β-Amino acids have found extensive application in the life sciences as components of biologically active peptides and small-molecule pharmaceuticals. 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. In organic synthesis, β-amino acids are commonly used as chiral building blocks, and a great deal of research has focused on facile, practical, and scalable methods for their preparation.

Given its inherent efficiency and atom economy, 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. Yet, despite significant advances in recent years, asymmetric hydrogenation has yet to find application in the large-scale preparation of enantiopure β-amino acids. Their practical preparation still relies on the resolution of racemates or the use of chiral auxiliaries.

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. This is the case for ester and amides, both of which are commonly used as chiral building blocks, and a great deal of research has focused on facile, practical, and scalable methods for their preparation.

We report here the first general method of high-yielding, highly enantioselective hydrogenations of unprotected β-amino esters and amides (Scheme 1). This transformation obviates the need for N-protecting group chemistry, directly yielding the desired β-amino acid derivative. β-Ammonium esters (I) and amides (3) are easily prepared in high yield by reaction of NH₄OAc with the corresponding readily available β-keto esters and amides. Both are obtained exclusively as the (Z)-isomer via direct crystallization from the reaction mixture.

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

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.

---

Table 1. Asymmetric Hydrogenation of Unprotected Enamines

<table>
<thead>
<tr>
<th>entry</th>
<th>ligand</th>
<th>yield %</th>
<th>ee %</th>
<th>configuration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>[(R,R)-DiPAMP]Rh(cod)BF₄</td>
<td>0.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>[(S,S)-Me-DuPHOS]Rh(cod)BF₄</td>
<td>71.4</td>
<td>9.3</td>
<td>S</td>
</tr>
<tr>
<td>3</td>
<td>(S)-BINAPHANE[Rh(cod)]Cl₂</td>
<td>11.1</td>
<td>10.8</td>
<td>R</td>
</tr>
<tr>
<td>4</td>
<td>(S)-f-BINAP[Rh(cod)]Cl₂</td>
<td>77.3</td>
<td>9.8</td>
<td>S</td>
</tr>
<tr>
<td>5</td>
<td>(S)-C₁-TUNEPHOS[Rh(cod)]Cl₂</td>
<td>8.9</td>
<td>2.4</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>[(R,R)-Et-FerroTANE]Rh(cod)BF₄</td>
<td>77.0</td>
<td>88.0</td>
<td>R</td>
</tr>
<tr>
<td>7</td>
<td>(R,-S)-I/[Rh(cod)]Cl₂</td>
<td>93.7</td>
<td>96.1</td>
<td>S</td>
</tr>
<tr>
<td>8</td>
<td>(R,-S)-I/[Rh(cod)]Cl₂</td>
<td>11.2</td>
<td>84.7</td>
<td>S</td>
</tr>
<tr>
<td>9</td>
<td>(+)-TMSTP/[Rh(cod)]Cl₂</td>
<td>15.0</td>
<td>78.4</td>
<td>S</td>
</tr>
<tr>
<td>10</td>
<td>(S)-BINAP[Rh(cod)]Cl₂</td>
<td>0.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>(R)-s-[Ir(cod)]Cl₂</td>
<td>2.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>(R,-S)-II/[Ir(cod)]Cl₂</td>
<td>11.2</td>
<td>84.7</td>
<td>S</td>
</tr>
</tbody>
</table>

* Reaction conditions: in 2,2,2-trifluoroethanol (TFE), S/C = 20, 1:1 ligand/metal, 90 psig H₂, 50 °C, 18 h. For information on the ligands, see Supporting Information. * Assayed by HPLC. * Assayed by chiral HPLC. * With 1 mol % catalyst. * In MeOH.
using only 0.3 mol % catalyst under relatively mild conditions (100 psig H2). 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. 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-ke-toester and -amide hydrogenations.8,22

In summary, we have discovered an unprecedented enantioselective reduction of unprotected enamine 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.

Acknowledgment. We thank Ms. Lisa DiMichele for assistance with NMR spectra, Mr. Roy Helmy for LCMS data, and Dr. Thomas J. Novak for HRMS data.

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.

References

(9) For example, the classic t-DOPA synthesis: Knowles, W. S. Acc. Chem. Res. 1983, 16, 106.
(20) It is postulated that the intramolecular hydrogen bond dictates this phenomenon. The (Z)-conformation of the substrate 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 D2 using catalyst II[(COD)-RhCl], we observed D-incorporation only in the β-position.

JA047901I