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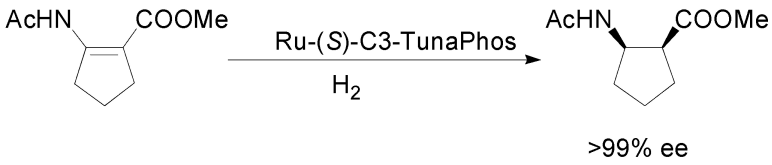

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Enantioselective Hydrogenation of Tetrasubstituted Olefins of Cyclic β-(Acylamino)acrylates

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Enantiomerically pure β-amino acids and their derivatives are key structural elements of many natural products and drugs. They are also important chiral building blocks for the synthesis of β-peptides for biomedical research.[1,2] Chiral cyclic β-amino acids have recently gained much attention due to their increasing importance for the synthesis of β-peptides.[3] For instance, *trans*-aminocyclopentanecarboxylic acid (**1**, *trans*-ACPC, Figure 1) and *trans*-4-aminopyrrolidine-3-carboxylic acid (**2**, *trans*-APC) have been successfully used by Gellman and co-workers for constructing β-peptide antibiotics,[3a] while (1*R*,2*S*)-*cis*-aminocyclopentanecarboxylic acid (**3**, cispentacin) itself is a strong antifungal antibiotic.[4] Although some stoichiometric asymmetric synthesis or resolution methods of chiral cyclic β-amino acids and their derivatives have been reported,[5] the development of new, efficient, and catalytic asymmetric synthetic methods remains an important goal. Herein we report the first catalytic synthesis of chiral cyclic β-amino acids via asymmetric hydrogenation of cyclic β-(acylamino)acrylates, and excellent enantioselectivities have been achieved.

Although great success has been achieved in asymmetric hydrogenation of trisubstituted functionalized olefins, hydrogenation of tetrasubstituted olefins is generally more difficult, and much fewer successful results have been reported.[6] While many excellent chiral catalytic systems have been developed for hydrogenation of trisubstituted olefins of acyclic β-(acylamino)acrylates,[7,8] enantioselective hydrogenation of tetrasubstituted olefins of cyclic or acyclic β-(acylamino)acrylates remains an unexplored area. We were interested in developing an efficient catalyst for hydrogenation of tetrasubstituted olefins of cyclic β-(acylamino)acrylates. Thus, a series of cyclic β-(acylamino)acrylates were synthesized from their corresponding cyclic β-keto esters through amination and acylation in high yields. 2-Acetylamino-cyclopent-1-enecarboxylic acid ethyl ester (**4**) was selected as the hydrogenation substrate for testing different hydrogenation methods. A Rh−(*S*,*S*,*R*,*R*)-TangPhos complex[7e] was first used as the catalyst for asymmetric hydrogenation. It was found that this catalyst, which was very successful for hydrogenation of trisubstituted olefins of β-(acylamino)acrylates,[7e] exhibited no reactivity under similar conditions. A low conversion was observed even when a higher hydrogen pressure (50 atm) and temperature (50 °C) were employed.

Bruneau et al.[9a] and Rautenstrauch et al.[9b] have recently reported hydrogenation of tetrasubstituted enamides and a vinylogous β-oxoester, respectively, by employing Ru catalysts generated in situ from a monomeric Ru precursor, a chiral phosphorus ligand, and HBF_4. We thus switched to the use of chiral Ru catalysts for hydrogenation of the tetrasubstituted olefin of **4**. The Ru catalysts were prepared in situ by protonation of a mixture of Ru(COD)(methallyl)$_2$ and a chiral bisphosphorus ligand with two equivalents of HBF_4·Me_2O in CH_2Cl_2. After evaporation of the solvent, the residue was directly used for hydrogenation. The reactions were performed at room temperature under 50 atm of H_2 pressure in MeOH. As shown in Table 1, different chiral ligands exhibited dramatically different enantioselectivities. While DIOP, DuPhos, and TangPhos gave only moderate enantioselectivities (entries 1−3), chiral biaryl ligands such as MeO−BIPHEP and BINAP provided 99% ee's (entries 4−5). To test the effect of the dihedral angle of chiral biaryl ligand on enantioselectivity of the reaction, a set of TunaPhos ligands[11] with different dihedral angles was employed. With the exception of C1-TunaPhos and C6-TunaPhos that provided slightly lower ee's, other TunaPhos ligands showed comparably high enantioselectivities (entry 6−11). The preparation method of the Ru catalysts is important for the high reactivity. When a Ru catalyst precursor such as $[NH_2Me_2][\{RuCl((S)\text{-C3-TunaPhos})\}_2(\mu\text{-Cl})_3]$[11] was applied for hydrogenation under identical conditions, a lower conversion (80%) was obtained although the high enantioselectivity was maintained. Alcoholic solvents such as MeOH and EtOH are beneficial for the reactivity; lower conversion was observed when THF, CH_2Cl_2, or toluene was used as the solvent.

We then used C3-TunaPhos as the ligand for Ru-catalyzed asymmetric hydrogenation of a series of cyclic β-(acylamino)-acrylates. As shown in Table 2, over 99% ee was obtained in hydrogenation of 2-acetylamino-cyclopent-1-enecarboxylic acid methyl ester (**5**, entry 2). Excellent enantioselectivity (98% ee) was also achieved in hydrogenation of substrate **6** containing a BocNH−

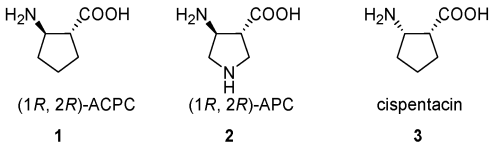
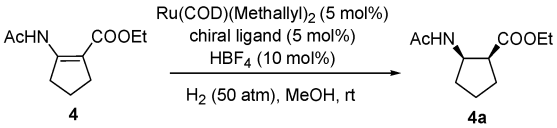


Figure 1. Cyclic β-amino acids.

Table 1. Ru-Catalyzed Hydrogenation of 2-Acetylamino-cyclopent-1-enecarboxylic Acid Ethyl Ester



entry[a]	chiral P* ligands	conv. (%)	% ee (config)
1	(*S*,*S*)-DIOP	91	34 (1*S*,2*R*)
2	(*R*,*R*)-Me-DuPhos	100	69 (1*R*,2*S*)
3	(*S*,*S*,*R*,*R*)-TangPhos	100	57 (1*R*,2*S*)
4	(*S*)-BINAP	100	99 (1*S*,2*R*)
5	(*S*)-MeO−BIPHEP	100	99 (1*S*,2*R*)
6	(*S*)-C1-TunaPhos	100	98 (1*S*,2*R*)
7	(*S*)-C2-TunaPhos	100	99 (1*S*,2*R*)
8	(*S*)-C3-TunaPhos	100	99 (1*S*,2*R*)
9	(*S*)-C4-TunaPhos	100	99 (1*S*,2*R*)
10	(*S*)-C5-TunaPhos	100	99 (1*S*,2*R*)
11	(*S*)-C6-TunaPhos	100	97 (1*S*,2*R*)

[a] For a detailed procedure of catalyst preparation, see Supporting Information. Ru:P*:HBF_4:substrate = 1:1:2:20, The hydrogenations were performed at room temperature under 50 atm of H_2 pressure in MeOH for 18 h.

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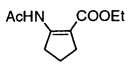
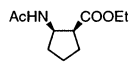
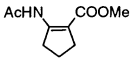
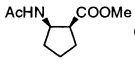
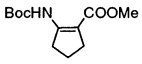
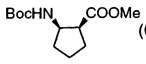
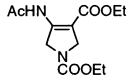
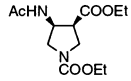
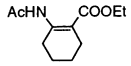
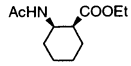
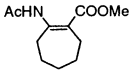
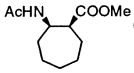
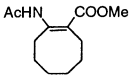
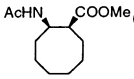
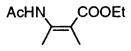
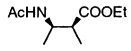
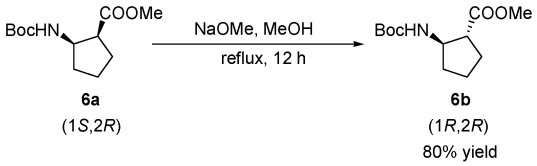
Table 2. Hydrogenation of Cyclic or Acyclic β-(Acylamino)crylates with a Ru−(*S*)-C3-TunaPhos Catalyst

entry[a]	substrate		product		%ee[b] (confign)[c]
1		(**4**)		(**4a**)	99 (+)
2		(**5**)		(**5a**)	>99 (+)
3		(**6**)		(**6a**)	98 (+)
4		(**7**)		(**7a**)	95 (+)
5		(**8**)		(**8a**)	92 (+)
6		(**9**)		(**9a**)	80 (+)
7		(**10**)		(**10a**)	44 (-)
8		(**11**)		(**11a**)	72 (+)

[a] For a detailed procedure of catalyst preparation, see Supporting Information. Ru:(*S*)-C3-TunaPhos:HBF_4:substrate = 1:1:2:20, The hydrogenations were performed at room temperature under 50 atm of H_2 pressure in EtOH for 18 h. [b] The enantiomeric excesses were determined by chiral GC on a chiralselect 1000 or γ-dex 225 column. [c] The sign of optical rotation. The absolute configuration of **6a** (entry 3) is determined as (1*S*,2*R*).

Scheme 1. Epimerization of **6**a



group (entry 3). The chiral cis product **6a** has been used as a synthon for the peptide synthesis.[5i] A heterocyclic β-(acylamino)acrylates **7** is also hydrogenated to give the cis product **7a** in excellent enantioselectivity (entry 4). Hydrogenation of a cyclohexenyl substrate **8** provided the cis hydrogenation product in 92% ee. However, lower ee's were observed in hydrogenation of the cycloheptenyl and cyclooctenyl substrates **9** and **10**. An acyclic β-(acylamino)acrylate **11** with a tetrasubstituted olefin was also hydrogenated, and the product **11a** was obtained in 72% ee. Hydrogenation with other biaryl ligands such as BINAP, MeO−BIPHEP, C2-, C4-, and C5-TunaPhos provided similar hydrogenation results.

To demonstrate the synthetic utility of the chiral cis hydrogenation products for the synthesis of trans cyclic β-amino acid derivatives, compound **6a** was heated in a basic alcoholic solution to yield its trans epimer *trans*-(1*R*,2*R*)-2-*tert*-butoxycarbonylamino-cyclopentanecarboxylic acid methyl ester (**6b**) in high yield (Scheme 1). The chiral trans product **6b** has been frequently used by Gellman and co-workers for the synthesis of β-peptides.[3c]

In conclusion, we have developed the first catalytic asymmetric synthesis of chiral cyclic β-amino acid derivatives via asymmetric hydrogenation. The Ru catalysts combined with chiral biaryl ligands such as C3-TunaPhos are found to be efficient for hydrogenation of tetrasubstituted olefins of cyclic β-(acylamino)acrylates and up to 99% ee's have been achieved. Since the hydrogenation substrates are easy to synthesize,[11] we believe that this methodology may be potentially practical for the synthesis of both cis and trans chiral cyclic β-amino acids.

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Supporting Information Available: Detail hydrogenation procedure and spectroscopic data of substrates and products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) See Supporting Information.

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