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Catalytic Asymmetric Hydrogenation of β-Substituted α,β,γ,δ-Unsaturated Amino Acids

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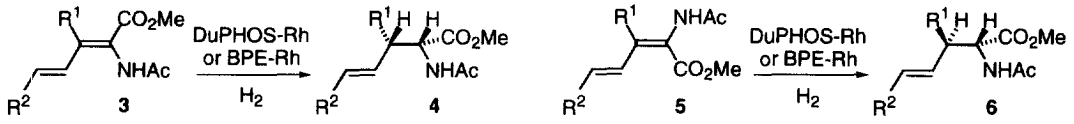
Abstract: The Rh-DuPHOS and Rh-BPE catalyzed hydrogenation of β-substituted α,β,γ,δ-unsaturated amino acids establishes two contiguous stereogenic centers simultaneously. Both high regioselectivity and good to excellent enantioselectivity have been demonstrated in this process leading to β-branched allyl glycine derivatives. Enamide geometry was found to influence stereoselectivity. Studies aimed at defining the scope and limitations of this process are described.

Didehydroamino acids are valuable substrates for enantioselective asymmetric hydrogenation reactions catalyzed by chiral transition-metal complexes.[4] A formidable challenge is presented in the case of β-substituted α,β,γ,δ-unsaturated acetamide ester **3** and its 2*E*-isomer, **5** ($R_1 \neq H$, Scheme 1) whereby selective hydrogenation of a hindered tetrasubstituted olefin must take place in the presence of a disubstituted olefin. Successful asymmetric catalytic hydrogenation of β-substituted dienamides requires both high enantioselectivity and high regioselectivity favoring reduction of the enamide within these conjugated diene systems. In previous studies, we have demonstrated both high regioselectivity and high enantioselectivity in the hydrogenation of dienamides[5] of type **3** where R_1=H using the Et-DuPHOS-Rh[6] catalyst.[7] In this case, high regioselectivity was attributed to substrate chelation through the dienamide *N*-acetyl group,[8] providing strong precedent for regioselective monoreduction in β-substituted dienamides **3** and **5**, ($R_1 \neq H$).

In terms of enantioselectivity, hindered β,β-disubstituted enamides present an additional challenge. However, we recently have reported that Me-DuPHOS-Rh and Me-BPE-Rh catalysts are very effective for highly enantioselective hydrogenation of this class of substrates.[9] In the present study we hoped to merge these two effects to develop a process for efficient and enantioselective hydrogenation of β-substituted dienamides **3** and **5** where $R_1 \neq H$. Importantly, selective hydrogenation of β-substituted dienamides would allow the simultaneous introduction of two contiguous stereogenic centers and could provide simple access to highly functionalized chiral building blocks.



Scheme 1

Exploratory investigation of catalytic efficiency was performed using the (2*Z*,4*E*)-dienamide **3b** (Table, entries 2 and 3) as a model substrate.[5] During optimization of reaction conditions, the first difficulty encountered was achieving full conversion of the starting materials to reduced products. Generally, higher catalyst loadings were required (0.4-1.0 mol%) in comparison to earlier studies[7] which employed substrate-to-catalyst ratios of 500:1. A survey of solvent effects indicated that *i*-PrOH was superior to other solvents for this transformation, although, generally, solvent effects should be examined for each individual substrate.

As we found with β,β-disubstituted enamides,[9a] cursory screening studies revealed that catalysts derived from the least hindered bis(phospholane) ligands, Me-DuPHOS and Me-BPE, were most effective for

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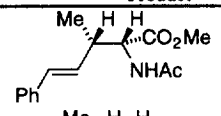
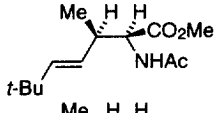
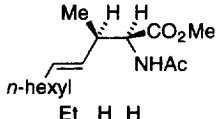
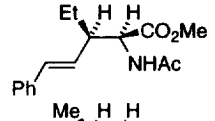
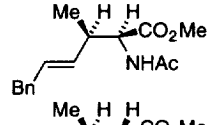
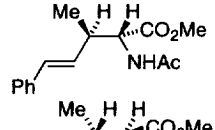
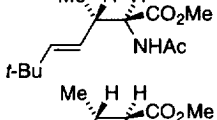
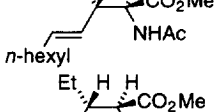
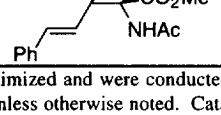
hydrogenation of β-substituted dienamide substrates of types **3** and **5**. On the basis of these results all remaining studies involving dienamides **3** and **5** centered on the Me-DuPHOS-Rh and Me-BPE-Rh catalysts.

Table. Asymmetric Catalytic Hydrogenations of (2*Z*)- and (2*E*)-Unsaturated Amino Acids 3 and 5[a]

Entry	Substrate	Product		Ligand	Conv'n (%)	%ee (Config.)[b]	Over-reduction(%)[c]
1	**3a**		(**4a**)	(*R*,*R*)-MeBPE[d]	100	90.6 (2*R*,3*S*)	≤ 5
	R_1=Me R_2=Ph						
2	**3b**		(**4b**)	(*S*,*S*)-MeDuPHOS[e]	100	81.9 (2*S*,3*R*)	5.1
3	R_1=Me R_2=*t*-Bu		(***ent*-4b**)[f]	(*R*,*R*)-MeBPE	100	78.0 (2*R*,3*S*)	2.5
4	**3c**		(**4c**)	(*S*,*S*)-MeDuPHOS[e]	100	75.6 (2*S*,3*R*)	9.4
5	R_1=Me R_2=*n*-hexyl		(***ent*-4c**)	(*R*,*R*)-MeBPE[e]	47	83.4 (2*R*,3*S*)	0
6	**3d**		(**4d**)	(*S*,*S*)-MeDuPHOS	92[g]	73.0 (2*S*,3*R*)	3.0
7	R_1=Et R_2=Ph		(***ent*-4d**)	(*R*,*R*)-MeBPE	100[g]	93.0 (2*R*,3*S*)	0
8	**3e**		(**4e**)	(*S*,*S*)-MeDuPHOS[e]	100	83.1 (2*S*,3*R*)	7.5
	R_1=Me R_2=Bn						
9	**5a**		(**6a**)	(*R*,*R*)-MeBPE[d]	100	95.9 (2*R*,3*R*)	≤ 5
	R_1=Me R_2=Ph						
10	**5b**		(**6b**)	(*S*,*S*)-MeDuPHOS	75	92.4 (2*S*,3*S*)	2.8
11	R_1=Me R_2=*t*-Bu		(***ent*-6b**)	(*R*,*R*)-MeBPE	45	95.6 (2*R*,3*R*)	4.2
12	**5c**		(**6c**)	(*S*,*S*)-MeDuPHOS	21	85.0 (2*S*,3*S*)	6.3
	R_1=Me R_2=*n*-hexyl						
13	**5d**		(**6d**)	(*S*,*S*)-MeDuPHOS	44[g,h]	94.0 (2*S*,3*S*)	0
14	R_1=Et R_2=Ph		(***ent*-6d**)	(*R*,*R*)-MeBPE	17[g]	96.0 (2*R*,3*R*)	0

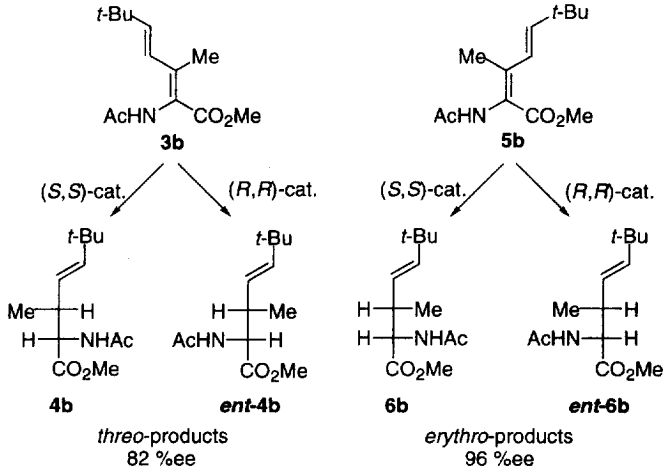
[a] Reactions are unoptimized and were conducted at 20-25 °C for 24-48 h under 90 psi H_2, using 0.10 M solutions of substrate in *i*-PrOH and S/C=250 unless otherwise noted. Catalyst precursors were the corresponding [COD-Rh-Ligand]OTf complexes. Analysis by NMR and chiral capillary GC on a Chrompak Chirasil-L-Val column followed passage through a short plug of silica. See reference 10 for a sample procedure. [b] Absolute configurations were assigned by comparing the sign of optical rotation of hydrolyzed (1M NaOH) product with that of known *N*-acetyl amino acids, by analogy, and through comparison of sign of optical rotation and chiral GC elution order with configurationally defined samples. [c] Enantiomeric purity of the overreduced material was not determined. [d] Result taken from reference 9a. [e] S/C=150. [f] *ent*-prefix indicates enantiomer of structure shown. [g] Reaction performed in MeOH. [h] Reaction time was 72h.

Results of studies involving catalytic asymmetric hydrogenation of a series of (2*Z*,4*E*)-dienamides **3** are shown in the Table[11] (entries 1-8). In most cases, the reaction performed with the Me-DuPHOS-Rh and Me-BPE-Rh catalysts proceeded with full conversion over 24h to furnish predominantly monoreduced product. In general, less than 10 % of the saturated or overreduced material was observed in these reactions. Two stereogenic centers at the α- and β-positions were set simultaneously with good to excellent enantiomeric excesses (73-93 %ee), despite the steric conjestion about the α,β-double bond. Styrene derivatives **3a** and **3d**

(entries 2, 7 and 8) were the most suitable substrates for this reaction, being reduced with enantiomeric excesses higher than 90 %.

Hydrogenations involving (2*E*,4*E*)-dienamides **5** were particularly challenging with regard to achieving complete conversion of the starting materials (Table, entries 9-14). Full conversion was demonstrated only with the β-methyl styrene derivative **5a**, and the stereoselectivities and regioselectivities achieved were excellent. Hydrogenations using the Me-DuPHOS-Rh catalyst tended to give better conversion, but lower selectivity than those using the Me-BPE-Rh catalyst.[12]

In accord with earlier studies,[11] the enantiomeric purity of monoreduced products was seen to fall as the reduction of the pendant double bond was allowed to proceed. In general these findings suggest that the predominant enantiomer initially formed is the matched substrate for subsequent reduction of the γ,δ-double bond.[13] Therefore, stopping the reaction before overreduction occurs is critical for obtaining products of higher enantiomeric purity. Due to increased hinderance about the α,β-double bond relative to the γ,δ-double bond, overreduction was difficult to control in many cases, particularly as the reaction approached completion. For several substrates, full conversion required us to sacrifice some material to overreduction and to accept a consequently lower enantiomeric purity in the product, as seen in **4b**, **4c**, and **4e**.[13] Although in the case of **6c** full conversion was not achieved, a similar correlation between overreduction and decreased enantiomeric purity was observed. Optimization of conditions on a case-by-case basis clearly is required to achieve high enantiomeric excess and maximal yield of the desired mono-reduced products **4** and **6**.



Scheme 2

This new method allows access to all four stereoisomeric β-substituted allylglycine derivatives with high levels of enantioselectivity. For example, the *Z*-*t*-butyl substrate (**3b**) was converted either to D- or L-*threo*-products **4b** (Scheme 2)[14] in diastereomerically pure form and with good enantioselectivity. Hence, with (*S*,*S*)-Me-DuPHOS-Rh, (2*S*,3*R*)-**4b** was obtained in 82 %ee, whereas the (2*R*,3*S*) product, ***ent*-4b**, resulted when (*R*,*R*)-Me-BPE was used (78 %ee). Furthermore the D- and L-*erythro* products, (2*S*,3*S*)-**6b** or (2*R*,3*R*)-***ent*-6b**, were produced in 92 %ee and 96 %ee through hydrogenation of (*E*)-*t*-butyl substrate **5b** using (*S*,*S*)-Me-DuPHOS or (*R*,*R*)-Me-BPE, respectively. Application of this process to (*Z*)- and (*E*)-3-ethyl-5-phenyl substrates **3d** and **5d** similarly yielded all four diastereomers **4d**, ***ent*-4d**, **6d**, and ***ent*-6d** in 73-96 %ee.

We have demonstrated the utility of the DuPHOS and BPE ligands in the asymmetric catalytic hydrogenation reactions of both (2*E*,4*E*)- and (2*Z*,4*E*)-β-substituted α,β,γ,δ-unsaturated amino acids. Catalysts derived from Me-BPE were found to afford the highest regioselectivity and enantioselectivity, while higher substrate conversion was achieved with Me-DuPHOS-Rh in several cases, particularly for the less reactive (2*E*,4*E*)-substrates. This method can be used to set contiguous stereogenic centers in a single step. Work is

underway to examine in more detail temperature effects in an effort to optimize these catalytic hydrogenation reactions.

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References and Notes

1. Please address correspondance to Chirotech Technology Limited, Cambridge Science Park, Milton Road, Cambridge, England, CB4 4WE.
2. Present address: Bristol-Meyers Squibb Incorporated, Department 203, Wallingford, CT, 06492.
3. Present address: Biogen Incorporated, 14 Cambridge Center, Cambridge MA, 02142.
4. (a) Burk, M. J.; Gross, M. F.; Harper, T. G. P.; Kalberg, C. S.; Lee, J. R.; Martinez, J. P. *Pure & Appl. Chem.* **1996**, *68*, 37 and references therein. (b) Burk, M. J.; Bienewald, F. "Unnatural α-Amino Acids *via* Asymmetric Hydrogenation of Enamides," in *Transition Metals for Organic Synthesis and Fine Chemicals*; C. Bolm and M. Beller Eds. Wiley VCH: Wienheim, 1998; Chapter 1, pp. 13-25.
5. For the synthesis of dienamide substrates, please see Burk, M. J.; Allen, J. G.; Kiesman, W. F.; Stoffan, K. M. *Tetrahedron Lett.* **1997**, *38*, 1309.
6. Abbreviations: DuPHOS 1,2-bis(phospholano)benzene; BPE 1,2-bis(phospholano)ethane.
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10. Sample procedure: **(2*S*,3*R*)-(4*E*)-methyl-2-acetamido-6-benzyl-3-methyl-hex-4-enoate (4e).** Under an inert atmosphere, a Fisher-Porter bottle was charged with degassed **3e** (0.050 g, 0.19 mmol), *i*-PrOH (2 mL) and 0.125 mL of a 0.01M solution of [(COD)Rh(*S,S*)-Me-DuPHOS]OTf (0.83 mg, 1.25 μmol). After five vacuum/H_2 cycles, the Fisher-Porter bottle was pressurized to 90 psi of H_2. The reaction was stirred for 24 hours at room temperature. Evaporation of the *i*-PrOH gave a yellow residue which was diluted in acetone (5 mL). The residue was filtered through a plug of silica gel and was eluted with 10-20 mL of acetone. The solvent was removed *in vacuo*: ee = 83.1%; $[\alpha]^{20}_D$ = +34.3 (c = 0.63, $CHCl_3$); ^{1}H NMR (acetone-d_6) δ 1.02-1.04 (d, 3H), 1.90 (s, 3H), 2.59-2.61 (m, 1H), 3.30-3.33 (d, 2H), 3.59 (s, 3H), 4.43-4.48 (dd, 2H), 5.46-5.52 (m, 1H), 5.57-5.65 (m, 1H), 7.17-7.31 (m, 5H); ^{13}C NMR (acetone-d_6) δ 15.00, 21.03, 37.90, 38.59, 50.29, 55.95, 125.16, 127.56, 12.72, 129.41, 131.56, 139.80, 168.37, 171.04; FAB-HRMS calcd for $C_{16}H_{22}NO_3$ (MH^+) *m/z* 276.1599, found 276.1600. Enantiomeric excess determination, Chirasil-L-Val column, inj. press. 25 psi, T=180 °C, t_R= 6.51 minutes.
11. All substrates and hydrogenated products gave satisfactory characterization data.
12. Preliminary results show that heating the reaction mixtures to 50-60 °C greatly improves reaction rate and substrate conversion without significantly diminishing stereoselectivity.
13. We proposed that stereoselectivity in the overreduction reaction took place due to double differentiation between the asymmetric catalyst and chiral monoreduced product. Where the major **4/6** enantiomer was the favored substrate for the overreduction reaction, the enantiomeric excess of **4/6** remaining would be expected to fall.
14. When (*R,R*)- and (*S,S*)-enantiomers of the same catalyst were used to give both enantiomeric products, the %ee's achieved were essentially identical, as is indicated in Scheme 2 for the most enantioselective catalyst, Me-BPE-Rh.