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Rh(I)-Catalyzed Enantioselective Hydrogenation of (*E*)- and (*Z*)-*β*-(Acylamino)acrylates Using 1,4-Bisphosphine Ligands under Mild Conditions

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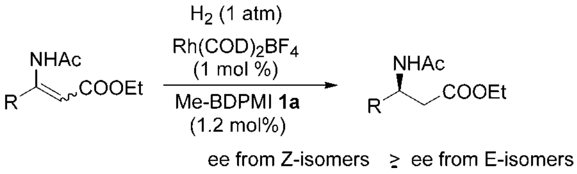
ABSTRACT



Rh−Me-BDPMI (1a) complex can be an effective catalyst for the hydrogenations of (*E*)- and (*Z*)-*β*-(acylamino)acrylates, in which the *Z*-isomers hydrogenated with the same or even higher ee values than the corresponding *E*-isomers. The conversion yield and enantioselectivity of *E*- and *Z*-isomers were largely dependent on the solvent, and thus, the *E*-isomers were hydrogenated more effectively in CH_2Cl_2, whereas the *Z*-isomers were hydrogenated more effectively in polar MeOH solvent.

Optically pure *β*-amino acids are crucial structural features of numerous biologically active natural products as well as important building blocks for the synthesis of *β*-peptides and *β*-lactam antibiotics.[1] Several stoichiometric chiral auxilaries and catalytic methods have been developed to make chiral *β*-amino acids.[2] Among these methods, catalytic asymmetric hydrogenation of *β*-dehydroamino acid derivatives potentially offers one of the most convenient routes. However, in striking contrast to α-amino acids, only a few chiral bisphosphine−metal complexes (i.e., Rh(I) complexes of BPPM,[3] BICP,[4] and DuPhos[4,5] and MiniPhos[6] and Ru(II) complex of BINAP[7]) have been applied as catalysts for the asymmetric hydrogenation of *β*-acylamino acrylates. Moreover, the intrinsic problem consists of the different catalytic behaviors attributed to *Z*- and *E*-isomeric substrates. In general, an *E*-isomer hydrogenated with higher enantioselectivity than the corresponding *Z*-isomer. For examples, the Ru−BINAP catalyst hydrogenated the (*E*)-methyl 3-acetamido-2-butenoate (*E*)-**2a** in 96% ee, while its *Z*-isomer, (*Z*)-**2a**, hydrogenated in only 5% ee with a different configuration.[7] Recently, Zhang et al. reported an important breakthrough on the

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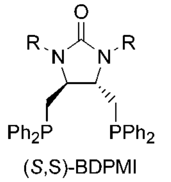
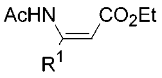
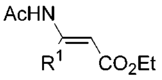
enantioselective hydrogenation of (*Z*)-alkyl 3-acetamido-2-butenoates with Rh(I)−BICP complex. In the reduction of (*E*)-**2a** and (*Z*)-**2a**, 96% ee and 88% ee, respectively, were observed in nonpolar toluene solvent.[4] It has been also reported that the rate of hydrogenation of (*Z*)-**2a** using Rh(I)−Me-DuPhos catalyst was dramatically increased in a polar MeOH solvent.[5] Nevertheless, the enantioselectivity obtained from (*Z*)-**2a** (87.8% ee) was still lower than that obtained from (*E*)-**2a** (98.2% ee). Therefore, the development of a catalytic system exhibiting high enantioselectivity for (*Z*)-**2**, which formed as a major isomer in most synthetic protocols, is important. Here, we report enantioselective hydrogenation of ethyl (*E*)- and (*Z*)-*β*-(acylamino)acrylates **2** using Rh(I)−(*S*,*S*)-BDPMI **1a**, in which the *Z*-isomers provided the same or even higher ee values than the corresponding *E*-isomers.



(*S*,*S*)-BDPMI
1a: R = Me, **1b**: R = H



(*Z*)-2

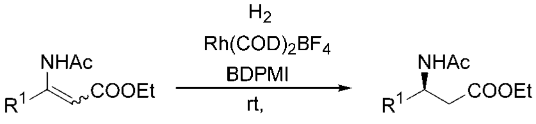


(*E*-)-2

a: R^1 = Me
b: R^1 = Et
c: R^1 = *i*-Pr
d: R^1 = *i*-Bu
e: R^1 = Ph

Quite recently, we have demonstrated that Rh(I) complexes of 1,4-bisphosphine ligands bearing an imidazolidin-2-one backbone ((*S*,*S*)-BDPMI **1a**) are highly enantioselective catalyst for hydrogenation of an isomeric mixture of *E*- and Z-enamides.[8] Zhang's Rh(I)−BICP[9] and Burk's Rh(I)−DuPhos[10] catalysts also effectively hydrogenated an isomeric mixture of *Z*/*E*-enamides. Prompted by these results, we have applied the Rh(I)−BDPMI catalyst to hydrogenation of ethyl 2-acylaminoacrylates **2a**−**e**, which can be conveniently made according to the reported procedure.[3,7] The *E*- and *Z*-isomers of **2a**−**d** can be separated by silica gel column chromatography except **2e**. To search for the optimal conditions, we have examined the hydrogenation of ethyl (*E*)- and (*Z*)-3-acetoamido-2-butenoate (**2a**) using 1 mol % of [Rh((*S*,*S*)-Me-BDPMI (**1a**)(COD))BF_4] as precatalyst in various organic solvents under 14.7 and 100 psi of H_2 pressure (Table 1). We were very pleased to find that the *Z*-isomer of **2a** was hydrogenated with almost the same or even higher enantioselectivity than those obtained from the *E*-isomer of **2a**. It is important to note that the conversion yields of (*E*)-**2a** and (*Z*)-**2a** were largely dependent on the solvent used and H_2 pressure. For instance, (*E*)-**2a** could be hydrogenated completely using Rh-**1a** catalyst in CH_2Cl_2 solvent at both 14.7 psi (94.6% ee, entry 1) and 100 psi (93.2% ee, entry 2) of H_2 pressures in high enantioselectivities. However, the corresponding *Z*-isomer, (*Z*)-**2a**, was hydrogenated at 14.7 psi in only 66.1% conversion yield, but the same enantioselectivity (94.6% ee, entry 3) with (*E*)-**2a** was observed. As the H_2 pressure was increased, both the conversion (100%) and enantioselectivity (95.0% ee) increased (entry 4). *This is the first asymmetric hydrogenation of (Z)-β-(acylamino)acrylates exhibiting higher enantioselectivity than the corresponding E-isomers.* In THF solvent, both (*E*)- and (*Z*)-**2a** were not completely converted at 14.7 and 100 psi of H_2 pressures, but the enantioselectivity of (*Z*)-**2a** was still higher than those obtained from (*E*)-**2a** (compare entries 5 vs 7 and 6 vs 8). Similar catalytic activities were observed in acetone and *i*-PrOH solvents at 14.7 psi, but the conver-

Table 1. Rh-BDPMI-Catalyzed Asymmetric Hydrogenation of (*E*)- and/or (*Z*)-**2**[a]



2 **3**

entry	ligand	**2**	solvent	*p* (psi)	time (h)	convn[b] (%)	% ee[c] (conf)[d]
1	**1a**	(*E*)-**2a**	CH_2Cl_2	14.7	12	100	94.6 (*R*)
2	**1a**	(*E*)-**2a**	CH_2Cl_2	100	4	100	93.2 (*R*)
3	**1a**	(*Z*)-**2a**	CH_2Cl_2	14.7	12	66.1	94.6 (*R*)
4	**1a**	(*Z*)-**2a**	CH_2Cl_2	100	4	100	95.0 (*R*)
5	**1a**	(*E*)-**2a**	THF	14.7	12	11.1	94.1 (*R*)
6	**1a**	(*E*)-**2a**	THF	100	4	58.4	92.3 (*R*)
7	**1a**	(*Z*)-**2a**	THF	14.7	12	21.0	97.4 (*R*)
8	**1a**	(*Z*)-**2a**	THF	100	4	86.4	95.3 (*R*)
9	**1a**	(*E*)-**2a**	acetone	14.7	12	94.6	91.0 (*R*)
10	**1a**	(*E*)-**2a**	acetone	100	4	100	92.6 (*R*)
11	**1a**	(*Z*)-**2a**	acetone	14.7	12	57.3	93.4 (*R*)
12	**1a**	(*Z*)-**2a**	acetone	100	4	100	93.2 (*R*)
13	**1a**	(*E*)-**2a**	IPA	14.7	12	58.8	94.3 (*R*)
14	**1a**	(*E*)-**2a**	IPA	100	4	100	92.6 (*R*)
15	**1a**	(*Z*)-**2a**	IPA	14.7	12	44.4	95.9 (*R*)
16	**1a**	(*Z*)-**2a**	IPA	100	4	100	90.8 (*R*)
17	**1a**	(*E*)-**2a**	MeOH	14.7	12	100	92.3 (*R*)
18	**1a**	(*E*)-**2a**	MeOH	100	4	100	91.5 (*R*)
19	**1a**	(*Z*)-**2a**	MeOH	14.7	12	100	94.6 (*R*)
20	**1a**	(*Z*)-**2a**	MeOH	100	4	100	91.3 (*R*)
21[e]	**1a**	(*E*/*Z*)-**2a**	CH_2Cl_2	14.7	12	52.0	95.1 (*R*)
22[e]	**1a**	(*E*/*Z*)-**2a**	CH_2Cl_2	100	4	100	92.6 (*R*)
23[e]	**1a**	(*E*/*Z*)-**2a**	MeOH	14.7	12	100	93.4 (*R*)
24	**1b**	(*E*)-**2a**	CH_2Cl_2	14.7	12	100	87.0 (*R*)
25	**1b**	(*Z*)-**2a**	MeOH	14.7	12	100	70.1 (*R*)
26	(*S*,*S*)-DIOP	(*E*)-**2a**	CH_2Cl_2	14.7	12	100	83.7 (*R*)
27	(*S*,*S*)-DIOP	(*Z*)-**2a**	MeOH	14.7	12	100	33.3 (*R*)
28	**1a**	(*E*)-**2b**	CH_2Cl_2	14.7	12	100	94.0 (*R*)
29	**1a**	(*Z*)-**2b**	MeOH	14.7	12	100	94.0 (*R*)
30[e]	**1a**	(*E*/*Z*)-**2b**	MeOH	14.7	12	100	93.0 (*R*)
31	**1a**	(*E*)-**2c**	CH_2Cl_2	14.7	12	100	92.0 (*S*)
32	**1a**	(*Z*)-**2c**	MeOH	14.7	12	100	91.9 (*S*)
33[e]	**1a**	(*E*/*Z*)-**2c**	MeOH	14.7	12	100	91.2 (*S*)
34[f]	**1a**	(*E*)-**2d**	CH_2Cl_2	14.7	12	100	90.3 (*R*)
35[f]	**1a**	(*Z*)-**2d**	MeOH	14.7	12	100	90.1 (*R*)
36[e,f]	**1a**	(*E*/*Z*)-**2d**	MeOH	14.7	12	100	89.4 (*R*)
37[g]	**1a**	(*E*/*Z*)-**2e**	MeOH	40	12	100	75.6 (*S*)

[a] $[Rh(COD)_2]BF_4$/ligand/substrate = 0.01:0.012:1. [b] Determined by ^1H NMR. [c] Determined by chiral GC using CP-Chirasil-Dex CB column. [d] Determined by comparing the sign of optical rotations with that of the reported ones.[4] [e] *E*/*Z* = 1:1. [f] Determined by chiral HPLC using Daicel Chiracel OD-H column. [g] *E*/*Z* = 1:1.7.

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sions were completed when the H_2 pressure was increased to 100 psi (entries 9−16). Interestingly, both of (*E*)-and (*Z*)-**2a** were completely hydrogenated in MeOH at 14.7 psi [(*E*)-**2a**: 92.3% ee, entry 17; (*Z*)-**2a**: 94.6% ee, entry 19] and 100 psi (entries 18 and 20) within 12 and 4 h, respectively. However, a 1:1 mixture of (*E*)/(*Z*)-**2a** was hydrogenated in CH_2Cl_2 at 14.7 psi in only 52% of conversion with 95.1% ee (entry 21). In ^1H NMR analysis, the remained starting material was the *Z*-isomer, indicating that the *E*-isomer is more reactive in CH_2Cl_2 solvent. When the same reaction was conducted at 100 psi of H_2 pressure, the conversion was completed, but the ee value decreased to 92.6% (entry 22). In contrast to the reaction in CH_2Cl_2, the hydrogenation of a 1:1 mixture of (*E*)/(*Z*)-**2a** in MeOH proceeded completely at 14.7 psi with 93.4% ee (entry 23). This ee value corresponds to the mean value of the individual hydrogenations of (*E*)-**2a** and (*Z*)-**2a** in MeOH solvent. These results suggested that the hydrogenation of (*E*)-**2a** in CH_2Cl_2 solvent became more effective, whereas the hydrogenation of (*Z*)-**2a** in polar MeOH solvent was more effective. Although the reason for the superiority of MeOH for the hydrogenation of the *Z*-isomer is not clear yet, the intramolecular hydrogen bond between the NH of acylamide and the carbonyl oxygen of ester in (*Z*)-*β*-(acylamino)acrylates, which prevents the desired bidentate coordination of the substrate to the metal as pointed by Noyori,[7] may be broken down easily in MeOH solvent and thus allow the olefin to coordinate at the metal center. We next examined the catalytic activities of Rh(I)−(*S*,*S*)-**1b** and Rh(I)−(*S*,*S*)-DIOP complexes for the hydrogenation of (*E*)-**2a** in CH_2Cl_2 and (*Z*)-**2a** in MeOH solvents at 14.7 psi of H_2 pressure. Both (*E*)-**2a** and (*Z*)-**2a** were completely converted to **3a** with low to moderate enantioselectivities (entries 24−27). The enantioselectivity difference between the ee values obtained from hydrogenations of (*E*)- and (*Z*)-**2a** using ligand **1b** (entries 24 and 25) is much smaller than the that obtained using (*S*,*S*)-DIOP ligand (entries 26 and 27). However, like other catalytic systems, both of these catalysts hydrogenated (*E*)-**2a** with higher enantioselectivities than the (*Z*)-**2a**.

A variety of *E*- and *Z*-isomers of ethyl *β*-alkyl-*β*-(acylamino)acrylates (**2b**−**d**) and a 1:1.7 mixture of (*E*)/(*Z*)-*β*-phenyl-*β*-(acylamino)acrylate (**2e**), which cannot be separated by silica gel column chromatography, were hydrogented using 1 mol % of Rh(I)−Me-BDPMI (**1a**) complex (entries 28−37). For *E*-isomers and *Z*-isomers, CH_2Cl_2 and MeOH solvents, respectively, and MeOH solvent for a mixture of *E*/*Z*-isomers have been used. High enantiomeric excesses have been achieved with both of the (*E*)- and (*Z*)-*β*-alkyl-*β*-(acylamino)acrylates **2a**−**d**. Compared to the ee values obtained from individual hydrogenations of *E*- and *Z*-isomers, slightly decreased enantioselectivity was observed in the hydrogenation of a 1:1 mixture of *E*/*Z*-isomer, which may be due to the decreased enantioselectivity of *E*-isomer in MeOH solvent. It has been also found that the enantioselectivity was slightly decreased as the size of *β*-alkyl substituent was increased. Moreover, as found by Zhang with Rh−BICP catalyst, the sense of enantioselection observed for all *E*-isomers is the same as that for *Z*-isomers.[4] Mechanistic studies by Imamoto with Rh-complexes of BisP* and MiniPhos on the hydrogenation of enamides and (*E*)-*β*-alkyl-*β*-(acylamino)acrylates indicated that the first hydrogen atom is transferred to the α-position yielding monohydrides with a *β*-carbon atom bound to rhodium.[6,11] Therefore, it could be expected that the sense of enantioselection in Rh-catalyzed hydrogenation of *β*-alkyl-*β*-(acylamino)acrylates **2a**−**d** is not strongly dependent on their *E*/*Z* geometry.

In contrast to the *β*-alkyl-substituted prochiral compounds **2a**−**d**, the *β*-phenyl-substituted substrate **2e** was hydrogenated under 40 psi of H_2 pressure in only moderate enantioselectivity (75.6% ee, entry 37). It is notorious that the enantioselectivities obtained from the hydrogenation of *β*-aryl-*β*-(acylamino)acrylate such as **2e** are not higher than the *β*-alkyl-*β*-(acylamino)acrylates. During preparation of this manuscript, Zhang reported highly effective chiral ortho-substituted BINAP ligands (*o*-BINAPO), which showed extremely high enantioselectivities in Ru-catalyzed asymmetric hydrogenations of a mixture of (*E*)- and (*Z*)-*β*-aryl-*β*-(acylamino)acrylates.[12]

In summary, we have found that Rh-Me-BDPMI (**2a**) complex can be an effective catalyst for the hydrogenations of (*E*)- and (*Z*)-*β*-(acylamino)acrylates in which the *Z*-isomers provided the same or even the higher ee values than the corresponding *E*-isomers. The conversion yields of *E*- and *Z*-isomers were largely dependent on the solvent. The *E*-isomers were hydrogenated in CH_2Cl_2 solvent more effectively, whereas the *Z*-isomers were hydrogenated in polar MeOH solvent. The Rh−Me-BDPMI catalyst is especially effective for hydrogenation of a 1:1 mixture of (*E*)/(*Z*)-*β*-alkyl-*β*-(acylamino)acrylates. The highly enantioselective hydrogenation provides a useful way to prepare *β*-alkyl substituted *β*-amino acids. Further study with other enamides, especially *β*-aryl-*β*-(acylamino)acrylates using other transition metal complexes of BDPMI ligands, will be explored.

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Supporting Information Available: Experimental procedures for the syntheses of **2a**−**e** and the asymmetric hydrogenation. GC and HPLC chromatograms to determine enantiomeric excesses of **3a**−**e**. This material is available free of charge via the Internet at http://pubs.acs.org.

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