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

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β-Amino acids have found extensive application in the life sciences as components of biologically active peptides and small-molecule pharmaceuticals.[1] Synthetic derivatives of biologically relevant peptides incorporating β-amino acids often display interesting pharmacological activity, with increased potency and enzymatic stability relative to their native counterparts, and have played important roles in advancing the understanding of enzyme mechanisms, protein conformations, and properties related to molecular recognition.[2] In organic synthesis, β-amino acids are commonly used as chiral building blocks,[3] and a great deal of research has focused on facile, practical, and scalable methods for their preparation.[4,5]

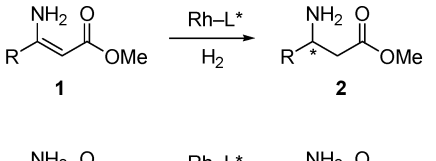
Given its inherent efficiency and atom economy,[6] catalytic asymmetric hydrogenation would seem to be an ideal approach to preparing enantiopure β-amino acids. Indeed, such methods are among the most studied and widely applied for the enantioselective preparation of α-amino acids.[7−9] Yet, despite significant advancements in recent years,[10] asymmetric hydrogenation has yet to find application in the large-scale preparation of enantiopure β-amino acids.[11] Their practical preparation still relies on the resolution of racemates[12] or the use of chiral auxiliaries.[13]

One significant drawback to current approaches to asymmetric hydrogenation of unsaturated β-amino acids is the requirement of an acyl protecting group on the nitrogen: this group is considered indispensable to satisfy the chelation requirement between the substrate and the metal, leading to high reactivity and selectivity.[14,15] Direct acylation of enamines is not a trivial chemical transformation, and there are no other efficient methods for enamide synthesis.[16] In addition, removal of the acyl group often requires heating in strongly acidic or basic conditions, which may be incompatible with other functional groups in the molecule. The difficulty and redundancy of introduction and removal of the acetamide group has seriously limited the use of this otherwise powerful synthetic method.

We report here the first general method of high-yielding, highly enantioselective hydrogenations of *unprotected* β-enamine esters **1** and amides **3** (Scheme 1).[17] This transformation obviates the need for N-protecting group chemistry, directly yielding the desired β-amino acid derivative. The β-enamino esters (**1**) and amides (**3**) are easily prepared in high yield by reaction of NH_4OAc with the corresponding readily available β-keto esters and amides.[18,19] Both are obtained exclusively as the (*Z*)-isomer via direct crystallization from the reaction mixture.[20]

Exploratory catalyst screening employed β-enamino ester **1a** and a diverse array of commercially available catalysts and nonracemic ligands. Representative results are summarized in Table 1.

Scheme 1. Asymmetric Hydrogenation of Unprotected Enamines



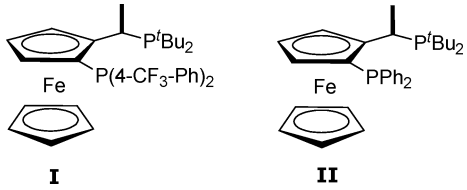
a: R = Ph; **b**: R = 4-MeO-Ph; **c**: R = 4-F-Ph; **d**: R = $PhCH_2$–; **e**: R =3-Py

Table 1. Asymmetric Hydrogenation of **1a**[a]

entry	ligand	yield[b] %	ee[c] %	configuration
1	[((*R*,*R*)-DiPAMP)Rh(cod)]BF_4	0.1		
2	[((*S*,*S*)-Me-DuPHOS)Rh(cod)]BF_4	71.4	9.3	*S*
3	(*S*)-BINAPHANE/[Rh(cod)]$Cl]_2$	11.1	10.8	*R*
4	(*S*)-f-BINAPHANE/[Rh(cod)]$Cl]_2$	77.3	9.8	*S*
5	(*S*)-C1-TUNEPHOS/[Rh(cod)]$Cl]_2$	8.9	2.4	*S*
6	[((R,R)-Et-FerroTANE)Rh(cod)]BF_4	77.0	88.0	*R*
7[d]	(*R*)-(*S*)-**I**/[Rh(cod)]$Cl]_2$	93.7	96.1	*S*
8[e]	(*R*)-(*S*)-**I**/[Rh(cod)]$Cl]_2$	trace		
9	(*R*)-PHANEPHOS/[Rh(cod)]$Cl]_2$	57.6	76.2	*R*
10	(+)-TMBTP/[Rh(cod)]$Cl]_2$	15.0	78.4	*S*
11	((*S*)-BINAP)$RuCl_2$	0.9		
12	(*R*)-(*S*)-**I**/[Ir(cod)Cl]$_2$	2.8		
13	(*R*)-(*S*)-**II**/[Ir(cod)Cl]$_2$	11.2	84.7	*S*

[a] Reaction conditions: in 2,2,2-trifluoroethanol (TFE), S/C = 20, 1:1 ligand/metal, 90 psig H_2, 50 °C, 18 h. For information on the ligands, see Supporting Information. [b] Assayed by HPLC. [c] Assayed by chiral HPLC. [d] With 1 mol % catalyst. [e] In MeOH.

Not surprisingly, a number of the metal−ligand complexes screened gave poor results. The Rh−ferrocenophosphine (**I**) complex, however, gave good conversion and enantiomeric excess. Further examination of a number of other Josiphos-type ligands with varying electronic and steric properties revealed that for ester **1a**, ligand **I** gave the best results in terms of conversion and enantioselectivity. With these encouraging results, we proceeded to investigate the scope of this reaction on both enamine esters and enamine amides.



As shown in Table 2, a wide variety of unprotected enamine esters and amides all gave the corresponding β-amino acid derivatives in high yield with good to excellent enantioselectivity

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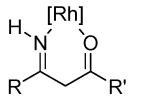
Table 2. Asymmetric Hydrogenation of Enamine Esters and Amides[a]

entry	enamine	ligand	solvent	time h	yield %[b]	ee %	configuration
1	**1a**	**I**	TFE	6	97.6	96.1	*S*
2	**1a**	**I**	MeOH	18	trace		
3	**1b**	**I**	TFE	11	87.5	95.0	*S*
4	**1c**	**I**	TFE	11	85.4[c]	96.1	(−)
5	**1d**	**I**	TFE	11	94.4	93.3	*R*
6	**1e**	**I**	TFE	24	90.5	95.7	(−)
7	**3a**	**II**	MeOH	8	74.6	95.6	(−)
8[d]	**3a**	**II**	TFE	18	94.1	82.2	(−)
9[e]	**3b**	**II**	MeOH	8	82.0	96.3	(+)
10	**3c**	**II**	MeOH	8	74.3	96.0	(+)
11	**3d**	**II**	MeOH	8	94.0	97.1	(−)

[a] Reaction conditions: 0.15 mol % $[(COD)RhCl]_2$, 0.3 mol % ligand, 50 °C, 90−100 psig H_2. [b] Assay yield. [c] Isolated yield. [d] With 1 mol % catalyst. [e] With 0.7 mol % catalyst.

using only 0.3 mol % catalyst under relatively mild conditions (100 psig H_2). Ligand **I** gave the best results in the hydrogenation of enamine esters, while ligand **II** gave the highest rates and enantioselectivities for the hydrogenation of enamine amides. Interestingly, this catalytic system exhibited a high sensitivity to solvent. For hydrogenation of enamine esters, TFE is preferred for high reactivity and selectivity. In MeOH, however, the reaction was almost totally inhibited (entry 2 in Table 2). On the other hand, the hydrogenations of enamine amides gave much higher selectivity in MeOH than in TFE (entry 8). It is believed that the solvent acidity plays an important role in the reaction.[21]

The success of this hydrogenation method despite the lack of a directing *N*-acyl group on the substrate begs the question of what sort of mechanism is operative that gives high rates of reaction and high enantiofacial selectivity in the Rh−H insertion step. Mechanistic studies are ongoing and will be reported in due course. However, preliminary results of deuterium labeling studies suggest the intriguing possibility that the reaction proceeds through the imine tautomer, making this reaction mechanistically analogous to β-ketoester and -amide hydrogenations.[8,22]



R' = OR^2, $NR^3{}_2$

In summary, we have discovered an unprecedented enantioselective reduction of unprotected enamino esters and amides using commercially available ligands under mild hydrogenation conditions. This method gives high enantioselectivity, high reactivity, and wide applicability and requires no protecting groups. Contrary to accepted thinking, our results clearly show that the *N*-acyl group is not a prerequisite for such transformations to be effected. It is our hope that this discovery will provide a practical and efficient method for the large-scale preparation of β-amino acids and their derivatives.

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Supporting Information Available: General procedures for synthesis of enamines and their hydrogenations; physical characterization data for substrates and products (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) It is postulated that the intramolecular hydrogen bond dictates this phenomenon. The (*Z*)-conformation of the substrates is confirmed by NMR (NOE).
(21) The effect of TFE in enamine ester hydrogenations can be mimicked by other acidic alcohols such as phenol derivatives.
(22) When amide **3a** was reduced in MeOH with D_2 using catalyst **II**/$[(COD)RhCl]_2$, we observed D-incorporation only in the β-position.

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