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Highly Efficient Synthesis of Chiral β-Amino Acid Derivatives via Asymmetric Hydrogenation

Wenjun Tang and Xumu Zhang*

Department of Chemistry, The Pennsylvania State University, 152 Davey Laboratory, University Park, Pennsylvania 16802

xumu@chem.psu.edu

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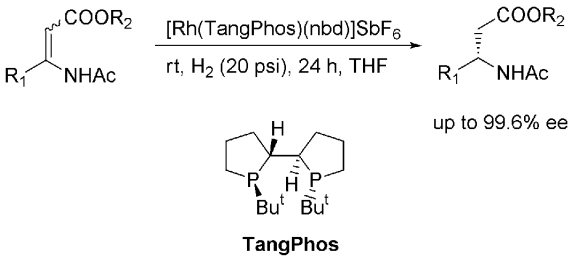
ABSTRACT



The Rh–TangPhos complex is an efficient hydrogenation catalyst for making chiral β-amino acid derivatives. With the Rh–TangPhos system, high enantioselectivities (up to 99.6%) and turnover numbers have been obtained in the hydrogenation of *E*/*Z* isomeric mixtures of both β-alkyl and β-aryl β-(acylamino)acrylates.

The synthesis of chiral β-amino acids has drawn a great deal of attention due to its importance in biomedical research and the pharmaceutical industry. Enantiomerically pure β-amino acids and their derivatives have been used as important building blocks for the synthesis of β-peptides, β-lactam antibiotics, and many important drugs.[1] Although several stoichiometric and catalytic methods have been reported for the synthesis of β-amino acids,[2] a practical and efficient synthesis is still highly desirable. Direct hydrogenation of 3-aminoacrylic acid derivatives represents one of the simplest and most efficient routes. While good to excellent enantioselectivities have been reported in Ru-[3] or Rh-catalyzed[4] asymmetric hydrogenation of (*E*)-β-(acylamino)acrylates derivatives with the use of chiral bisphosphine ligands such as BINAP,[3] BICP,[4] DuPhos,[4b,c] and BisP*,[4a] the results of hydrogenation of (*Z*)-β-(acylamino)acrylates derivatives are less than satisfying.[5] For example, hydrogenation of (*E*)-methyl 3-acetamido-2-butenoate with an Ru−BINAP system gave 96% ee, while (*Z*)-methyl 3-acetamido-2-butenoate gave only 5% ee with the opposite configuration. Since both (*Z*)-

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(5) Lee recently reported a new ligand, BMDPI, which shows good ees for both (*Z*)- and (*E*)-isomeric substrates, see: Lee, S.-G.; Zhang, Y. J. *Org. Lett.* **2002**, *4*, 2429.

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and (*E*)-isomeric substrates are formed simultaneously in most synthetic protocols, the development of a new catalytic system that can work well for both isomeric substrates is needed. This is especially important in the situation where the (*Z*)- and (*E*)-substrates cannot be easily separated and only their mixture can be employed as the starting material. Herein, we disclose a new catalyst, the Rh−TangPhos system, for hydrogenation of β-aminoacrylic acid derivatives. High enantioselectivities have been obtained for both (*Z*)- and (*E*)-isomeric substrates with the Rh−TangPhos system.

We have previously demonstrated that the Rh−TangPhos complexes are highly efficient catalysts for hydrogenation of dehydroamino acids and *E*/*Z* mixtures of enamides.[6] The structure of TangPhos has been confirmed by comparison with the X-ray structure of its corresponding phosphine sufide **1**[7] (Figure 1). To further expand the utility of this electronic-rich phosphine in asymmetric hydrogenation, the Rh−TangPhos system was employed for hydrogenation of both (*Z*)- and (*E*)-isomers of methyl 3-acetamido-2-butenoate. (Table 1) The hydrogenation was conducted at room temperature under 20 psi of H_2 in the presence of 0.5 mol % [Rh(TangPhos)nbd]SbF_6 (nbd = 3,5-norbornadiene) as the catalyst precursor. It was found that, with the Rh−TangPhos catalyst, both (*Z*)- and (*E*)-isomers were hydrogenated to form (*R*)-methyl 3-acetamidobutanoate. Our study showed that the solvent had a pronounced influence on both the reactivity and the enantioselectivity of the reaction (Table 1). While the (*E*)-isomer showed complete conversions in most solvents except toluene (entries 1−5), the (*Z*)-isomer showed lower reactivities (entries 6−10). THF was found to be an excellent solvent for the reaction, as complete conversions were obtained for both (*Z*)- and (*E*)-isomers. To our surprise, excellent enantioselectivities (*E* = 99.6% ee; *Z* = 98.5% ee) were obtained for both (*Z*)- and (*E*)-isomers (entries 2 and 7). *To the best of our knowledge, these are among the highest enantioselectivities to date for hydrogenation of methyl 3-acetamido-2-butenoate, especially for hydrogenation of the (Z)-isomer* (other ligands: Me-DuPhos, 87.8% ee;[4b] BICP, 86.9% ee;[4c] BINAP, 5% ee[3]). A 1:1 *E*/*Z* isomeric mixture of methyl 3-acetamido-2-butenoate was also subjected to hydrogenation. When THF was used as the solvent, (*R*)-methyl 3-acetamidobutanoate was obtained in 100% yield and 99.5% ee (entry 11). The H_2 pressure had a large influence on the enantioselectivity. Higher H_2 pressure deteriorated the ee, which was consistent with Börner's observation.[4b] When the hydrogenation of the 1:1 *E*/*Z* isomeric mixture was conducted under 80 psi of H_2 pressure, a lower ee (96.5%) was obtained.

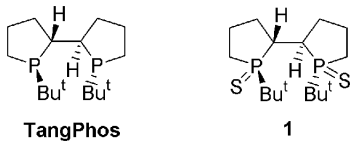
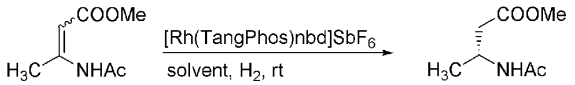


Figure 1. Structure of TangPhos and its phosphine sulfide **1**.

Table 1. Solvent Effect of Hydrogenation of Methyl 3-Acetamido-2-butenoate with the Rh−TangPhos System



(*E*)-**2** or/and (*Z*)-**2** → **3**

entry[a]	substrate	solvent	conversion (%)	ee (%)
1	(*E*)-**2**	CH_3OH	100	97.0
2	(*E*)-**2**	THF	100	99.6
3	(*E*)-**2**	toluene	82	98.0
4	(*E*)-**2**	CH_2Cl_2	100	99.4
5	(*E*)-**2**	EtOAc	100	99.5
6	(*Z*)-**2**	CH_3OH	13	83.7
7	(*Z*)-**2**	THF	100	98.5
8	(*Z*)-**2**	toluene	55	96.9
9	(*Z*)-**2**	CH_2Cl_2	88	98.5
10	(*Z*)-**2**	EtOAc	99	98.5
11	(*E*)-**2**/(*Z*)-**2** (1:1)	THF	100	99.5

[a] Absolute configurations were determined to be *R* by comparing the optical rotations with reported values. Reactions were carried out under 20 psi of H_2 in solvent at room temperature for 24 h. Substrate/[Rh(TangPhos)nbd]SbF_6 = 200:1. The ees were determined by chiral GC using a chiralselect 1000 column.

Our study showed that the solvent had a pronounced influence on both the reactivity and the enantioselectivity of the reaction (Table 1). While the (*E*)-isomer showed complete conversions in most solvents except toluene (entries 1−5), the (*Z*)-isomer showed lower reactivities (entries 6−10). THF was found to be an excellent solvent for the reaction, as complete conversions were obtained for both (*Z*)- and (*E*)-isomers. To our surprise, excellent enantioselectivities (*E* = 99.6% ee; *Z* = 98.5% ee) were obtained for both (*Z*)- and (*E*)-isomers (entries 2 and 7). *To the best of our knowledge, these are among the highest enantioselectivities to date for hydrogenation of methyl 3-acetamido-2-butenoate, especially for hydrogenation of the (Z)-isomer* (other ligands: Me-DuPhos, 87.8% ee;[4b] BICP, 86.9% ee;[4c] BINAP, 5% ee[3]). A 1:1 *E*/*Z* isomeric mixture of methyl 3-acetamido-2-butenoate was also subjected to hydrogenation. When THF was used as the solvent, (*R*)-methyl 3-acetamidobutanoate was obtained in 100% yield and 99.5% ee (entry 11). The H_2 pressure had a large influence on the enantioselectivity. Higher H_2 pressure deteriorated the ee, which was consistent with Börner's observation.[4b] When the hydrogenation of the 1:1 *E*/*Z* isomeric mixture was conducted under 80 psi of H_2 pressure, a lower ee (96.5%) was obtained.

To test the synthetic utilities of the Rh−TangPhos system for the synthesis of β-amino acid derivatives, a series of β-alkyl- and β-aryl-substituted β-(acylamino)acrylates were tested for hydrogenation. As shown in Table 2, a wide array of β-alkyl and β-aryl β-amino acid derivatives were obtained in excellent ees. For hydrogenation of (*E*)-β-alkyl β-(acylamino)acrylates, extremely high enantioselectivities (98−100%) have been obtained (entries 1 and 3−6). These results are comparable with those obtained with Imamoto's BisP*.[4a] Entries 1 and 2 showed another example in which both (*Z*)- and (*E*)-isomeric substrates gave the hydrogenation product with the same configuration in high ees. These results further demonstrated that an *E*/*Z* mixture of β-(acylamino)acrylates could be hydrogenated in high ee with the Rh−TangPhos system.

Asymmetric hydrogenation of β-aryl β-(acylamino)acrylates remains a challenging task. Since the (*Z*)- and (*E*)-isomeric substrates are not separable by column chromatography, hydrogenation of their *E*/*Z* mixtures is crucial for the synthesis of chiral β-aryl β-amino acid derivatives. While many β-aryl β-amino acid derivatives have been important intermediates for drug synthesis,[8] little success has been

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(7) Crystallographic data for the X-ray structure of **1** have been deposited with Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-190907. For a graphical structure, see Supporting Information.

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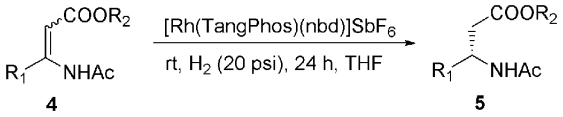
Table 2. Hydrogenation of β-Alkyl or β-Aryl β-(Acylamino)acrylates with the Rh−TangPhos System



entry[a]	R_1	R_2	geometry[c]	ee[b] (%)	configuration
1	Me	Et ((*E*)-**4a**)	*E*	99.5 (**5a**)	*R*
2	Me	Et ((*Z*)-**4a**)	*Z*	97.3 (**5a**)	*R*
3	Me	*i*-Pr (**4b**)	*E*	99.3 (**5b**)	*R*
4	Et	Me (**4c**)	*E*	99.6 (**5c**)	*R*
5	*n*-Pr	Et (**4d**)	*E*	99.6 (**5d**)	*R*
6	*i*-Bu	Me (**4e**)	*E*	98.5 (**5e**)	*R*
7	Ph	Me (**4f**)	*E*/*Z*	93.8 (**5f**)	*S*
8	*p*-F-Ph	Me (**4g**)	*E*/*Z*	95.0 (**5g**)	*S*
9	*p*-Cl-Ph	Me (**4h**)	*E*/*Z*	92.3 (**5h**)	*S*
10	*p*-Br-Ph	Me (**4i**)	*E*/*Z*	95.1 (**5i**)	*S*
11	*p*-Me-Ph	Me (**4j**)	*E*/*Z*	94.0 (**5j**)	*S*
12	*p*-MeO-Ph	Me (**4k**)	*E*/*Z*	98.5[d] (**5k**)	*S*
13	*p*-BnO-Ph	Me (**4l**)	*E*/*Z*	98.5 (**5l**)	*S*
14	*o*-Me-Ph	Me (**4m**)	*E*/*Z*	74.3 (**5m**)	*S*
15	*o*-MeO-Ph	Me (**4n**)	*E*/*Z*	83.1 (**5n**)	*S*

[a] Reactions were carried out under 20 psi of H_2 in THF at room temperature for 24 h. Substrate/[Rh(TangPhos)nbd]SbF_6 = 200:1. Absolute configurations were determined by comparing the optical rotations with reported values. [b] The ee (%) values were determined by chiral GC using a Chiralselect 1000 column. [c] For *E*/*Z* ratios of *E*/*Z* mixtures, see refs 4c and 8. [d] The ee was determined by chiral HPLC using an (*s*,*s*)-whelk-01 column.

achieved for their syntheses through asymmetric hydrogenation. Previous reports showed only moderate ees with Rh−DuPhos,[4c] Rh−BICP,[4c] and Ru−BINAP[3] systems. We recently developed a Ru-*o*-BINAPO system for the hydrogenation of β-aryl β-(acylamino)acrylates.[9] Although excellent ees were obtained, the catalytic efficiencies were low (less than 100 turnovers). We found that the Rh−TangPhos system is very efficient for this type of substrate. As shown in Table 2 (entries 7−15), good to excellent ees (74.3−98.5%) have been obtained for a series of β-aryl β-(acylamino)acrylates. While no major electronic effect was observed for para-substituted β-aryl β-(acylamino)acrylates, electron-rich substrates gave slightly higher ees (entries 12 and 13). For ortho-substituted β-aryl β-(acylamino)acrylates, lower enantioselectivities were observed (entries 14 and 15). To further demonstrate the catalytic efficiency of the Rh−TangPhos system for hydrogenation of β-(acylamino)-acrylates, **4l** was subjected to hydrogenation in THF under 20 psi of H_2 in the presence of 0.1 mol % [Rh(TangPhos)-nbd]SbF_6. The product (*S*)-**5l** was obtained in 100% yield and in 98.5% ee (TON = 1000), with no deterioration of enantioselectivity.

In conclusion, an efficient catalytic system for rhodium-catalyzed asymmetric hydrogenation of β-(acylamino)acrylates has been developed. With TangPhos as the chiral ligand, high enantioselectivities (up to 99.6%) and turnover numbers have been obtained in the hydrogenation of *E*/*Z* isomeric mixtures of both β-alkyl and β-aryl β-(acylamino)acrylates. Under these conditions, a variety of chiral β-alkyl and β-aryl β-amino acids can be efficiently synthesized. Since the substrates are easy to prepare according to known procedures,[4c,9] the Rh−TangPhos system provides an efficient and practical way for making chiral β-amino acid derivatives.

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Supporting Information Available: X-ray structure of **1**, experimental procedure for hydrogenation, and analytical data of new substrates and products. This material is available free of charge via the Internet at http://pubs.acs.org.

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