Enantioselective Hydrogenation of (E)-and (Z)-Isomeric Ethyl 3-Acetamidobutenoates with Rh-Bisphosphine Complexes: Effects of Substrate Geometry and Solvents on Reaction Rates and Catalyst Reusability

Yong Jian Zhang,[†] and Eun Joo Rho, and Sang-gi Lee[*]

Life Sciences Division, Korea Institute of Science and Technology, Seoul 130-650, Korea. [*]E-mail: sanggi@kist.re.kr
[†]School of Chemistry and Chemical Technology, Shanghai Jiao Tong University, Shanghai 200240, P. R. China
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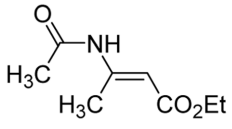
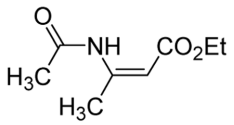
Enantiopure β-amino acids are crucial structural features of numerous biologically active natural products as well as important building blocks for the synthesis of β-peptides and β-lactam antibiotics.[1] Numbers of stoichiometric chiral auxilaries and catalytic methods have been developed to make chiral β-amino acids.[2] One of the most promising processes for the convenient preparation of chiral β-amino acids on large scale is the asymmetric hydrogenation of suitable unsaturated precursors such as β-acetamido acrylates with Rh(I) catalysts bearing chiral phosphine ligands. The requisite prochiral substrates are easily available by treatment of β-keto carboxylates with NH_4OAc and subsequent acylation. However, while literally thousands of reports are concerned with the Rh-catalyzed enantioselective hydrogenation of related prochiral α-acetamido acrylates, only a few devoted to the hydrogenation of β-analogues as substrates exist.[3] The main reason for this is probably different behavior in the asymmetric hydrogenation, which had for a long time been attributed to particular substrates such as the isomeric ethyl 3-acetoamido butenoates (*E*)-**1** and (*Z*)-**1**.

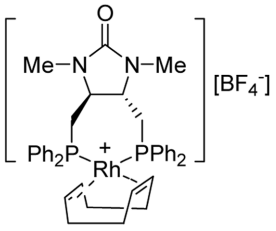


(*E*)-**1**

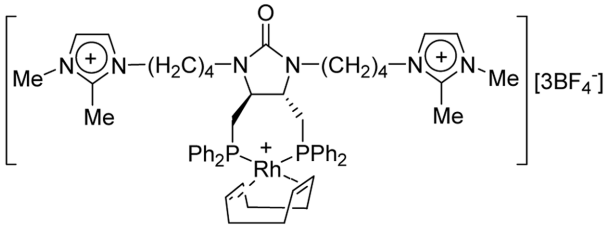


(*Z*)-**1**

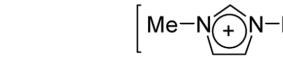
Both isomers are produced simultaneously in most synthetic procedures and their individual hydrogenation demands prior separation. Moreover, most reports suggest that the hydrogenation of *Z*-isomers requires much higher hydrogen pressures and longer reaction times than the reduction of their E analogues and gives inferior enantioselectivity. Recently, we showed for the first time that Rh-Me-BDPMI (**2**)[4] 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.[5] 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 in polar MeOH solvent. In order to understand this important catalytic transformation in more detail, we investigated the effects of solvent on reaction rate using Rh-complex of Me-BDPMI **2**. We also studied the reusability of the catalysts in an ionic liquid, [bmim][SbF_6], for asymmetric hydrogenation of isomeric ethyl 3-acetoamido butenoates (*E*)-**1** and (*Z*)-**1** using Rh-complexes of Me-BDPMI **2** and ionic liquid-grafted BDPMI, ILG-BDPMI **3**, which has been designed and used for the asymmetric hydrogenation of simple *N*-acetyl-β-arylenamides in ionic liquids.[6] Room temperature molten salts (ionic liquids), especially 1-*n*-butyl-3-methylimidazolium (bmim) salts, emerged recently as a potential solvent for catalyst immobilization in catalytic processes. The decisive advantages of ionic liquids over other immobilization systems such as aqueous or fluorous phases with respect to activity, selectivity and re-usability are well documented.[7]



(S,S)-Me-BDPMI (**2**)



(S,S)-ILG-BDPMI (**3**)



1-Buthyl-3-methylimidazolium hexafluoro antimoate
[bmim][SbF_6]

Recently, Heller and Bruneau studied the effects of H_2 pressure and reaction temperature on the catalytic activity in asymmetric reduction of E and Z isomeric methyl 3-acetamidobutenoates with Rh(I)-bisphsophine complexes, and found that the highest enantioselectivities can be achieved for the hydrogenation of both isomeric substrates at room temperature and below, whereas the fastest conversion takes place at 30-50 °C.[8] However, as we showed recently, the reactivity of the isomeric substrates are largely dependent on the solvent.[5] To investigate the effects of solvent on reaction rate in the hydrogenation of isomeric ethyl 3-acetoamido butenoates (*E*)-**1** and (*Z*)-**1**, both isomeric substrates was hydrogenated separately in various solvent (1 M solution) using 1 mol% of Rh-Me-BDPMI **2** under 1 atm of H_2 pressure at 25 °C for 30 min, and the reaction was monitored by ^{1}H NMR. As shown in Figure 1, the reaction rate of the isomeric substrates was largely dependent on the solvent. In non-polar solvent, CH_2Cl_2, both *E*-**1** and *Z*-**1** hydrogenated slowly, and the *E*-**1** was hydrogenated faster than the *Z*-**1** as generally known (Figure 1a). When the reaction time was prolonged to 12 h, the *E*-**1** was completely converted to the product, ethyl (3*R*)-3-acetamido butanoate, with 95% ee. Although, the enantioselectivity and configuration are the same with those from *E*-**1**, the reaction with *Z*-**1** was not completed (only 66% conversion). However, in polar protic solvents such as MeOH and ^{i}PrOH, the *Z*-**1** was hydrogenated faster than the *E*-**1**. Especially, in MeOH solvent, the *E*-**1** and *Z*-**1** isomers were hydrogenated with quite different reaction rate, and thus, over 90% of the starting *Z*-**1** was converted to the hydrogenated product within 5 min and completely converted within 20 min with 95% ee. In contrast, only 23% of *E*-**1** was hydrogenated in 30 min (Figure 1b), but the reaction was completed with 92 % ee when the reaction was carried out for 12 h. Very promising results were observed when the reactions were carried out in ^{i}PrOH solvent, which frequently employed as co-solvent for the reactions conducted in imidazolium cation-based ionic liquids. In ^{i}PrOH, both isomeric *E*-**1** and *Z*-**1** were hydrogenated faster than to the reactions carried out in other solvents. In

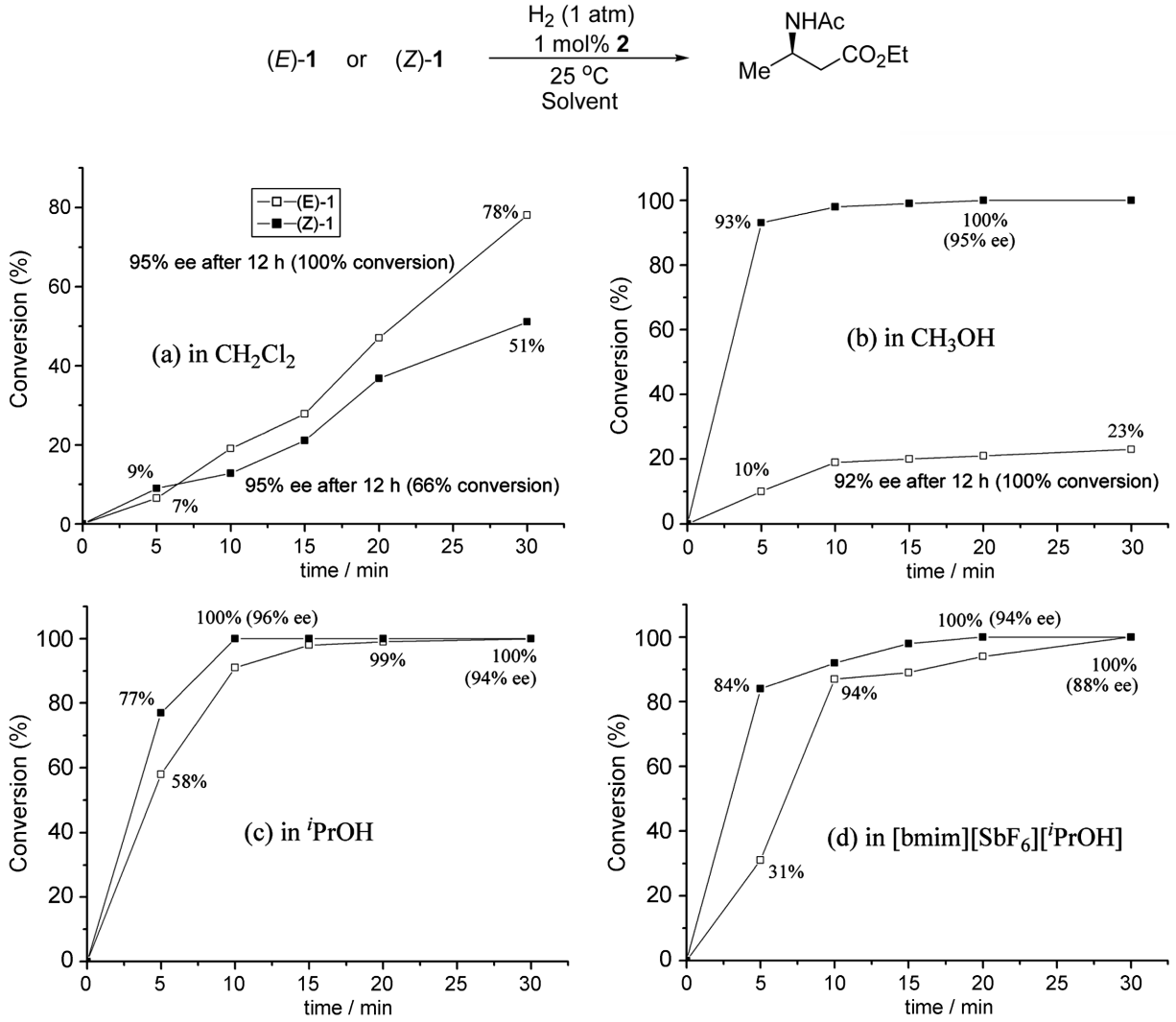
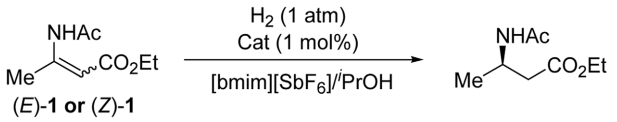


Figure 1. Hydrogenation of (*E*)-**1** and (*Z*)-**1** (0.5 mmol) was carried out in (a) CH_2Cl_2, (b) CH_3OH, (c) ^{i}PrOH, (d) [bmim][SbF_6]/^{i}PrOH (1/2, v/v) using 1 mol% of Rh-Me-BDPMI complex under 1 atm of H_2 pressure at 25 °C. The conversion was determined by ^{1}H NMR analysis.

particular, the *Z*-**1** was hydrogenated completely within 10 min with 96% ee.[9] The less reactive *E*-**1** (generally known as more reactive in non-polar solvents) was also hydrogenated with increased reaction rate compared to the reactions in other solvents, thus, the reaction was completed within 30 min with 94%ee. We also investigated the effects of the ionic liquid, [bmim][SbF_6], on the reaction rate.[10] As shown in Figure 1d, when the reactions were carried out in [bmim][SbF_6]/^{i}PrOH (1/2, v/v) co-solvent, both *E*-**1** and *Z*-**1** showed decreased reaction rates compared with those in ^{i}PrOH solvent only. Nevertheless, the reactions were completed within 30 min with slightly decreased % ees (88% ee for *E*-**1**, 94% ee for *Z*-**1**). These results suggest that the asymmetric hydrogenation of isomeric *E*-**1** and *Z*-**1** could be carried out in an ionic liquid without any significant deterioration of catalytic efficiencies.

With these results in hand, we next investigated the reusability of the catalyst immobilized in an ionic liquid. For this purpose, the hydrogenation of isomeric (*E*)-**1** and (*Z*)-**1** was conducted at 25 °C for 1 h in an ionic liquid [bmim][SbF_6]/^{i}PrOH co-solvent using 1 mol% of Rh-BDPMI **2** first. After 1 h reaction, the ^{i}PrOH layer was separated and the ionic liquid layer was extracted 3 times with ^{i}PrOH to remove the hydrogenated product and the unreacted starting material if the reaction did not completed, and the catalyst immobilized in ionic liquid reused for the next run. As shown in Table 1 (entries 1-7), although the enantioselectivities were retained, decreased conversion was observed upon re-use of the catalyst immobilized in ionic liquid layer. Interestingly, the catalyst reusability was largely depends on the geometry of the starting substrate. In the case of (*E*)-**1**, the catalytic activity was dramatically decreased in 2nd run (entry 2) whereas it retained in 2nd run for (*Z*)-**1** (entry 5). Similar trend was observed in the hydrogenation with Rh-complex of ionic liquid grafted BDPMI ligand **3** (entries 8-14). Although, compared with Rh-BDPMI **2**, increased reusability has been observed with Rh-ILG-BDPMI **3**, the catalytic activity was also decreased upon reuse. Especially, in the hydrogenation of (*E*)-**1**, the conversions were more significantly decreased. In ICP-AES analysis of the *i*PrOH layer separated from the first runs (entries 8 and 11) with **3**, no Rh (< 1 ppm) and phosphorus (< 3 ppm) were detected under detection limit, which may due to the increased the preferential solubility to ILs by attachment of imidazolium ionic tag. Therefore, the catalyst leaching is not the only reason for the decreased catalytic activity of the catalyst **2** and **3** upon recycling. Although the reason for the substrate dependency of the reusability of the catalyst immobilized in ionic liquid is not clear yet, the active catalytic species or the complexes with the substrates (*E*)-**1** and (*Z*)-**1** may have different stability in ionic liquid.

Table 1. Rh-Catalyzed Asymmetric Hydrogenation of (*E*)-**1** and (*Z*)-**1** in [bmim][SbF_6]/^{i}PrOH using **2** and **3** as catalysts[a]



entry	run	substrate	catalyst	Conv. (%)[b]	%ee[c]
1	1st	(*E*)-**1**	**2**	100	88
2	2nd			39	87
3	3rd			18	86
4	1st	(*Z*)-**1**	**2**	100	94
5	2nf			100	93
6	3rd			61	93
7	4th			36	91
8	1st	(*E*)-**1**	**3**	100	95
9	2nd			87	95
10	3rd			53	95
11	1st	(*Z*)-**1**	**3**	100	90
12	2nf			100	91
13	3rd			83	90
14	4th			71	89

[a]The reaction carried out at 25 °C for 1 h under 1 atm of H_2 pressure using 1 mol% of catalyst prepared in situ from **2** (or **3**) and [$Rh(COD)_2$][BF_4] in [bmim][SbF_6]/^{i}PrOH (1/2, v/v). [b]Determined by ^{1}H NMR. [c]Determined by GC using CP-Chiralsil-Dex-CB column.

In summary, kinetic study for the effects of solvents on catalytic activity in Rh-BDPMI complex-catalyzed asymmetric hydrogenation of (*E*)-and (*Z*)-isomeric ethyl 3-acetamidobutenoates reveals that both isomers were hydrogenated with high reaction rate in protic ^{i}PrOH whereas much lower reaction rate in non-polar CH_2Cl_2 solvent. It has been also found that the reusability of the catalyst immobilized in an ionic liquid is largely depends on the geometry of the prochiral substrates. The superior catalyst reusability has been observed in the hydrogenation of (*Z*)-isomer than in (*E*)-isomer. These results may provide an important insight for the Rh-catalyzed asymmetric hydrogenation of other β-amidoacetylacrylates.

Experimental Section

The Rh complex prepared *in situ* from the ligand **2** (2.8 mg, 3.7×10^{-3} mmol) and [$Rh(cod)_2$]BF_4 (1.3 mg, 3.1×10^{-3} mmol) was dissolved in an ionic liquid, [bmim][SbF_6](1 mL), and a solution of **1** (50 mg, 3.1×10^{-1} mmol) in ^{i}PrOH (2 mL) were added. The mixture was hydrogenated under 1 atmosphere of H_2 pressure at room temperature for 1 h. To determine the conversion and enantioselectivity, the ^{i}PrOH layer was separated, and subjected without any purification into GC equipped with CP-Chirasil-Dex-CB chiral column and ^{1}H NMR. For catalyst recycling, a degassed solution of substrate in ^{i}PrOH was added again to the ionic liquid layer remained in reaction vessel.

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9. In previous study in reference 5, the reaction in ^{i}PrOH did not completed, which has been corrected.
10. [bmim][SbF_6] was selected because of its lower solubility in ^{i}PrOH, which was found in our previous study, see reference 6.