Influence of the Heterocyclic Ring on the Asymmetric Synthesis of β-Hetarylalanines by Homogeneous Catalytic Hydrogenation

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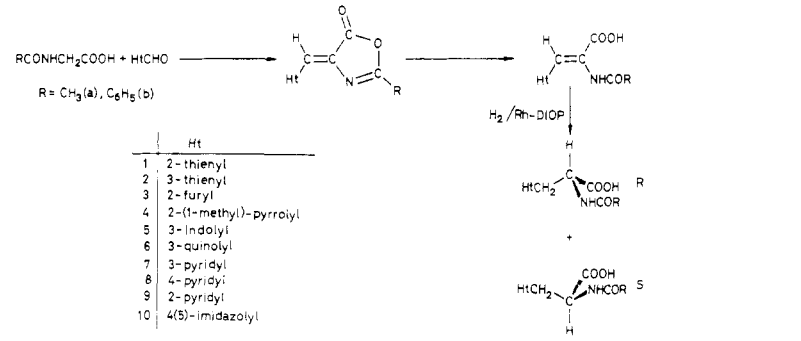
The use of chiral catalysts to effect asymmetric hydrogenation of prochiral olefinic substrates with high optical yields represents one of the most impressive achievements to date in catalytic selectivity. Results approaching 100% enantiomeric excess were achieved in the hydrogenation of prochiral enamides [(*Z*)-2-acetamidocinnamic acid derivatives] to the corresponding amides, using homogeneous neutral and cationic rhodium complexes containing chiral phosphine (especially chelating bis tertiary phosphine) ligands as catalysts.[1] The high enantioselectivity of reduction of various substrates with 2,3-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane (DIOP) metal systems may be attributed to the conformational rigidity of the trans-fused dioxolane within a chelate ring where diphosphine ligands are firmly bound to the metal.[2]

Several studies have shown the empirical dependence of the rates and stereoselectivities of these reductions on the electronic and structural features of the substrates. For example, the influence of steric and electronic factors on the homogeneous asymmetric hydrogenation of (*Z*)-2-(acylamino)cinnamic acids and esters by Rh–DIOP complexes has recently been reported.[3]

We present in this work our results concerning the asymmetric homogeneous hydrogenation of (*Z*)-2-acetamido- or -benzamido-3-hetarylpropenoic acids, readily available by standard methods,[4] to obtain the corresponding 2-acetamido- or -benzamido-3-hetarylpropanoic acids, using neutral and cationic Rh–DIOP systems as catalyst precursors. As far as we are aware the only precedents for the hydrogenation of prochiral precursors of this type are the asymmetric synthesis of tryptophan[5] and related compounds and the hydrogenation of (*Z*)-2-acetamido- and -benzamido-3-(2-thienyl)propenoic acids.[6]

Scheme I



The prochiral precursors, (*Z*)-2-acetamido- or -benzamido-3-hetarylpropenoic acids **1–10**, obtained by standard methods[4] (Scheme I) were hydrogenated in the presence of neutral or cationic Rh–DIOP complexes (see Experimental Section). The ten starting aldehydes (2-thiophenecarboxaldehyde, 2-furancarboxaldehyde, 2-pyrrolecarboxaldehyde, 3-indolecarboxaldehyde, 2-pyridinecarboxaldehyde, 3-pyridinecarboxaldehyde, 4-pyridinecarboxaldehyde, 3-quinolinecarboxaldehyde, 4-(5)-imidazolecarboxaldehyde, and 3-thiophenecarboxaldehyde) were derived from a representative set of heterocycles. For synthetic reasons it was decided to use *N*-methyl-2-pyrrolecarboxaldehyde instead of 2-pyrrolecarboxaldehyde.[7] Products **4a** and **9a** could not be obtained by any of the methods we tried.

All prochiral precursors were hydrogenated under the same experimental conditions, which were previously chosen with **1a** and **1b** in order to obtain a fast hydrogenation with a reasonable enantioselectivity[6] (1 mmol of substrate in 15 mL of absolute ethanol; [substrate]/[Rh] = 30; temperature = 50 °C; [Rh]/[DIOP] = 1; pressure = 1 atm). However a pressure of 4 atm was employed with those compounds that did not undergo complete hydrogenation under standard conditions. DIOP was chosen as ligand due to require less time for complete the reaction than other five-membered chelators in the hydrogenation of **1a** and **1b**.[8]

All reduction products were directly converted into the methyl esters with diazomethane, and the enantiomeric excess was determined by ^{1}H NMR spectroscopy in the presence of Eu(tfc)$_3$, by determining the relative peak areas of the ester methyl singlets. The results are summarized in Table I.

We have previously reported[3f] our results in the hydrogenation of the (*Z*)-2-acetamido- or -benzamido-3-arylpropenoic acids to the corresponding *N*-acylphenylalanines. In both this series and the heterocyclic one, the use of (−)-DIOP always results in the formation of (−)-*N*-acetyl and (+)-*N*-benzoyl amino acids. A reverse situation was, of course, observed for (+)-DIOP hydrogenation, with similar enantiomeric excess.

On the basis of the earlier work on *N*-acylphenylalanines,[9] we tried to find a relation between the position of the peaks of both enantiomers in ^{1}H NMR and the

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Table I. Homogeneous Asymmetric Hydrogenation of (Z)-2-Acetamido- or -Benzamido-3-hetarylpropenoic Acids, Catalyzed by Rh–DIOP Systems[a] at 1 atm

compd	catalyst precursor[b]	Et_3N/Rh	time,[c] min	% ee[d]
1a	N(−)	0	240	62
1a	N(−)	1	240	55[e]
1a	C(−)	0	<1	72
1a	C(−)	1	30	67[e]
1b	N(−)	0	120	22
1b	N(−)	1	120	14[e]
1b	C(−)	0	<1	22
1b	C(−)	1	30	19[e]
2b	N(−)	0	90	10
3a	N(−)	0	180	9[e]
3a	C(−)	0	150	3[e]
3b	N(−)	0	270	6
3b	N(−)	1	270	8[e]
3b	C(−)	0	7	13
3b	C(−)	1	10	19[e]
4b	N(−)	0	255	33
4b	N(−)	1	240	13[e]
4b	C(−)	0	2	30
4b	C(−)	1	8	21[e]
5a	N(−)	0	105	86
5a	N(−)	1	105	49[e]
5a	N(−)	30	120	4[e]
5a	C(−)	0	2	75
5a	C(−)	1	7	66[e]
5a	C(−)	30	50	30[e]
5b	N(−)	0	120	32
5b	N(−)	1	120	21[e]
5b	N(−)	30	120	6[e]
5b	C(−)	0	2	27
6a	N(−)	0	360	54
6a	C(−)	0	300	70
6b	N(−)	0	1440[f]	45
6b	C(−)	0	1440[f]	45
6b	N(−)	0	1440[i]	55
7a	N(−)	0	2880[f]	35
7a	C(−)	0	2880[f]	34
7b	N(−)	0	2880[f,i]	20

[a] 1 mmol of substrate in 15 mL of absolute ethanol; [substrate]/[Rh] = 30; temperature = 50 °C. [b] N(−) = $^1/_2$[RhCl(COD)]$_2$ + (−)-DIOP; C(−) = [Rh(COD)(−)-DIOP]ClO_4. [c] Time required for complete hydrogenation under standard conditions except where indicated. [d] Percentage enantiomeric excess determined by ^{1}H NMR with Eu(tfc)$_3$. [e] Some decomposition of the catalyst precursor to rhodium metal. [f] Hydrogenation incomplete in time indicated. [g] Compounds **8a**, **8b**, **9b**, and **10b** underwent no hydrogenation. [h] Similar results were obtained when (+)-DIOP was used. [i] 4-atm pressure.

absolute configuration of the major enantiomer.

When the specific rotation of the obtained *N*-acyl amino acid was known, we were able to determine by polarimetry the configuration of the major enantiomer and assign to this enantiomer the major peak of the ester methyl singlets in ^{1}H-NMR spectrum in the presence of Eu(tfc)$_3$.

The results support the relative generality of the asymmetric hydrogenation of enamides showing that (*S*)-hydrogenated products are formed from (+)-DIOP–Rh systems, while (*R*)-hydrogenated products are obtained when (−)-DIOP–Rh catalysts are used.

The ten heterosubstitutents chosen displayed very different behavior in hydrogenation. As seen in Table I, the prochiral substrates may be divided into two groups, (a) those with a five-membered heterocyclic ring with one heteroatom (**1–5**) and (b) those with a five-membered ring with two heteroatoms or a six-membered ring (**6–10**). The members of the first group required less time for complete hydrogenation than the members of the second one.

In agreement with similar work[10] on other substrates, hydrogenations of substrates of the first group (**1–5**) were faster with the cationic catalyst than with the neutral ones, but the enantiomeric excess was of the same order. The low enantioselectivity, and the small differences in the hydrogenation rate, in the reduction of **3a** could be attributed to extensive decomposition of the catalyst observed in this case, the metallic rhodium so formed contributes heterogeneously to the hydrogenation of the prochiral substrate to the racemic product.

It is known[3e] that when 1 equiv of triethylamine is added to the hydrogenation systems, the substrate will probably be in the (Et_3^+NH)(RCO_2^-) form. Furthermore, triethylamine may facilitate the formation of neutral catalytic species by deprotonation of the cationic ones. The addition of triethylamine, especially when a large excess was used, increased the time required for total hydrogenation with cationic catalyst, whereas variations were hardly noticed with neutral catalytic systems. The low enantioselectivity observed in some cases (especially when a large excess of triethylamine was used) could be attributed to the extensive decomposition of the catalyst to rhodium metal, which ocurred in these instances and which would lead to a partial heterogeneous hydrogenation.

As previously reported[3b] the enantiomeric excess was better for (*Z*)-2-acetamido-3-hetarylpropenoic acids than for their benzamido analogues with the exception of **3a,b** for the reasons previously explained.

In contrast, only small differences were found for the second group (**6–10**) between cationic and neutral systems when hydrogenation was observed. Particularly acetamido derivatives seem to undergo hydrogenation more easily than benzamido derivatives.

Experimental Section

Synthesis of Prochiral Substrates. Infrared spectra were determined on a Perkin-Elmer Model 283 instrument. Proton magnetic resonance spectra were obtained on a Perkin-Elmer R-12B spectrometer. Mass spectra were recorded on a Hewlett-Packard 5930A spectrometer at an ionization potential of 70 eV. The prochiral substrates, (*Z*)-2-acetamido- and -benzamido-3-hetarylpropenoic acids were obtained by alkaline hydrolysis of the corresponding (*Z*)-2-methyl- or -phenyl-4-hetarylidene-5(4*H*)-oxazolones, which were prepared from the carboxaldehyde and aceturic or hippuric acid, respectively. The chemistry of 5(4*H*)-oxazolones has repeatedly been reviewed[4] and the prochiral substrates were prepared by standard procedures. In a typical experiment 1 mol of carboxaldehyde, 1 mol of aceturic or hippuric acid, 1 mol of anhydrous sodium acetate, and 3 mol of acetic anhydride were heated for a variable time. The solid azlactone was filtered and recrystallized by using a suitable solvent and was then hydrolyzed to the corresponding propenoic acid. (*Z*)-2-Acetamido-3-(3-indolyl)propenoic acid was prepared by decarboxylative condensation of the 3-indolcarboxaldehyde with the ethyl half-ester of acetamidomalonic acid in acetic anhydride–pyridine in high yield.[5c] All the compounds exhibited the expected infrared, proton magnetic resonance, and mass spectra.

Catalytic Hydrogenations. Catalytic hydrogenations were carried out following standard procedures, previously reported,[6] in a glass apparatus at atmospheric pressure and 50 °C; alternatively a Parr apparatus was used. Most reactions mixtures were allowed to stand until hydrogenation of the prochiral substrates was complete; the reaction was stopped after a predetermined time when total hydrogenation was not reached. In a typical experiment, 1 mmol of substrate in 15 mL of absolute ethanol was hydrogenated in the presence of the complexes [RhCl(COD)]$_2$ or [Rh(COD)$_2$]ClO_4 and DIOP as chiral diphosphine, which was purchased from Strem Chemicals Inc. and used as received.

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Workup of Hydrogenation Product. The corresponding solutions of 2-acetamido- or -benzamido-3-hetarylpropanoic acids after hydrogenation were evaporated to dryness, and one of the following procedures was used to isolate the hydrogenation product.

A. In the cases of 2-acetamido-3-(3-pyridyl)propanoic acid (**7a**) and 2-acetamido-3-(3-quinolyl)propanoic acid (**6a**) the residue was dissolved in water and separated from the insoluble catalyst by filtration. Evaporation to dryness afforded the product; yields were essentially 100% except for the slowest reactions (time ≳1440 min).

B. In the cases of 2-benzamido-3-(2-thienyl)propanoic acid (**1b**), 2-benzamido-3-(2-furyl)propanoic acid (**3b**), 2-benzamido-3-[1-methylpyrrol-2-yl]propanoic acid (**4b**), 2-benzamido-3-(3-indolyl)propanoic acid (**5b**), 2-benzamido-3-(3-pyridyl)propanoic acid (**7b**), 2-benzamido-3-(3-quinolyl)propanoic acid (**6b**), and 2-benzamido-3-(3-thienyl)propanoic acid (**2b**), the residue was dissolved in 0.5 N sodium hydroxide and separated from the insoluble catalyst by filtration. The filtrate was acidified with dilute hydrochloric acid and the precipitate filtered and dried, giving the desired product.

C. In the cases of 2-acetamido-3-(2-thienyl)propanoic acid (**1a**), 2-acetamido-3-(2-furyl)propanoic acid (**3a**), and 2-acetamido-3-(3-indolyl)propanoic acid (**5a**), the residue was dissolved in 0.5 N sodium hydroxide and separated from the insoluble catalyst by filtration. The filtrate was acidified with dilute hydrochloric acid and extracted with diethyl ether. The ethereal extract was dried and evaporated to dryness to afford the product.

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Registry No. **1a**, 83396-73-0; **1b**, 83396-72-9; **2b**, 88991-22-4; **3a**, 89908-19-0; **3b**, 89890-88-0; **4b**, 89890-89-1; **5a**, 70082-70-1; **5b**, 85622-38-4; **6a**, 89890-90-4; **6b**, 89890-91-5; **7a**, 89890-92-6; **7b**, 89890-93-7; $[RhCl(COD)]_2$, 12092-47-6; (-)-DIOP, 32305-98-9; $[Rh(COD)$-(-)-$DIOP]ClO_4$, 70832-57-4; (*R*)-2-acetamido-3-(2-thienyl)propanoic acid, 83396-77-4; (*R*)-2-benzamido-3-(2-thienyl)propanoic acid, 83396-74-1; (*R*)-2-benzamido-3-(3-thienyl)propanoic acid, 89921-39-1; (*R*)-2-acetamido-3-(2-furyl)propanoic acid, 89890-94-8; (*R*)-2-benzamido-3-(2-furyl)propanoic acid, 89955-20-4; (*R*)-2-benzamido-3-[2-(1-methyl)pyrrolyl]propanoic acid, 89890-95-9; (*R*)-2-acetamido-3-(3-indolyl)propanoic acid, 2280-01-5; (*R*)-2-benzamido-3-(3-indolyl)propanoic acid, 55629-71-5; (*R*)-2-acetamido-3-(3-quinolyl)propanoic acid, 89890-96-0; (*R*)-2-benzamido-3-(3-quinolyl)propanoic acid, 89890-97-1; (*R*)-2-acetamido-3-(3-pyridyl)propanoic acid, 89890-98-2; (*R*)-2-benzamido-3-(3-pyridyl)propanoic acid, 89955-25-9.

Chromatographic Separation of the Enantiomers of N-Acylated Heterocyclic Amines

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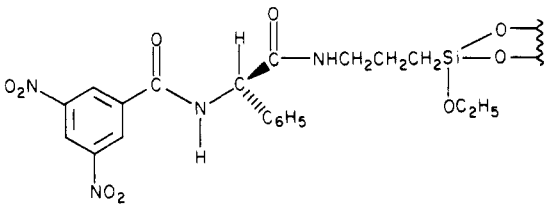
In a previous paper, we have described the use of chiral stationary phase (CSP) 1 for the liquid chromatographic separation of enantiomers of assorted amines, amino alcohols, esters, and C-terminal amides of α-amino acids, all as the N-α-naphthoyl derivatives. Herein, we extend this method to cover a number of heterocyclic amines.

The column used in this study is a commercial version[1] of our previously reported[2] covalently bound (R)-*N*-(3,5-dinitrobenzoyl)phenylglycine stationary phase, 1.[3] Table



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I gives data pertinent to the elution order and chromatographic separability of the enantiomers of a variety of N-α-naphthoyl heterocyclic amines, some of which are themselves or are closely related to compounds that are of pharmacological interest. Accordingly, this technique should be of considerable utility to chemists and pharmacologists as a means of both determining enantiomeric purity and absolute configuration on microgram quantities of material and preparatively resolving large quantities of material.[5]

The order of elution of the enantiomers from a given chiral column is determined by their stereochemistry. The absolute configuration of a given amine may be determined by chromatographic comparison with authentic, configurationally known material, collection of one enantiomer for chiroptic evaluation, or from chiral recognition models that relate stereochemistry to elution order. While the absolute configurations of relatively few of the compounds in the table have thus far been rigorously related to elution order, it is believed that, for all of the compounds of type **2**, **3**, and **5** shown in the table, the most strongly retained enantiomer has the configuration indicated. Note that the elution order of enantiomers from this type of column, coupled with asymmetric synthesis data, has already been used in the assignment of absolute configuration of several of the tetrahydroisoquinolines listed in the table.[6]

Although we have postulated chiral recognition models to account for the separation of other enantiomeric amides on CSP 1, we defer detailed discussion of the mechanism(s) presently operative. Such discussion would require knowledge of the conformational preferences of both CSP and solutes. Arguments relevant to the former have been presented, but conformational behavior of the latter is still unknown. In the case of the naphthamide solutes, the amide nitrogen and its adjoining carbons would prefer, for electronic reasons, to be coplanar with the α-naphthoyl system. However, steric interaction with the proximate peri and β-hydrogens of the naphthyl system undoubtedly cause some departure from coplanarity. The sense and

(1) Regis Chemical Co., 8010 Austin Ave., Morton Grove, IL 60053. J. T. Baker Chemical Co. also offers a covalent column of this type that is satisfactory in this application.

(2) Pirkle, W. H.; House, D. W.; Finn, J. M. *J. Chromatogr.* **1980**, *192*, 143.

(3) The reported separations can also be effected with use of commercial columns (Regis, J. T. Baker, Chemical Co.) packed with the ionically bound version[4] of CSP 1.

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