solvents played an important

Table 2. Solvent and Concentration Screening for Rh-Catalyzed Asymmetric Hydrogenation of 1a[a]



1a **2a**

entry	solvent	concn (M)	conv (%)[b]	ee (%)[c]
1	MeOH	0.05	30	95
2	EtOH	0.05	83	97
3	^{i}PrOH	0.05	81	98
4	CH_2Cl_2	0.05	80	97
5	THF	0.05	68	95
6	toluene	0.05	27	98
7	TFE	0.05	78	98
8	^{i}PrOH	0.25	51	60
9	^{i}PrOH	0.025	95	98
10	^{i}PrOH	0.017	99	98
11[d]	^{i}PrOH	0.017	99	98

[a]Unless otherwise mentioned, **1a** was hydrogenated with the conditions: $Rh(NBD)_2BF_4$/(*Sc*,*Rp*)-DuanPhos/**1a** ratio of 1:1.1:50, in 1 mL of solvent under 80 atm of H_2 at room temperature for 24 h. **1a** is the mixture of *Z*/*E* isomers, and the ratio is 2:1. [b]Determinde by ^1H NMR spectroscopy. [c]Determined by HPLC analysis using a chiral stationary phase. [d]**1a** is the mixture of *Z*/*E* isomers, and the ratio is 2.5:1.

role in the asymmetric hydrogenation of **1a**. The solvent screening revealed ^{i}PrOH was the best choice (entries 1−7). We found that both the conversion and enantioselectivity dropped sharply when the concentration of **1a** was increased (entry 8). In contrast, decreasing the concentration was beneficial for the improvement of conversion and enantioselectivity (entries 9−10). When the concentration of the substrate was decreased to 0.017 M, the reaction worked smoothly, affording the hydrogenated product with full conversion and excellent ee. The possible reason was that the low concentration of **1a** was helpful for the formation of the hydrogen bond between ^{i}PrOH and the S atom of **1a** which inhibited the combination of the S atom with the catalyst to some extent. In addition, when the ratio of the *Z*/*E* isomer of **1a** was changed, the same ee was obtained, which disclosed that the *Z*/*E* ratio had no influence on the reaction enantioselectivity (for more details, see SI).

With the optimized reaction conditions in hand, a variety of β-acetylamino vinylsulfides were examined, and the results are summarized in Table 3. It was found that high yields and excellent ee's were achieved in most cases. The substituents of the R group, whether they are electron-withdrawing or -donating groups introduced at the *ortho*-, *meta*-, or *para*-positions of the phenyl group, had little influence on the reactivity and enantioselectivity, providing the corresponding compounds in good yields and with excellent enantioselectivities (entries 1−12). In the case of the heteroaryl substituted substrate, high yields and ee's were obtained (entries 14, 15). However, a 2-naphthyl-substituted substrate was hydrogenated

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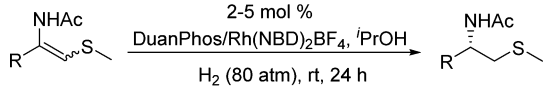
Table 3. Rh-Catalyzed Asymmetric Hydrogenation of β-Acylamino Vinylsulfide 1[a]



1 2

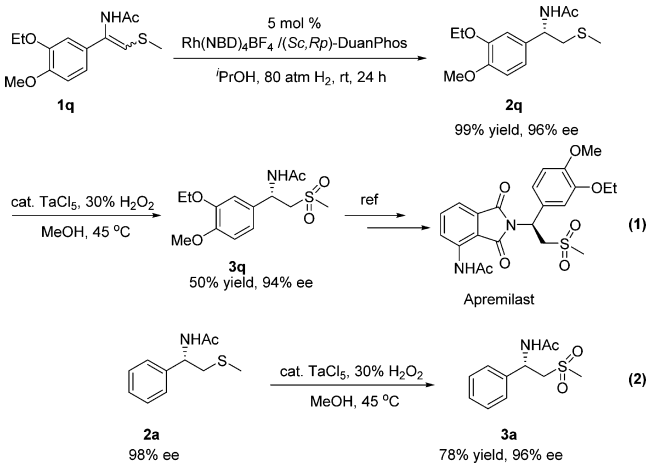
entry	R	product	yield (%)[b]	ee (%)[c]
1	Ph (**1a**)	**2a**	97	98
2	4-Me-C_6H_4 (**1b**)	**2b**	93	97
3	3-Me-C_6H_4 (**1c**)	**2c**	94	94
4	2-Me-C_6H_4 (**1d**)	**2d**	99	86
5	4-OMe-C_6H_4 (**1e**)	**2e**	96	94
6[d,e]	4-CF_3-C_6H_4 (**1f**)	**2f**	93	89
7	4-F-C_6H_4 (**1g**)	**2g**	88	98
8[d]	4-Cl-C_6H_4 (**1h**)	**2h**	98	98
9[d]	4-Br-C_6H_4 (**1i**)	**2i**	98	99
10[d]	4-I-C_6H_4 (**1j**)	**2j**	98	97
11[d]	3-F-C_6H_4 (**1k**)	**2k**	96	94
12[d]	2-F-C_6H_4 (**1l**)	**2l**	94	96
13[d]	2-naphthyl (**1m**)	**2m**	76	92
14	2-furyl (**1n**)	**2n**	99	99
15	2-thienyl (**1o**)	**2o**	99	97
16	^{t}Bu (**1p**)	**2p**	–	–

[a]Unless otherwise mentioned, all the substrates **1** were hydrogenated with the conditions: $Rh(NBD)_2BF_4$/(*Sc,Rp*)-DuanPhos/substrate ratio of 1:1.1:50, in 3 mL of ^{i}PrOH under 80 atm of H_2 at room temperature for 24 h. [b]Isolated yields. [c]Determined by HPLC analysis using a chiral stationary phase. [d]The reaction conditions: 5 mol % catalyst, under 100 atm of H_2 at 30 °C for 30 h. [e]When the catalyst loading was 2 mol %, the conversion was low and the ee was only 48%.

with excellent ee but only moderate conversion (entry 13). When alkyl substituted substrate **1p** was examined for this reaction, it did not work for this transformation (entry 16).

To explore the potential synthetic utility of this methodology, further derivatization and applications were carried out. As shown in Scheme 2, eq 1, Rh-catalyzed asymmetric hydrogenation of **1q** proceeds smoothly to give the corresponding product **2q** in high yield with excellent ee. Then **2q** was oxidized by H_2O_2 in the presence of $TaCl_5$, affording β-acetylamino sulfone **3q** in moderate yield without any loss of enantiomeric excess. Starting from **3q**, Apremilast,[9] a drug approved by the FDA in 2014 for treatment of adults

Scheme 2. Synthetic Transformations



patients with active psoriatic arthritis, could be synthesized readily following literature procedures.[10] In addition, in order to determine the absolute configuration of the product, **3a** was prepared by oxidation of **2a**[11] (Scheme 2, eq 2). The absolute configuration of **2a** was confirmed to be S by comparing the optical rotation of **3a** with the known literature value.[12]

In summary, we have developed an efficient approach for asymmetric hydrogenation of β-acetylamino vinylsulfides to generate chiral β-acetylamino sulfides. Using Rh/(*Sc,Rp*)-DuanPhos as a catalyst, a series of β-acetylamino vinylsulfides could be hydrogenated smoothly to give the desired products in high yields with excellent ee's. In addition, an effective and concise synthetic route to Apremilast was developed. Further investigations on asymmetric hydrogenation of functionalized enamides are underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01115.

Experimental details and characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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