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Rhodium-Catalyzed Asymmetric Hydrogenation of β-Acetylamino Acrylosulfones: A Practical Approach to Chiral β-Amido Sulfones

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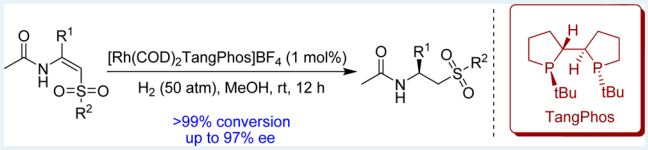
Supporting Information

ABSTRACT: The efficient and highly enantioselective catalytic asymmetric hydrogenation of β-acetylamino acrylosulfone has been achieved by employing Rhodium-TangPhos as catalyst. A series of β-amido sulfone products are obtained with excellent yields and good enantioselectivities.



KEYWORDS: *asymmetric hydrogenation, enantioselectivity, rhodium, β-amido sulfones, diphosphine ligand*

Chiral β-amido sulfones are privileged scaffolds found in many natural products and biologically active compounds (Figure 1).[1] The β-amido sulfones can be readily transformed

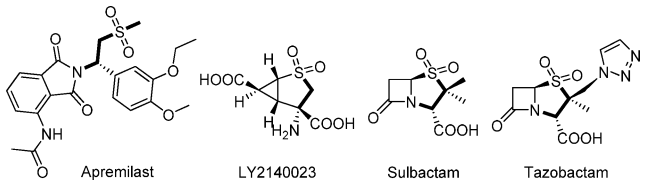
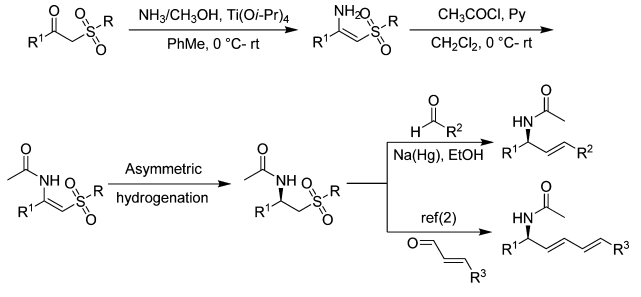


Figure 1. Examples of natural products containing β-amido sulfone scaffolds.

to chiral amino acids,[2] amino alcohols,[3] alkaloids,[4] carbohydrate derivatives,[5] and other functionalized chiral amines.[6] For example, the Julia–Lythgoe olefination of β-amido sulfones can be utilized to generate various kinds of chiral allylic amines (Scheme 1). Therefore, the synthesis of β-amido sulfones has

Scheme 1. Synthesis of Chiral β-Amido Sulfones through Hydrogenation of Enamides and Their Derivatizations



received considerable attention. The most applied approach to β-amido sulfones is multistep transformations of amino acids; in addition, several other interesting methodologies, including stereoselective additions of sulfonyl carbanions to chiral *N*-sulfinyl imines[7] and aza-Michael additions to α,β-unsaturated sulfones.[8] However, most of these approaches require expensive chiral auxiliaries or afford low diasteroselectivities. The catalytic enantioselective synthesis of β-amido sulfones is far less established.

Asymmetric hydrogenation represents one of the most efficient approaches to generate chiral compounds through the reduction of prochiral olefins, ketones, and imines[9] utilizing molecular hydrogen. The hydrogenation of enamides has been widely used in the synthesis of chiral amines and their derivatives;[9,10] however, functionalized enamides, such as β-amido sulfones, are rarely used in an asymmetric hydrogenation reaction. In connection with our previous research on the chiral phosphine ligands for asymmetric hydrogenation, herein, we report the synthesis of chiral β-amido sulfones through the asymmetric hydrogenation of enamide-possessing sulfone groups.

So far, the preparation of β-acetylamino acrylosulfone substrates relies on several known methods, such as a rearrangement reaction,[11] reduction of nitro alkenes[12] or ketoximes,[13] the acylation of imines,[14] and the direct condensation of ketone with amide.[15] We adopted the condensation method because of the acceptable yields and readily available starting materials. The condensation reaction between a ketone and ammonia provided the N-unsubstituted enamine[16] as an intermediate, which reacted with acetyl chloride to give the target product with *Z* and *E* isomers, as shown in Table 1. *Z* isomers were, in most cases, a little more numerous than *E* isomers, possibly because of the presence of the stronger intramolecular N–H···O(S) hydrogen bonding interaction (Table 1, entries 1–12). When R^1 was cyclohexyl or thienyl group, only the *Z* isomer was obtained (Table 1, entries 13–14). It might be attributed to the combination of a steric and an electronic effect, which strengthen the intramolecular N–H···O(S) hydrogen bonding interaction. The X-ray structure of (*E*)-**2a** is shown in Figure 2.

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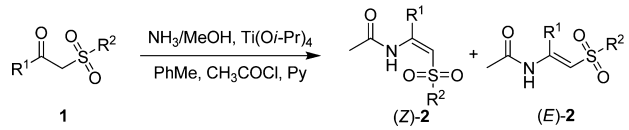
Table 1. Preparation of β-Acetylamino Acrylosulfones



entry	ketone[a]	R_1	R_2	enamide	Z/E[b]	Z/E (%)[c]	combined yield (%)[d]
1	1a	Ph	Me	2a	55:45	40/33	73
2	1b	*m*-MePh	Me	2b	47:53	29/32	61
3	1c	*p*-MePh	Me	2c	60:40	35/23	58
4	1d	*p*-MeOPh	Me	2d	56:44	33/26	59
5	1e	*p*-FPh	Me	2e	52:48	32/29	61
6	1f	*m*-FPh	Me	2f	41:59	23/32	55
7	1g	*p*-ClPh	Me	2g	50:50	34/33	67
8	1h	*m*-ClPh	Me	2h	50:50	26/26	52
9	1i	*p*-BrPh	Me	2i	63:37	41/25	66
10	1j	*p*-tBuPh	Me	2J	67:33	47/24	71
11	1k	Ph	Ph	2k	75:25	55/18	73
12	1l	*p*-CF_3Ph	Me	2l	56:44	30/23	53
13	1m	cyclohexyl	Me	2m	100:0	46/0	46
14	1n	2-thienyl	Me	2n	100:0	41/0	41

[a]See the Supporting Information for their preparation. [b]The Z/E ratios of the crude reaction mixture were estimated by ^{1}H NMR spectroscopy analysis. [c]Isolated yields of Z and E isomers by silica gel column chromatography, respectively. [d]Combined yield of isolated Z and E isomers.

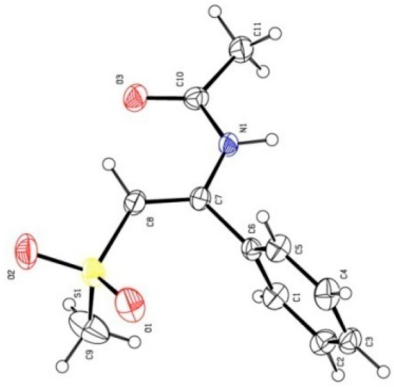
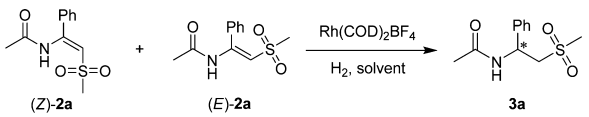


Figure 2. X-ray crystal structure of (*E*)-**2a**.

Table 2. Solvent and Ligand Screening for Rh-Catalyzed Asymmetric Hydrogenation of (*Z*)-2a and (*E*)-2a[a]



entry	subtrate	ligand[b]	solvent	conv (%)	ee (%)[c]
1	(*Z*)-**2a**	L1	MeOH	>99	92
2	(*Z*)-**2a**	L2	MeOH	>99	63
3	(*Z*)-**2a**	L3	MeOH	>99	57
4	(*Z*)-**2a**	L4	MeOH	>99	74
5	(*Z*)-**2a**	L5	MeOH	>99	81
6	(*Z*)-**2a**	L6	MeOH	>99	31
7	(*Z*)-**2a**	L7	MeOH	>99	25
8	(*Z*)-**2a**	L8	MeOH	>99	34
9	(*Z*)-**2a**	L1	EtOAc	>99	92
10	(*Z*)-**2a**	L1	EtOH	>99	89
11	(*Z*)-**2a**	L1	dioxane	>99	88
12	(*Z*)-**2a**	L1	CH_2Cl_2	trace	
13	(*E*)-**2a**	L1	MeOH	58	−27
14	(*E*)-**2a**	L2	MeOH	12	−29
15	(*E*)-**2a**	L3	MeOH	31	−19
16	(*E*)-**2a**	L4	MeOH	37	−70
17	(*E*)-**2a**	L5	MeOH	24	−43
18[d]	(*E*/*Z*)-**2a**	L1	MeOH	99	31

[a]All reactions were carried out with a substrate/catalyst ratio of 100:1 at room temperature under 50 atm hydrogen pressure for 12 h. [b]L1 = (1*S*,1*S*′,2*R*,2*R*′)-TangPhos, L2 = (*Sc*,*Rp*)-DuanPhos, L3 = (*S*)-Binapine, L4 = (*S*)-SegPhos, L5 = (*S*)-BINAP, L6 = WalPhos, L7 = (*R*,*S*)-JosiPhos, L8 = (*R*)-QuinoxP*. [c]The ee value was determined by HPLC on a chiral phase. [d]The ratio of (*E*)-**2a**/(*Z*)-**2a** was 1:1.

After the synthesis of β-acetylamino acrylosulfones (*Z*)-**2** and (*E*)-**2**, they were used as the substrates for the hydrogenation reaction to screen the reaction conditions; the results are summarized in Table 2. A variety of diphosphine ligands developed by our group and some commercially available chiral ligands were examined (Figure 3).

Although all these ligands can efficiently promote the hydrogenation of (*Z*)-**2a** with almost quantitative conversion, only electron-rich, rigid TangPhos affored good ee values (Table 2, entries 1−8). Solvent screening shows that methanol was the best solvent we chose(Table 2, entries 1, 9−12). The reactions of (*E*)-**2a** with different ligands resulted in only low to moderate conversions and opposite enantioselectivities (Table 2, entries 13−17), which indicated that the configuration of the double bond in substrates **2** played a critical role.[17] When the mixture of *Z* and *E* isomers ((*E*)-**2a**/(*Z*)-**2a** = 1:1) was used for the hydrogenation, it afforded only β-amido sulfone with 33% ee (Table 2, entry 18).

Inspired by these promising results of the hydrogenation of (*Z*)-**2a** catalyzed by $Rh(COD)_2BF_4$−TangPhos, the hydrogen pressure and reaction temperature were examined as shown in Table 3. The enantioselectivities gradually improved when the hydrogen pressure increased from 4 to 30 atm (Table 3, entries 1−3), but with a further increase in the pressure, there was no positive effect on the ee value (Table 3, entries 3−5). Lowering the reaction temperature to 0 °C resulted in a dramatic decrease in the reactivity, and and increase in the temperature

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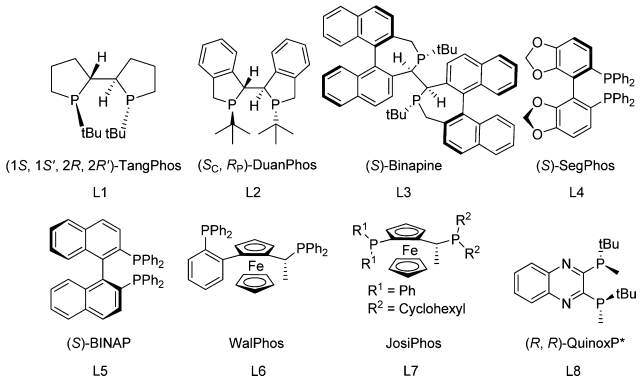


Figure 3. Structures of the phosphine ligands for hydrogenation of (*Z*)-**2a** and (*E*)-**2a**.

Table 3. Pressure and Temperature Screening for Rh-Catalyzed Asymmetric Hydrogenation of (Z)-2a[a]

entry	pressure (atm)	temp (°C)	conv (%)	ee (%)
1	4	25	>99	80
2	10	25	>99	86
3	30	25	>99	91
4	50	25	>99	92
5	80	25	>99	91
6	50	0	21	93
7	50	50	>99	86
8	50	100	>99	75

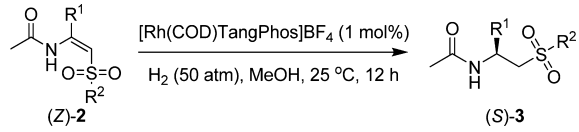
[a]All reactions were carried out with a substrate/Rh-TangPhos catalyst ratio of 100:1 in MeOH for 12 h.

led to a decrease in the enantioselectivity (Table 3, entries 4, 6−8).

Under the optimized conditions, a variety of *β*-acetylamino acrylosulfones (*Z*)-**2** were examined, and the results are summarized in Table 4. Excellent yields and good to excellent enantioselectivities were achieved when R^1 was different substituted aryl groups (84−94% ee; Table 4, entries 1−12). When R^2 was changed from alkyl to aryl, a better enantioselectivity was obtained (97% ee; Table 4, entry 11). This might be attributed to the steric hindrance of an aryl group, which can enhance the enantioselectivity. Good enantioselectivity was also achieved when R^1 was a heteroaryl group (91% ee; Table 4, entry 14); however, when both R^1 and R^2 are alkyl groups, it did not give satisfactory results (Table 4, entry 13). The absolute configuration of product **3a** was confirmed to be *S* by X-ray crystal structure analysis, as illustrated in Figure 4.[18]

In summary, we have developed a novel asymmetric hydrogenation approach for the generation of chiral *β*-amido sulfones from *β*-acetylamino acrylosulfones. The hydrogenation of substrates with *Z* configuration gave the the desired products in excellent yields with good to excellent enantioselectivities. It is believed that this strategy will provide a novel way for the development of synthetic strategies for chiral *β*-amido sulfones. Further investigations to improve the enantioselectivity and extending the substrate scope of this reaction are underway in our laboratory.

Table 4. Rh-Catalyzed Asymmetric Hydrogenation of *β*-Acetylamino Acrylosulfones (Z)-2[a]



entry	substrate	R^1	R^2	product	conv (%)[b]	ee (%)[c]
1	(*Z*)-**2a**	Ph	Me	**3a**	>99 (95)	92
2	(*Z*)-**2b**	*m*-MePh	Me	**3b**	>99 (96)	90
3	(*Z*)-**2c**	*p*-MePh	Me	**3c**	>99 (96)	89
4	(*Z*)-**2d**	*p*-MeOPh	Me	**3d**	>99 (95)	87
5	(*Z*)-**2e**	*p*-FPh	Me	**3e**	>99 (95)	84
6	(*Z*)-**2f**	*m*-FPh	Me	**3f**	>99 (94)	94
7	(*Z*)-**2g**	*p*-ClPh	Me	**3g**	>99 (94)	94
8	(*Z*)-**2h**	*m*-ClPh	Me	**3h**	>99 (95)	94
9	(*Z*)-**2i**	*p*-BrPh	Me	**3i**	>99 (94)	95
10	(*Z*)-**2j**	*p*-tBuPh	Me	**3j**	>99 (95)	87
11	(*Z*)-**2k**	Ph	Ph	**3k**	>99 (95)	97
12	(*Z*)-**2l**	*p*-CF_3Ph	Me	**3l**	>99 (96)	96
13	(*Z*)-**2m**	cyclohexyl	Me	**3m**	>99 (96)	23
14	(*Z*)-**2n**	2-thienyl	Me	**3n**	>99 (95)	91

[a]Unless mentioned otherwise, all reactions were carried out with a substrate/catalyst ratio of 100:1 in MeOH at room temperature under 50 atm hydrogen pressure for 12 h. [b]Determined by ^{1}H NMR; data in parentheses are the yields of the isolated product based on consumed starting material. [c]Determined by chiral HPLC analysis.

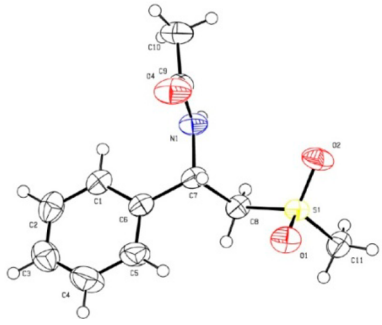


Figure 4. X-ray crystal structure of (*S*)-**3a**

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

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Notes

The authors declare no competing financial interest.

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(18) The X-ray crystal data of (*E*)-**2a** and (*S*)-**3a** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication on CCDC 961623 and CCDC 961624, respectively. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: +44 (1223) 336033 or E-mail: deposit@ccdc.cam.ac.uk].