Homogeneous Hydrogenation of Tetrasubstituted Alkene Moieties in Prochiral Didehydro Amino Acid Derivatives Catalysed by Iridium Complexes

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The hydrogenation of the tetrasubstituted alkene moieties of the prochiral didehydro amino acid derivatives (**1a** and **b**), (**2a** and **b**), (**3b**), (+)- and (−)-(**6**), (+)-(**7**), and (−)-(**9**) has been successfully achieved under very mild homogeneous conditions (1 atm of H_2; 293 K) by using iridium complexes of the type $[Ir(cod)(bzn)(L)][ClO_4]$ [cod = cyclo-octa-1,5-diene, bzn = benzonitrile, L = tricyclohexylphosphine, (−)-neomethyldiphenylphosphine, or (+)-phenyl-(*o*-methoxyphenyl)methylphosphine] as catalyst precursors. The presence of chiral groups in the catalysts or in the unsaturated substrates produces little optical induction; the enantiomeric excesses obtained were less than 27% in all cases.

During the last few years, many efforts have been devoted to the synthesis of optically active amino acid precursors *via* asymmetric hydrogenation of prochiral didehydro amino acid derivatives over rhodium catalysts containing chiral phosphine ligands.[1,2] Carrying on with our search for synthetic routes to new amino acids,[2–4] we have recently reported the preparation of the tetrasubstituted didehydro amino acid derivatives (**2a** and **b**) and (**3b**),[4] but unfortunately the rhodium catalytic systems for asymmetric hydrogenation are unable to reduce tetrasubstituted alkenes under mild conditions. Since optically active new amino acids may be of great biological interest,[5] we looked for a system capable of hydrogenating tetrasubstituted didehydro amino acid derivatives homogeneously and asymmetrically under mild conditions (1 atm of H_2; 293 K).

Ten years ago, Crabtree *et al.*[6] reported that the mixed-ligand complex $[Ir(cod)(py)(PCy_3)][PF_6]$ (cod = cyclo-octa-1,5-diene, py = pyridine, Cy = cyclohexyl) is a very active olefin hydrogenation catalyst in non-co-ordinating solvents, although it is generally deactivated in absence of substrate. This complex is able to hydrogenate the tetrasubstituted olefin 2,3-dimethylbut-2-ene,[6a] but the catalyst is deactivated progressively during the reaction giving rise to an inactive trinuclear hydride cluster.[7] As far as we are aware, no iridium complexes containing monodentate phosphine ligands have been studied as asymmetric hydrogenation catalysts. In addition, although iridium complexes containing chelating diphosphines have been used to model some intermediates in the rhodium-catalysed system for asymmetric hydrogenation of prochiral didehydro amino acids,[8] they are not effective catalysts at 293 K.[6a,8]

In this paper we report on the effectiveness of mixed-ligand cationic iridium(I) complexes for the hydrogenation of prochiral tetrasubstituted didehydro amino acid derivatives and on how the presence of chiral groups in the catalysts or in the substrates affects the optical activity of the products. Part of this work has been communicated in preliminary form.[9]

Results and Discussion

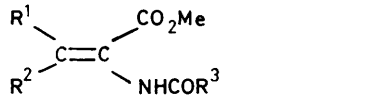
The results (Table 1) show that the complex $[Ir(cod)(py)(PCy_3)][ClO_4]$ is an effective catalyst precursor for the hydrogenation of the tetrasubstituted olefins (**1a** and **b**). However, the analogous complex $[Ir(cod)(py)(nmdpp)][ClO_4]$, containing the chiral ligand (−)-neomenthyldiphenylphosphine (nmdpp), is inactive under similar conditions. Although we still do not know the reason for this difference in reactivity it must arise from either the different size or the lower basicity (or both) of the nmdpp ligand as compared with those of PCy_3. Since benzonitrile (bzn) is a sterically less demanding and weaker ligand than pyridine, we thought that it could be appropriate for the iridium catalytic systems. In fact, excellent results were obtained with the benzonitrile derivatives $[Ir(cod)(bzn)(L)][ClO_4]$ (L = PCy_3 or nmdpp). Thus, 200 mg of substrate [(**1a** or **b**) or (**2a** or **b**)] were completely hydrogenated after 15 s with 20 mg of $[Ir(cod)(bzn)(PCy_3)][ClO_4]$ as catalyst precursor, whereas 30 min [for (**1a** or **b**)] or 48 h [for (**2a** and **b**)] were required when $[Ir(cod)(bzn)(nmdpp)][ClO_4]$ was used.

As shown in Table 1, with the iridium-catalysed systems some unexpected and interesting features were observed. In

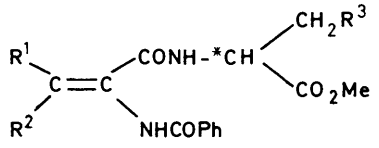
Table 1. Results for the hydrogenation of methyl *N*-acetyl α,β-didehydro α-amino acid esters[a]

Catalyst precursor	Substrate	Time	Yield (%)	E.e. (%)[b]
$[Ir(cod)(py)(PCy_3)][ClO_4]$	(**1b**)	6 h	100	
	(**1b**)	6 h	100	
$[Ir(cod)(py)(nmdpp)][ClO_4]$	(**1a**)	21 h	0	
	(**1b**)	21 h	0	
$[Ir(cod)(bzn)(PCy_3)][ClO_4]$	(**1a**)	15 s	100	
	(**1b**)	15 s	100	
	(**2a**)	15 s	100	
	(**2b**)	15 s	100	
$[Ir(cod)(bzn)(nmdpp)][ClO_4]$	(**1a**)	30 min	100	7
	(**1b**)	30 min	100	4
	(**2a**)	48 h	100	27
	(**2b**)	48 h	100	19
	(**3b**)	5 h	100	8
	(**4a**)	6 h	17	
	(**4b**)	50 h	18	
	(**5b**)	50 h	75[c]	
$[Ir(cod)(bzn)(pamp)][ClO_4]$[d]	(**1a**)	24 h	100	0
	(**1b**)	4 h	35	
	(**1b**)	48 h	75	0
	(**2b**)	62 h	41[e]	
	(**4b**)	48 h	30	

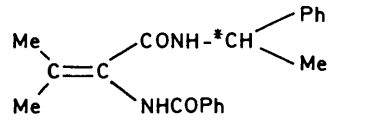
[a] At 293 K and 1 atm of H_2. [b] E.e. = enantiomeric excess; all the predominant products correspond to the (+)-enantiomers. [c] An 8% yield of (**4b**) was observed in the reaction mixture. [d] With this catalyst the reactions were carried out at 293 K and 5 atm of H_2. [e] A 46% yield of the hydrogenated product of (**3b**) was observed in the reaction mixture.



(1) $R^1 = R^2 = Me$ a; $R^3 = Me$
(2) $R^1 = Me, R^2 = Ph$ b; $R^3 = Ph$
(3) $R^1 = Ph, R^2 = Me$
(4) $R^1 = H, R^2 = Ph$
(5) $R^1 = Ph, R^2 = H$



(6) $R^1 = R^2 = Me, R^3 = Ph$
(7) $R^1 = Me, R^2 = R^3 = Ph$
(8) $R^1 = R^2 = Me, R^3 = CH_2$ -S-Me



(9)

particular, the hindered tetrasubstituted olefins (**1a** and **b**), (**2a** and **b**), and (**3b**) were hydrogenated much faster than the less hindered trisubstituted substrates (**4a** and **b**) and (**5b**), and the *E*-derivatives [(**3b**) and (**5b**)] were hydrogenated faster than the *Z*-compounds [(**2b**) and (**4b**)], in contrast with the reported observations with rhodium catalysts.[1h] Furthermore, the catalytic species were not deactivated either during the reactions or when the substrates had been consumed, probably being protected from deactivation by co-ordination of the hydrogenated products, which can be replaced subsequently by the unsaturated substrates. Unfortunately, all attempts to identify the iridium species after the hydrogenation ended were unsuccessful.

It is well known that *Z*-olefins co-ordinate to metals better than *E*-derivatives; this has been ascribed[10] to steric hindrance of the *pro-E* group R^1 to olefin co-ordination. The same effect must occur with trisubstituted as compared with tetrasubstituted olefins, since in a competitive experiment where a 1:1 ratio of the *Z*-tetrasubstituted (**2b**) and the *Z*-trisubstituted (**4b**) olefin was hydrogenated over $[Ir(cod)(bzn)(PPh_3)][ClO_4]$ (a less active catalyst than the nmdpp derivative, used in order to facilitate monitoring of the reaction course at different hydrogenation times), ^1H n.m.r. indicated that when 50% of (**4b**) had been consumed 80% of unchanged (**2b**) still remained in the solution. Nevertheless when the substrates were hydrogenated separately the *Z*-tetrasubstituted derivative (**2b**) was hydrogenated faster than the *E*-trisubstituted compound (**4b**) (Table 1).

Similarly, in another competitive experiment with a 1:1 ratio of the *Z*-trisubstituted olefin (**4b**) and the *E*-trisubstituted derivative (**5b**) (with the same catalyst as before), after 1.5 h hydrogenation more (**4b**) had been consumed than (**5b**), whereas when the substrates were hydrogenated separately the *E*-trisubstituted olefin (**5b**) was hydrogenated faster than the *Z*-trisubstituted derivative (**4b**) (Table 1).

These results indicate that the rate of the reaction is influenced by factors that, although related to the degree of substitution of the olefins and to the stereochemistry of the alkene moieties, are not connected with the co-ordination ability of the substrates.

Table 2. Results for the hydrogenation of chiral *N*-acyl α,β-didehydro α-amino acid amides[a]

Catalyst precursor	Substrate	Yield (%)	D.e. (%)[b]
$[Ir(cod)(bzn)(PCy)_3][ClO_4]$	(+)-(**6**)	100	7
	(−)-(**6**)	100	4
	(+)-(**7**)	100	6
	(+)-(**8**)	0	
	(−)-(**9**)	100	5
$[Ir(cod)(bzn)(nmdpp)][ClO_4]$	(+)-(**6**)	100	6
	(−)-(**6**)	100	4
	(+)-(**7**)	100	10
	(+)-(**8**)	0	
	(−)-(**9**)	100	0
$[Ir(cod)(bzn)(pamp)][ClO_4]$	(+)-(**6**)	100	10
	(−)-(**6**)	100	11
	(+)-(**7**)	100	13
	(−)-(**9**)	100	10

[a] At 293 K and 1 atm of H_2 for 48 h. [b] D.e. = Diastereoisomeric excess.

These remarkable hydrogenation results, as far as activity is concerned, are in contrast with the poor enantiomeric excesses obtained by using the chiral complex $[Ir(cod)(bzn)(nmdpp)][ClO_4]$ as catalyst precursor (Table 1). Trying to increase the optical yield of the hydrogenations, we tested the complex $[Ir(cod)(bzn)(pamp)][ClO_4]$, containing the chiral ligand (+)-phenyl-(*o*-methoxyphenyl)methylphosphine (pamp), as catalyst precursor, since this ligand is one of the few monophosphines which gives good optical yields in the hydrogenation of trisubstituted didehydro amino acid precursors with rhodium catalysts.[11] Surprisingly, the reactions were extremely slow at 293 K under 1 atm of H_2, and even under 5 atm of H_2 most of the reactions were incomplete after 48 h (Table 1), the optical yields being negligible. The tendency of iridium(I) towards pentaco-ordination is higher than that of rhodium(I) and probably the oxygen atom of the phosphine *o*-methoxyphenyl group interacts with the iridium in such a way that it blocks one or more of the steps of the catalytic hydrogenation process.

When chiral groups, L-phenylalanine [as in (+)-(**6**) or (+)-(**7**)], D-phenylalanine [as in (−)-(**6**)], or D-1-phenylethylamine [as in (−)-(**9**)], were incorporated in the unsaturated substrates in the form of amides, the hydrogenation activity was also very good, but the optical yields did not increase, regardless of whether chiral or achiral catalysts were used (Table 2). However, it has been reported[12] that rhodium catalysts hydrogenate didehydro dipeptide derivatives containing trisubstituted alkene moieties with optical yields as high as 99%.

The results reported by Brown *et al.*,[13] Crabtree *et al.*,[14] and Lukacs *et al.*[15] concerning the homogeneous hydrogenation of prochiral alkenes in which the presence of a co-ordinatively available group in the substrate directs the selectivity of the reactions towards one of the possible optical isomers, prompted us to introduce an L-methionine group into our tetrasubstituted substrates [as in (+)-(**8**)]; the presence of a sulphur atom in the substrate might be expected to direct the optical selectivity of the hydrogenation. Disappointingly, no hydrogenation was observed, perhaps owing to the presence of the sulphur atom on the substrate. However, (*Z*)-2-benzamido (or acetamido)-3-(2-thienyl)propenoic acid was efficiently hydrogenated by rhodium complexes;[2b] in this case, the catalysts are not affected by the presence of the sulphur atom.

Experimental

Analyses (C, H, and N) were carried out with a Perkin-Elmer 240-C microanalyser. I.r. spectra were recorded with a Perkin-

Elmer 783 spectrophotometer. ^{1}H N.m.r. spectra were recorded with a Bruker CW-80-SY or a Varian XL-200 spectrometer for solutions in $CDCl_3$ with $SiMe_4$ as internal standard. M.p.s were measured with a Büchi 510 capillary apparatus. Optical rotations were determined with a Perkin-Elmer 241-MC polarimeter. Solvents were dried and distilled prior to use. All reactions involving the synthesis of iridium compounds were carried out under nitrogen by using standard Schlenk techniques.

Synthesis of Substrates.—*N*-Acetyldidehydrovaline methyl ester (**1a**),[16] *N*-benzoyldidehydrovaline methyl ester (**1b**),[17] (*Z*)-*N*-acetyl-β-methyldidehydrophenylalanine methyl ester (**2a**),[4] (*Z*)-*N*-benzoyl-β-methyldidehydrophenylalanine methyl ester (**2b**),[4] (*E*)-*N*-benzoyl-β-methyldidehydrophenylalanine methyl ester (**3b**),[4] (*Z*)-*N*-acetyldidehydrophenylalanine methyl ester (**4a**),[18] (*Z*)-*N*-benzoyldidehydrophenylalanine methyl ester (**4b**),[18] (*E*)-*N*-benzoyldidehydrophenylalanine methyl ester (**5b**),[18] (+)-(*N*-benzoyldidehydrovalyl)-L-phenylalanine methyl ester (+)-(**6**),[19] and (−)-(*N*-benzoyldidehydrovalyl)-D-phenylalanine methyl ester (−)-(**6**)[19] were prepared according to previously described procedures.

(+)-[(*Z*)-N-*Benzoyl*-β-*methyldidehydrophenylalanyl*]-L-*phenylalanine methyl ester* (+)-(**7**). 2-Phenyl-4-(2-phenylethylideneoxazol)-5(4*H*)-one was treated with sodium L-phenylalaninate, by Bergman's procedure,[20] to afford (+)-[(*Z*)-*N*-benzoyl-β-methyldidehydrophenylalanyl]-L-phenylalanine, which on subsequent reaction with diazomethane gave the *methyl ester* (+)-(**7**) (78%), m.p. 136—138 °C (from EtOH–H_2O) (Found: C, 73.6; H, 6.2; N, 6.1. $C_{27}H_{26}N_2O_4$ requires C, 73.3; H, 5.9: N, 6.3%); δ(200 MHz; $CDCl_3$) 2.23 (3 H, s), 3.22 (2 H, d, *J* 6 Hz), 3.72 (3 H, s), 5.04 (1 H, dt, *J* 8 and 6 Hz), 6.91 (1 H, d, *J* 8 Hz), and 6.90—7.55 (16 H, m).

(+)-(N-*Benzoyldidehydrovalyl*)-L-*methionine methyl ester* (+)-(**8**). 2-Phenyl-4-isopropylideneoxazol-5(4*H*)-one was treated with sodium L-methioninate, by Bergman's procedure,[20] to afford (+)-(*N*-benzoyldidehydrovalyl)-L-methionine, which on subsequent reaction with diazomethane gave the *methyl ester* (+)-(**8**) (67%), m.p. 175—177 °C (from EtOH–H_2O) (Found: C, 58.9; H, 6.8; N, 7.5. $C_{18}H_{24}N_2O_4S$ requires C, 59.3; H, 6.6; N, 7.7%); δ(200 MHz; $CDCl_3$) 1.77 (3 H, s), 2.00 (3 H, s), 2.04 (3 H, s), 2.11 (2 H, m), 2.55 (2 H, t, *J* 6 Hz), 3.72 (3 H, s), 4.75 (1 H, m), 7.25—7.55 (4 H, m), 7.75—7.95 (2 H, m), and 8.37 (1 H, br s).

(−)-N-(D-1-*Phenylethyl*)-N$^{\alpha}$-*benzoyldidehydrovalylamide* (−)-(**9**). A solution of 2-phenyl-4-isopropylideneoxazol-5(4*H*)-one (1 mmol) and D-1-phenylethylamine (3 mmol) in benzene (10 cm^3) was refluxed for 30 h, then cooled to room temperature. The precipitate was filtered off, washed with benzene, and dried to give the *amide* (−)-(**9**) (78%), m.p. 215—217 °C (from EtOH–H_2O) (Found: C, 74.0; H, 7.2; N, 8.6. $C_{20}H_{22}N_2O_2$ requires C, 74.5; H, 6.9; N, 8.7%); δ(200 MHz; $CDCl_3$) 1.49 (3 H, d, *J* 7 Hz), 1.64 (3 H, s), 1.82 (3 H, s), 5.14 (1 H, m), 7.25—7.55 (9 H, m), 7.90—7.95 (2 H, m), and 8.68 (1 H, br s).

Synthesis of Catalyst Precursors.—**CAUTION**. Perchlorates present an explosion hazard and must be handled with care. They all were prepared generally as dichloromethane solvates following Crabtree's procedure[21] for synthesis of $[Ir(cod)(PCy_3)(py)][BF_4]\cdot CH_2Cl_2$, using the appropriate phosphine ligand, pyridine or benzonitrile, and $Ag[ClO_4]$ instead of $Ag[BF_4]$. All ligands were obtained commercially with the exception of pamp, which was prepared by reduction with trichlorosilane[22] of the corresponding phosphine oxide pampo (supplied by Professor H. B. Kagan). Analysis and yields *etc.* were as follows: $[Ir(cod)(py)(PCy_3)][ClO_4]\cdot CH_2Cl_2$, 78% (Found: C, 46.0; H, 6.1; N, 2.0. $C_{32}H_{52}Cl_3IrNO_4P$ requires C, 45.5; H, 6.2; N, 1.7%); $[Ir(cod)(py)(nmdpp)][ClO_4]\cdot CH_2Cl_2$, 73% (Found: C, 48.9; H, 5.0; N, 1.8. $C_{36}H_{48}Cl_3IrNO_4P$ requires C, 48.7; H, 5.45; N, 1.6%); $[Ir(cod)(bzn)(PCy_3)][ClO_4]\cdot CH_2Cl_2$, 68% (Found: C, 47.6; H, 6.4; N, 1.6. $C_{34}H_{52}Cl_3IrNO_4P$ requires C, 47.0; H, 6.0; N, 1.6%); $\nu_{max.}$ 2 252w cm^{-1} (CN); $[Ir(cod)(bzn)(nmdpp)][ClO_4]\cdot CH_2Cl_2$, 76% (Found: C, 49.6; H, 5.35; N, 1.8. $C_{38}H_{48}Cl_3IrNO_4P$ requires C, 50.0; H, 5.3; N, 1.5%); $\nu_{max.}$ 2 248w cm^{-1} (CN); $[Ir(cod)(bzn)(pamp)][ClO_4]\cdot CH_2Cl_2$, 85% (Found: C, 44.2; H, 4.3; N, 1.6. $C_{30}H_{34}Cl_3IrNO_5P$ requires C, 44.0; H, 4.2; N, 1.7%); $\nu_{max.}$ 2 243w cm^{-1} (CN); $[Ir(cod)(bzn)(PPh_3)][ClO_4]$, 87% (Found: C, 52.0; H, 4.4; N, 2.0. $C_{33}H_{32}ClIrNO_4P$ requires C, 51.8; H, 4.2; N, 1.8%); $\nu_{max.}$ 2 247w cm^{-1} (CN).

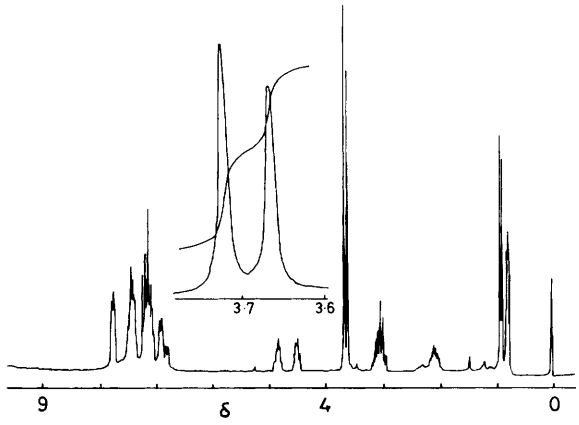


Figure. 200 MHz ^{1}H N.m.r. spectrum ($CDCl_3$) of the mixture of diastereoisomers obtained from a 48 h hydrogenation (293 K; 1 atm of H_2) of (−)-(**6**) with $[Ir(cod)(bzn)(pamp)][ClO_4]$ as catalyst precursor

Catalytic Hydrogenations.—The reactions under 1 atm of H_2 were performed in a previously described hydrogen-vacuum line.[2b] The hydrogenations at 5 atm of H_2 were carried out in a Parr reactor.

In a typical run, substrate (200 mg) and catalyst precursor (20 mg), dissolved in dichloromethane (12 cm^3), were shaken under the appropriate pressure of H_2 at 293 K. After the required time, the solvent was removed and the residue extracted several times with hot hexane and filtered to separate the catalyst; evaporation to dryness left the product. The results are shown in Tables 1 and 2. Yields were estimated by ^{1}H n.m.r. integration of the methyl ester singlets after (Table 1) or before (Table 2) the catalyst was removed. The enantiomeric excesses shown in Table 1 were measured by integration of the methyl ester singlets perturbed by tris-{3-[trifluoromethyl(hydroxy)-methylene]-(−)-camphorato}europium(III) [$Eu(tfc)_3$]. The diastereoisomeric excesses shown in Table 2 were measured by direct ^{1}H n.m.r. integration of the methyl ester singlets, since the products are diastereoisomers and have different ^{1}H n.m.r. spectra (Figure).

Acknowledgements

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