Asymmetric Catalytic Synthesis of β-Branched Amino Acids via Highly Enantioselective Hydrogenation Reactions

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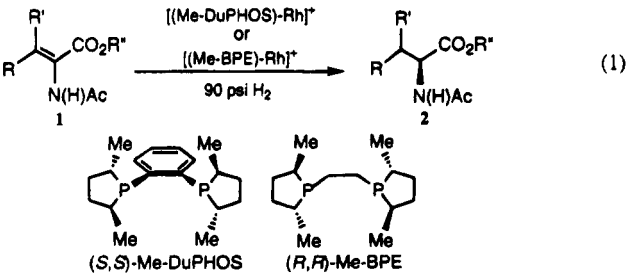
Asymmetric catalytic hydrogenation reactions represent one of the most efficient and convenient methods to prepare a wide range of enantiomerically pure compounds.[1] Historically, the desire for practical routes to α-amino acids ultimately led to the development of effective chiral diphosphine–rhodium catalysts for the enantioselective hydrogenation of α-(acylamino)acrylates (α-enamides).[1,2] In contrast to the success that has been achieved in the hydrogenation of α-enamides possessing a single β-substituent, α-enamides that are β,β-disubstituted have been notoriously difficult to reduce with high enantioselectivities.[1-3] Given the dearth of proteinogenic β-branched amino acids (Val, Ile, Thr), simple access to novel, constrained β,β-disubstituted alanine derivatives likely would afford vast opportunities in the design of peptide and peptidomimetic therapeutics.[4]

We recently have developed a variety of highly selective rhodium and ruthenium hydrogenation catalysts based on chiral 1,2-bis(phospholano)benzene (DuPHOS) and 1,2-bis(phospholano)ethane (BPE) ligands.[5,6] Interestingly, we observed that our cationic Et-DuPHOS–Rh catalysts allowed the hydrogenation of both (*E*)- and (*Z*)-α-enamides to provide α-amino acid derivatives with very high enantiomeric excesses and with the same absolute configuration, for a given catalyst configuration.[6] The unique ability of our catalysts to tolerate either *E* or *Z* β-substituents suggested that selective hydrogenation of α-enamides possessing substituents at both β-positions may be possible. Herein, we describe a practical and highly enantioselective method for the hydrogenation of β,β-disubstituted α-enamides (**1**) using our cationic Me-DuPHOS–Rh and Me-BPE–Rh catalysts (eq 1). When dissimilar groups occupy the two β-positions of α-enamide substrates (**1**, R ≠ R′), a second stereogenic center is established in the hydrogenation reaction, thus providing access to a broad range of diastereomerically pure β-branched amino acids with high levels of enantioselectivity.

Preliminary scouting studies were performed with a series of cationic DuPHOS–Rh hydrogenation catalysts under a standard set of reaction conditions (catalyst precursor = [(COD)Rh(DuPHOS)]$^+$OTf$^-$, MeOH, 25 °C, 60 psi H_2, S/C = 500, 24 h) and the α-enamide bearing two β-Me groups (**1a**; R, R′, R″ = Me) as a model substrate. The highest enantioselectivity previously reported for the hydrogenation of this substrate was 55% ee using a DIPAMP–Rh catalyst system.[3a] On the basis of the success that our Et-DuPHOS–Rh catalysts enjoyed in the hydrogenation of (*E*)- and (*Z*)-α-enamides, initial experiments using this catalyst were disappointing in that only moderate enantioselectivity (74% ee) was achieved in the hydrogenation of **1a**. The analogous *n*-Pr-DuPHOS–Rh and *i*-Pr-DuPHOS–Rh catalysts provided **2a** with even lower selectivity (45% and 14% ee, respectively). Upon moving to the less sterically congested Me-DuPHOS–Rh catalysts, however, a significant increase in selectivity was observed, and the valine derivative **2a** was obtained in 91.9% ee. Further optimization of the Me-DuPHOS–Rh catalyst indicated that higher enantioselectivity (96.0% ee) could be achieved at 90 psi of H_2 in benzene. In a similar study with a series of cationic BPE–Rh catalysts, the Me-BPE–Rh catalyst emerged superior and afforded **2a** in 98.2% ee. Consistent with our previous studies,[5,6] catalysts derived from (*R,R*)-DuPHOS or (*R,R*)-BPE ligands afforded (*R*)-**2a**, while *S,S* catalysts yielded the (*S*)-valine derivative.



(1)

An investigation of substrate generality revealed that both the (*S,S*)-Me-DuPHOS–Rh and (*R,R*)-Me-BPE–Rh catalysts are capable of smoothly hydrogenating a wide assortment of α-enamides of type **1** with very high enantioselectivity (Table 1).[7] As in our model studies involving **1a**, optimum enantioselectivities in the reduction of substrates **1b–j** consistently were observed in benzene and at 90 psi of H_2. Under these conditions, the series of β,β-dialkyl enamides **1a–c** were reduced to the corresponding β-branched amino acid derivatives with >96% ee (entries 1–3). The ester functionality of α-enamides **1** apparently is not a requirement for high enantioselectivities, as the free acid analog of **1a** was reduced in 94.4% ee using (*R,R*)-Me-BPE–Rh.

The Me-DuPHOS–Rh and Me-BPE–Rh catalysts also were found effective for the asymmetric hydrogenation of a variety of β-cyclic α-enamides to cycloalkylglycine derivatives. For instance, α-cyclopentylglycine (**2d**) and α-(2-indanyl)glycine derivatives (**2e**) were produced with selectivities as high as 97.2% and 99.0% ee, respectively. Interestingly, **2d** was obtained with slightly higher enantioselectivity (98.1% ee) in toluene using the (*R,R*)-Me-BPE–Rh catalyst. Similarly, high ee's were achieved in the reduction of β-cyclohexyl and β-cycloheptyl α-enamides **1f** and **1g**. Me-BPE–Rh-catalyzed hydrogenation of β-thiinane enamide **1h** provided the interesting, constrained methionine analog **2h** in 98.4% ee (entry 8). Chemoselective hydrogenation of keto enamide **1j** afforded the amino acid derivative in up to 98.0% ee without reduction of the keto group (entry 10).

Although the asymmetric synthesis of isomerically pure β-alkyl α-amino acids (e.g., β-methylphenylalanine) has proven challenging,[8,9] a number of these specifically constrained residues have found important application in the design of biologically active peptides.[10] Enantioselective hydrogenation

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(6) Burk, M. J.; Feaster, J. E.; Nugent, W. A.; Harlow, R. L. *J. Am. Chem. Soc.* **1993**, *115*, 10125.

(7) Preparations of β,β-disubstituted α-enamides **1** are provided in the supporting information.

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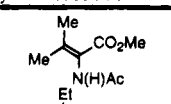
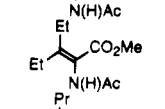
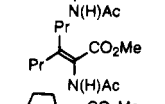
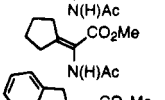
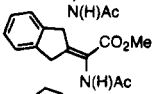
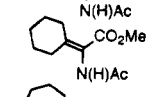
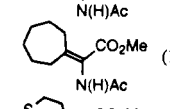
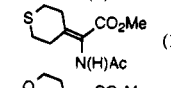
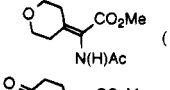
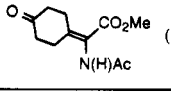
Table 1. Rh-Catalyzed Enantioselective Hydrogenation of β,β-Disubstituted Enamides **1**[a]

Entry	Substrate		ligand	% ee[b] (confign)[c]
1		(**1a**)	(*S,S*)-Me-DuPHOS (*R,R*)-Me-BPE	96.0 (*S*) 98.2 (*R*)
2		(**1b**)	(*S,S*)-Me-DuPHOS (*R,R*)-Me-BPE	96.2 (*S*) 97.5 (*R*)
3		(**1c**)	(*S,S*)-Me-DuPHOS (*R,R*)-Me-BPE	85.1[e] (*S*)[d] 96.8 (*R*)[d]
4		(**1d**)	(*S,S*)-Me-DuPHOS (*R,R*)-Me-BPE	96.8 (*S*) 97.2 (*R*)
5		(**1e**)	(*S,S*)-Me-DuPHOS (*R,R*)-Me-BPE	99.0 (*S*)[d] 98.6 (*R*)[d]
6		(**1f**)	(*S,S*)-Me-DuPHOS (*R,R*)-Me-BPE	96.2[e] (*S*) 98.6 (*R*)
7		(**1g**)	(*S,S*)-Me-DuPHOS (*R,R*)-Me-BPE	94.4 (*S*)[d] 96.0 (*R*)[d]
8		(**1h**)	(*S,S*)-Me-DuPHOS (*R,R*)-Me-BPE	95.0[e] (*S*)[d] 98.4[e] (*R*)[d]
9		(**1i**)	(*S,S*)-Me-DuPHOS (*R,R*)-Me-BPE	98.2 (*S*)[d] 98.6 (*R*)[d]
10		(**1j**)	(*S,S*)-Me-DuPHOS (*R,R*)-Me-BPE	93.7 (*S*)[d] 98.0 (*R*)[d]

[a] Reactions were conducted at 25 °C and an initial H_2 pressure of 90 psi using 0.10−0.25 M benzene solutions of substrate and the catalyst precursors [(*S,S*)-Me-DuPHOS−Rh(COD)]$^+$OTf$^-$ or [(*R,R*)-Me-BPE−Rh(COD)]$^+$OTf$^-$ (0.2 mol %), unless otherwise noted. Reaction time was 12−24 h, and complete (100%) conversion was observed in all cases. [b] Enantiomeric excesses were determined by chiral capillary GC using Chrompack's Chirasil-L-Val column (25 m). [c] Absolute configurations were assigned by comparing the sign of optical rotation of hydrolyzed (NaOH) product with that of known *N*-acetyl amino acids (see supporting information). [d] Absolute configurations assigned by analogy, and through comparison of sign of optical rotation and chiral GC elution order, with configurationally defined examples. [e] Reaction performed in methanol.

of enamides **1** containing two different β-substituents (**1**; R ≠ R′) could provide a very convenient and versatile route to these valuable amino acids. In particular, hydrogenation of both (*E*)- and (*Z*)-α-enamides of this type potentially could furnish all four amino acid stereoisomers. We were pleased to find that a range of β-branched α-amino acids possessing disparate β-substituents could be produced with high enantioselectivity via our Me-DuPHOS−Rh and Me-BPE−Rh catalysts in benzene (Figure 1).[11]

For example, the D-*allo*-isoleucine derivative (2*R*,3*S*)-**3a** and D-isoleucine derivative (2*R*,3*R*)-**3b** were generated in 98.2% and 98.3% ee, respectively, through (*R,R*)-Me-BPE−Rh-catalyzed hydrogenation of the corresponding (*Z*)-enamide (**1**; R = Et, R′ = Me) and (*E*)-enamide (**1**; R = Me, R′ = Et). In a similar fashion, the β-methylnorleucine derivatives *threo*-(2*R*,3*S*)-**4a** and *erythro*-(2*R*,3*R*)-**4b** were produced in 98.0% and 96.6% ee, respectively.[12] Hydrogenation of (*Z*)-β-phenyl enamides (**1**, R = Ph, R′ = Me or Et) with the (*S,S*)-Me-DuPHOS−Rh catalyst yielded β-methylphenylalanine and β-ethylphenylalanine derivatives, (2*S*,3*R*)-**5a** and (2*S*,3*R*)-**6a**, in 99.4% and 99.0% ee, respectively. Essentially identical enantioselectivities were obtained using the (*R,R*)-Me-BPE−Rh catalyst. While the corresponding (*E*)-β-phenyl enamides (**1**, R = Me or Et, R′ = Ph) were not reduced using the Me-DuPHOS−Rh catalyst, smooth hydrogenation with (*R,R*)-Me-BPE−Rh afforded (2*R*,3*R*)-**5b** (80.1% ee) and (2*R*,3*R*)-**6b** (88.3% ee). Interestingly, β-vinylic amino acid derivatives (2*R*,3*S*)-**7a** and (2*R*,3*R*)-**7b** were formed with high selectivity (90.6% and 95.9% ee, respectively) and with ≤5% overreduction of the corresponding (*E*)- and (*Z*)-α,γ-dienamides. Finally, β-methylaspartate ((2*R*,3*S*)-**8**, 96.6% ee) and β-phenylaspartate ((2*R*,3*S*)-**9**, 90.4% ee) derivatives were obtained via the (*R,R*)-Me-BPE−Rh catalyst.[11] It is noteworthy that the Me-DuPHOS−Rh catalyst produced **9** in only 62.5% ee.

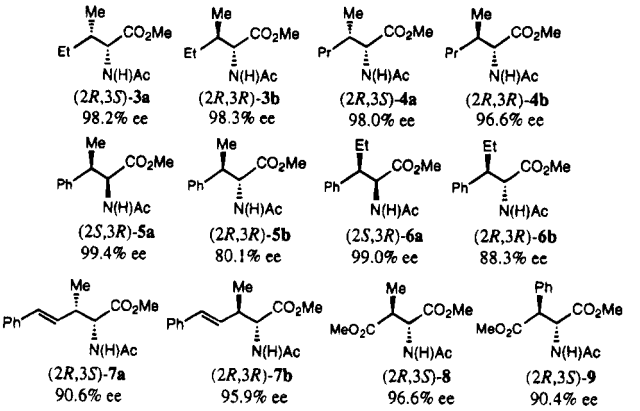


Figure 1. β,β-Disubstituted amino acid derivatives produced via enantioselective hydrogenation.

We have discovered that our Me-DuPHOS−Rh and Me-BPE−Rh catalysts allow the efficient and highly enantioselective hydrogenation of β,β-disubstituted α-enamides **1**, thus providing a convenient and practical route to a diverse range of valuable β-branched α-amino acid derivatives. The enantioselectivities achieved in these hydrogenation reactions are the highest yet reported for this challenging class of substrates. These results demonstrate a unique advantage of our ligand design. The ability to vary the phospholane substituents permits tuning of the steric environment imposed by our ligands to match the steric requirements of different types of substrates. In the present case, the least encumbered Me-DuPHOS−Rh and Me-BPE−Rh catalysts proved superior for hydrogenation of the sterically demanding α-enamides **1**. Moreover, the greater flexibility of the Me-BPE ligand appeared to allow the catalyst to accommodate a greater range of β-substituents on α-enamides **1** and generally provided enantioselectivities as high as, and often higher than, the Me-DuPHOS−Rh catalyst.

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Supporting Information Available: Experimental details, including preparation of α-enamides (**1**), hydrogenation procedure, spectral and analytical data, and ee determinations for all amino acid derivatives **2**−**9** (18 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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