Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 19 (2008) 273–278

Histidine and deuterium labelled histidine by asymmetric catalytic reduction with gaseous H_2 or D_2; the role of strong non-coordinating acids

E. Cesarotti,[a,*] I. Rimoldi,[a] D. Zerla[a] and G. Aldini[b]

[a] *Università di Milano, Facoltà di Farmacia, Dipartimento di Chimica Inorganica, Metallorganica e Analitica e Istituto CNR-ISTM. Via G. Venezian 21, 20133 Milano, Italy*

[b] *Università di Milano, Facoltà di Farmacia, Istituto di Chimica Farmaceutica e Tossicologica 'Pietro Pratesi' Via Mangiagalli 25, 20133 Milano, Italy*

Received 27 September 2007; accepted 18 December 2007
Available online 5 February 2008

Abstract—An efficient and convenient route for the preparation of natural and unnatural histidine by asymmetric hydrogenation with rhodium–phosphine complexes is described. The reductions were performed in the presence of HBF_4 to generate an essential imidazolyl cation. Stereoselective incorporation of D_2 in the α,β-positions was obtained by catalytic deuteration in the presence of MeOD.

1. Introduction

The discovery that a massive dose of L-dopa, a rare α-amino acid, was useful in treating Parkinson's disease created the conditions that led to the development of the catalytic asymmetric hydrogenation with a modified Wilkinson catalyst; at present, this technology is one of the methods of choice for the preparation of enantiomerically pure bioactive molecules, particularly α- and β-amino acids, both natural and unnatural ones.[1]

From the pioneering works of Knowles[2,3] and Kagan,[4] an enormous amount of literature and excellent books are now available on the industrial applications of transition metal asymmetric hydrogenation.[1,5,6]

When hydrogen is substituted by deuterium it is possible to prepare amino acids selectively dideuterated at the α and β carbon atoms; deuterium labelled amino acids are useful probes to establish protein/peptide biochemical and metabolic pathways, as well as for absolute protein quantization using stable isotope labelled peptides and HPLC–MS.[7] Hence, deuterium labelled amino acids represent a significant synthetic target and a substantial catalogue of synthetic and biosynthetic strategies for the preparation of labelled α-amino acids are currently available.

Not all the proteinogenic amino acids are available selectively deuterated in high enantiomeric purity and among the missing aminoacids, histidine **1** and its deuterium labelled analogue, especially stand out.

Among others, a potential application of deuterated L-histidine is to better understand the biochemical and metabolic fate of histidine dipeptides, such as carnosine **2** and homocarnosine (Fig. 1). Such peptides are contained in a mM concentration range in some tissues such as skeletal muscle, heart and brain, and in humans their source is food. Although carnosine **2** was discovered in the beginning of the 20th century, its biological function has not been clarified, and several theories have been put forward: intracellular buffer, immune modulator, neurotransmitter,

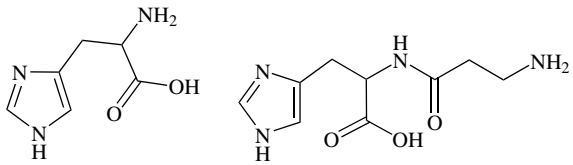


Figure 1.

* Corresponding author. Tel.: +39 02 503 14390; fax: +39 02 503 14405; e-mail: edoardo.cesarotti@unimi.it

0957-4166/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2007.12.013

metal-ion chelator, antioxidant, and free-radical scavenger.[8] More recently, it has been proposed that carnosine detoxifies reactive carbonyl species, cytotoxic compounds deriving from the oxidative degradation of polyunsaturated fatty acids and carbohydrates, involved in the development/progression of a variety of chronic diseases and recently recognized as potential drug target.[9] To gain a deeper insight into the biological functions of this class of histidine peptides, as well as to elucidate their metabolic and pharmacokinetic properties, deuterium labelled carnosine is required for MS studies. Moreover, we recently found that the isomerization of L- to D-histidine aminoacid leads to a derivative (D-carnosine),[10] which is not recognized by the catalytic site of carnosinase (a specific serum dipeptidase that rapidly hydrolyzes L-carnosine in vivo)[11] while maintaining its ability to detoxify reactive carbonyl species.

To study the bioavailability and pharmacokinetic profile of D-carnosine, a deuterium labelled derivative is needed to be distinguished by endogenous L-carnosine in LC–MS experiments. Hence, the aim of the present work is to synthesize deuterium labelled L- and D-histidine as synthons of labelled L- and D-carnosine, respectively.

D-Carnosine is cited as an equivalent to L-carnosine, but due to its favourable pharmacokinetic properties, durability to hydrolysis by the carnosinases, and stability in the plasma, D-carnosine seems to produce better therapeutic results than the L-form.

2. Results and discussion

Asymmetric hydrogenation by means of transition metal phosphine complexes gives access to both the enantiomers of histidine and to the corresponding deuterated analogues, which in turn can be used in the preparation of labelled peptides.

In this work, we present our results concerning the preparation of the precursor of D-carnosine, the unnatural enantiomer D-histidine, by asymmetric hydrogenation with [Rh(COD)(Diphosphine)]BF_4 of (*Z*)-2-benzamido-4(5)-*N*-imidazolylpropenoic acid **3a** and (*Z*)-2-benzamido-4(5)-*N*-imidazolylpropenoic acid methyl ester **3b**, readily available by standard azalactone methods (Fig. 2).[12] Many different routes are described to the α,β-didehydro-α-aminoacid derivatives;[13] usually the substituent on the nitrogen atom in the enamide precursor is an acetyl group; in the case of histidine, however, the *N*-acetyl imidazolyl propenoic acid is not accessible either with the Erlenmayer-azalactone method or with the Wadsworth–Emmons variation of the Wittig reaction;[14] on the other hand, benzamido **3a** and **3b** can be prepared by Erlenmayer method from hippuric acid in the pure *Z* form in an almost quantitative yield.

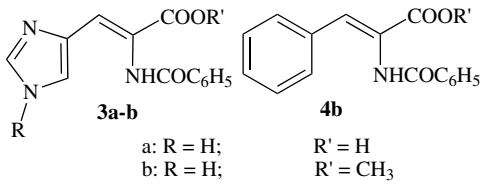


Figure 2.

The chiral diphosphine ligands investigated (Fig. 3) are the commercially available (*S*,*S*)-(+)-DIOP, (*R*,*R*)-(−)-Me-DuPHOS and (*S*,*S*)-(−)-BDPP, together with (*R*)-(−)-Prolophos,[15] the prototype of a successful class of chelating aminophosphine-phosphinite ligands derived from chiral α-amino alcohols developed in our laboratory.

The results are summarized in Table 1.

Reductions are performed in MeOH, at 293 K under 1 bar of H_2 if not otherwise stated; catalysts precursors are prepared by standard procedures, that is, by ligand exchange between [Rh(COD)$_2$]ClO_4 and the appropriate diphosphine in CH_2Cl_2 followed by evaporation of the solvent.

One of the oldest papers dealing with the preparation β-heteroarylalanines by asymmetric hydrogenation stated that (*Z*)-2-benzamido-4(5)-*N*-(*R*)-imidazolylpropenoic acid **3a** underwent no hydrogenation.[16]

More recently, non-natural nitrogen containing aminoacids such as 3- and 4-pyridylalanines have been obtained by asymmetric hydrogenation in the presence of 1 equiv of HBF_4 to generate the corresponding pyridinium salts.[17,18]

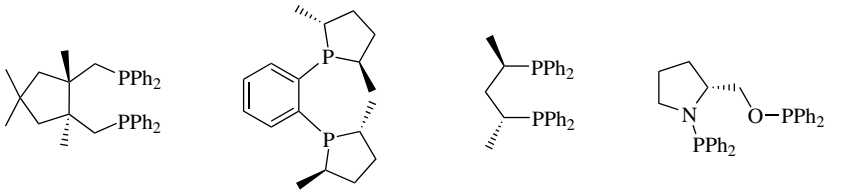
Really, we failed in reducing the free (*Z*)-2-benzamido-4(5)-*N*-imidazolylpropenoic acid **3a** in all the reaction conditions investigated as well as in the presence of 1 equiv (with respect to the substrate) of HCl (entry 2).

This confirms that basic nitrogen in the substrate, close to the metal when coordinated, may compete with the amido moiety and block the formation of the reactive enamide–rhodium complex. This could be avoided by protonation of the imidazolyl basic nitrogen with a strong non-coordinating acid.

Substrate **3a** is quantitatively reduced in high enantiomeric purity only when the ratio of HBF_4/substrate is increased to 4 (entry 3). It is worth mentioning however that, due to the great excess of HBF_4 necessary to ensure complete hydrogenation in a reasonable reaction time, *N*-benzoylhistidine is isolated only as methyl ester **3b**.

Because (*Z*)-2-benzamido-4(5)-*N*-imidazolylpropenoic acid methyl ester **3b** is hydrogenated with comparable rate and stereodifferentiation than acid **3a** and because **3a**·**HBF$_4$** and **3b**·**HBF$_4$**, quantitatively formed by the excess of HBF_4, are soluble only in methanol (or ethanol), the solvent of choice for the catalytic reduction, we did not investigate if esterification occurred prior or after hydrogenation as in both the cases, only methyl (or ethyl) ester **1b** was obtained.

In the absence of HBF_4 ester **3b** is reduced to a very low extent (6%, entry 4); decreasing the ratio of substrate/catalyst to 50/1 conversion increases to 57% (entry 5). Only reducing the substrate/catalyst ratio to an unacceptable



(*S*,*S*)-(+)-DIOP (*R*,*R*)-(-)-Me-DUPHOS (*S*,*S*)-(-)-BDPP (*R*)-(-)-PROLOPHOS

Figure 3.

Table 1. Asymmetric hydrogenation of substrates **3a** and **3b**

Entry	Sub.	Ligand	Acid	Sub/acid	Time (h)	Yield (%)	ee (%)
1	**3a**	(*S*,*S*)-(+)-DIOP	—	—	24	0	
2	**3a**	(*R*,*R*)-(−)-Me-DUPHOS	HCl	1/1	120	0	
3	**3a**	(*R*,*R*)-(−)-Me-DUPHOS	HBF_4	1/4	120	100	87.32
4	**3b**	(*R*,*R*)-(−)-Me-DUPHOS	—	—	120	6	N.D.
5[a]	**3b**	(*S*,*S*)-(+)-DIOP	—	—	120	57	5.53
6[b]	**3b**	(*R*,*R*)-(−)-Me-DUPHOS	—	—	72	100	25.02
7	**3b**	(*R*,*R*)-(−)-Me-DUPHOS	HBF_4	1/4	72	100	79.07
8	**3b**	(*S*,*S*)-(+)-DIOP	HBF_4	1/4	72	100	14.93
9	**3b**	(*R*)-Prolophos	HBF_4	1/4	72	100	71.01
10	**3b**	(*S*,*S*)-BDPP	HBF_4	1/4	48	100	67.96

[a] Sub/cat 50/1, P_{H_2} 30 atm.
[b] Sub/cat 6/1.

6/1 means that it is possible to obtain complete conversion but with a moderate stereodifferentiation (25% ee, entry 6).

Increasing the ratio of HBF_4/substrate from 0/1 to 4/1 conversion becomes quantitative and ee% reaches the highest values (compare entries 4 vs 7 and entries 5 vs 8, respectively). The best stereodifferentiation is obtained with (*R*,*R*)-(−)-Me-DUPHOS (entry 3) followed by (*R*)-(−)-Prolophos (entry 9), (*S*,*S*)-(−)BDPP (entry 10), and (*S*,*S*)-(+)-DIOP (entry 8).

Labelled aminoacids and peptides are of paramount importance in life sciences; because labelled histidine seems not to be commercially available in any form, we found it obvious to extend our research to prepare L- and D-histidine in the double deuterated form by catalytic asymmetric deuteration; the results are summarized in Table 2 and in Scheme 1.

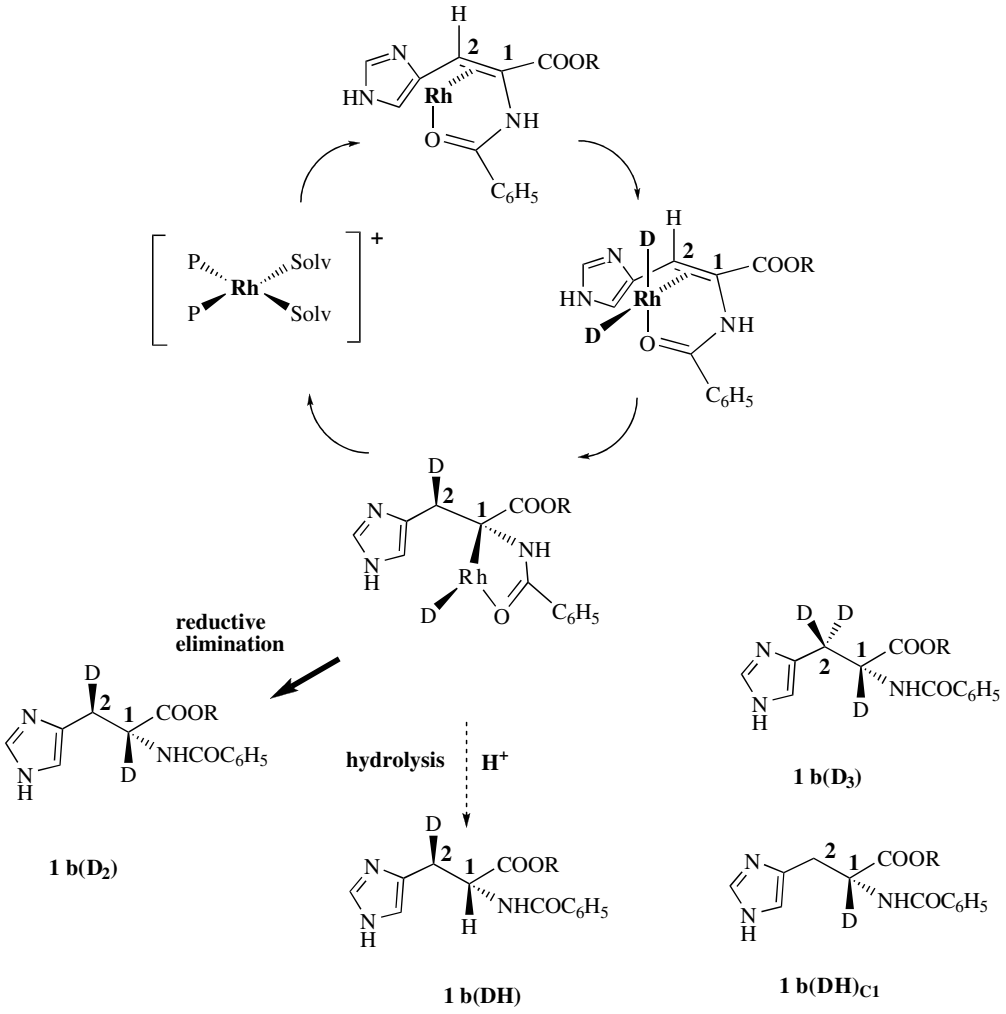
The extent of deuterium incorporation is determined by mass spectrometry (ESI) and confirmed by ^{1}H NMR. The reduction under D_2 in MeOH/HBF_4 gives the desired dideuterated *N*-benzoyl-histidine methyl ester **1b**($\mathbf{D_2}$) together with a variable percentage of monodeuterated *N*-benzoyl-histidine methyl ester **1b**(**DH**) incorporating deuterium only at the C_2 carbon (entries 1, 2, and 4).

In Figure 4a are shown the ^{1}H NMR spectra of **1b**($\mathbf{H_2}$) (M^++1 = 274) obtained by asymmetric hydrogenation under H_2 as reported in Table 1, entry 7. Figure 4b shows the ^{1}H NMR spectra of **1b**($\mathbf{D_2}$) (M^++1 = 276) obtained by asymmetric reduction under D_2 in MeOD as reported in Table 2, entry 3; in this case, the hydrogen on C_1 at 4.8 ppm is not detectable. Because the mass spectrometry (MS-ESI$^+$) does not indicate the presence of **1b**(**D3**) (M^++1 = 278), we conclude that the product is exclusively the α,β-dideuterated product **1b**($\mathbf{D_2}$); this is confirmed by the 3:1 integration of the methyl ester at 3.65 ppm versus the signal of the hydrogen on C_2 at 3.15 ppm. For the sake of clarity, Figure 4c shows the ^{1}H NMR spectra of a mixture of **1b**($\mathbf{D_2}$) (89%) and **1b**(**DH**) (11%), obtained by asymmetric reduction under D_2 as reported in Table 2, entry 5, and confirmed by MS-ESI$^+$ spectroscopy.

The mechanism of asymmetric hydrogenation of α-amino-acid precursors with rhodium(I) complexes has been elucidated in detail[19,20] and the rate determining step has been identified in the oxidative addition of hydrogen (or deuterium) to the square planar Rh(I)phosphine/substrate adduct. Because no trideuterated **1b**(**D3**) or monodeutereted **1b**($\mathbf{DH})_{C1}$ species of histidine incorporating deuterium at the C_1 are detected, we argue that the monodeutereted histidine incorporating hydrogen selectively at the C_1 is essen-

Table 2. Asymmetric deuteration of (*Z*)-2-benzamido-4(5)-*N*-imidazolylpropenoic acid methyl ester **3b**

Entry	Solv.	S/C	Ligand	Time (h)	Yield (%)	ee (%)	**1b** (DH)%
1	MeOH	1000/1	(−)-Me-DUPHOS	72	12	N.D.	40
2	MeOH	200/1	(−)-Me-DUPHOS	72	100	87.73	27.3
3	MeOD	200/1	(−)-Me-DUPHOS	72	100	89.15	0
4	MeOH	200/1	(*R*)-PROLOPHOS	72	100	67.94	75
5	MeOD	200/1	(*R*)-PROLOPHOS	72	72	69.32	11



Scheme 1.

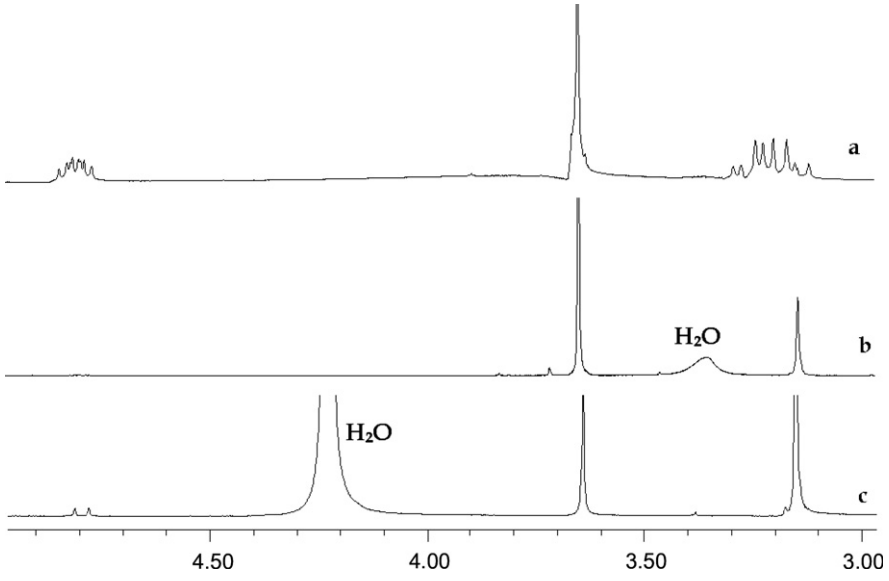


Figure 4. ^{1}H NMR spectra of (*R*)-(+)-*N*-benzoyl-histidine-methylester, **1b**($\mathbf{H_2}$), 4a; 100% incorporating D_2, **1b**($\mathbf{D_2}$), 4b; a mixture of **1b**($\mathbf{D_2}$) and monodeuterated **1b**(**DH**), 4c.

tially due to the competition between reductive elimination and external protonation of the σ-deutero-Rh-alkyl intermediate by H+ of the solvent (Scheme 1); because the rate of protonation could be assumed to be constant, the percentage of monodeuterated **1b**(**DH**) should depend on the overall activity of the catalysts; thus, to obtain the desired dideuterated *N*-benzoyl-histidine methyl ester **1b**($\mathbf{D_2}$) in 100% chemical purity we are forced to use MeOD, as solvent (entry 3). But even in MeOD the less reactive but cheaper [Rh(*R*)-Prolophos] catalyst still gives 11% monodeuterated histidine **1b(DH)**, incorporating deuterium selectively at C_2.

The reason is the essential presence of HBF_4 as it is demonstrated by the asymmetric deuteration of *N*-benzoyl-cinnamic acid methyl ester **4b** (Scheme 2).

The results are summarized in Table 3.

[Rh((*R*,*R*)-(−)-Me-DUPHOS)] gives higher enantiodifferentiation and affords *N*-benzoyl-phenylalanine methyl ester **5b**($\mathbf{D_2}$), 100% dideuterated, either in MeOH or in MeOD (entries 1 and 2); addition of 4 equiv of HBF_4 in MeOH gives 4% of the monodeuterated **5b**(**DH**) (entry 3), in turn suppressed completely when MeOD is used as a solvent (entry 4).

[Rh((R)-(−)-Prolophos)] gives 29% of **5b**(**DH**) (entry 5) in MeOH, completely suppressed when MeOD is used (entry 6). Addition of HBF_4 in MeOH brings back the percentage of monodeuterated **5b**(**DH**) to 30% (entry 7); lowered but is not completely suppressed when MeOD is used (entry 8).

3. Conclusion

We have demonstrated that it is possible to prepare histidine derivatives in high enantiomeric purity and to incorporate deuterium regiospecifically to obtain D_2 isotopically labelled histidine. Our results confirm that deuterium is introduced onto the α and β-positions from gaseous D_2; the competitive incorporation of deuterium or hydrogen in the α-position is probably dependent on the competition between reductive elimination and protonation of the intermediate σ-alkylrhodium by the H^+ of the solvent; anyway we cannot definitively rule out an exchange reaction of type [Rh]-D ↔ [Rh]-H between the σ-monohydride complex and the solvent, at least until we are be able to obtain pure DBF_4.

Work is in progress to investigate the role of strong acids other than HBF_4 and the substrates with different substituents on the imidazolyl ring.

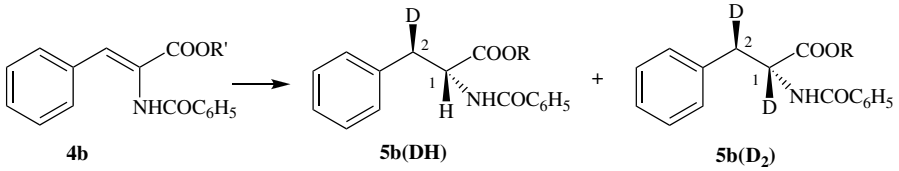
4. Experimental

Catalytic reactions are performed in a 100 mL glass autoclave equipped with magnetic stirrer. Unless otherwise stated, materials are obtained from commercial source and used without further purification. The rhodium catalyst is prepared according to the established literature procedure.[21]

^{1}H NMR spectra: Bruker DRX Avance 300 MHz equipped with a non-reverse probe and Bruker DRX Avance 400 MHz. HPLC analysis: Merck-Hitachi L-7100 equipped with Detector UV6000LP and Diacel Chiralcel OD or Chiralpak AD. Polarimetry analyses: Perkin Elmer 343 Plus equipped with Na/HaI lamp.

4.1. Preparation of 3a, 3b, and 4b

(*Z*)-4-((1*H*-Imidazol-5-yl)methylene)-2-phenyloxazolidin-5-one, (*Z*)-2-benzamido-3-(1*H*-imidazol-5-yl)acrylic acid **3a**, (*Z*)-methyl 2-benzamido-3-(1*H*-imidazol-5-yl)acrylate **3b**, and (*Z*)-methyl 2-benzamido-3-phenylcrylate **4b** are prepared according to the literature methods.[22]



4b **5b(DH)** **5b(D_2)**

Scheme 2.

Table 3. Asymmetric deuteration of *N*-benzoyl-cinnamic acid methyl ester **4b**

Entry	Solv.	Acid	Ligand	Time (min)	Yield (%)	ee (%)	**5b** (DH)%
1	MeOH	—	(−)-Me-DUPHOS	30	100	95.12	0
2	MeOD	—	(−)-Me-DUPHOS	120	100	88.14	0
3	MeOH	HBF_4	(−)-Me-DUPHOS	30	100	94.03	4
4	MeOD	HBF_4	(−)-Me-DUPHOS	120	100	95.07	0
5	MeOH	—	(*R*)-PROLOPHOS	15	100	73.96	29
6	MeOD	—	(*R*)-PROLOPHOS	15	100	87.015	0
7	MeOH	HBF_4	(*R*)-PROLOPHOS	15	100	67.95	30
8	MeOD	HBF_4	(*R*)-PROLOPHOS	20	100	79.01	4

4.2. General procedure for asymmetric hydrogenation

In a Schlenk tube under argon, a suspension of substrate and the proper amount of HBF_4 in ether is stirred for 30 min at room temperature. The resulting solution is transferred with a cannula to a Schlenk tube containing the proper amount of Rh(I) catalyst and then into a glass autoclave connected to a gas burette filled with H_2 or D_2.

4.3. Preparation of racemic and (*S*)-(−)-methyl 2-benzamido-3-(4,5-dihydro-1*H*-imidazol-5-yl)propanoate as HPLC standards

Thionyl chloride (1.05 mL, PM = 118.97, $d = 1.63$, 14.38 mmol) is added dropwise to the suspension of commercially available (*S*)-(+)-histidine monohydrochloride (2.2967 g, PM = 193, 11.9 mmol) in 50 mL of methanol and the solution is refluxed for 12 h then reduced under vacuum to give racemic or (*S*)-(+)-histidine methyl ester dihydrochloride as a white solid. Elemental Anal. Calcd for $C_7H_{13}N_3O_2Cl_2$: C, 34.73; H, 5.41; N, 17.36. Found: C, 34.66; H, 5.52; N, 17.52. ^{1}H NMR: ppm 2.25 (m, 2H), 3.73 (s, 3H), 7.52 (s, 1H), 9.07 (s, 1H), 14.63 (s, 2H). 2.7799 g, yield 96.6%.

Under an inert atmosphere, a solution of benzoyl chloride (2.1 mL, PM = 140, $d = 1.212$, 18.5 mmol) and TEA (5.12 mL, PM = 101, $d = 0.726$, 36.8 mmol) is added dropwise to the suspension of racemic or (*S*)-(+)-histidine methyl ester dihydrochloride (2.2118 g, 9.2 mmol) in 30 mL of dry chloroform. The suspension is stirred at room temperature for 2 days, then 30 mL of water is added and the solution is extracted with 2 × 20 mL of chloroform.

The combined organic layers are dried and evaporated in vacuum to give yellow oil. The crude oil residue is dissolved in 50 mL of MeOH saturated with $NaHCO_3$; after 15 min of vigorous stirring at room temperature the excess of $NaHCO_3$ is neutralized with glacial acetic acid. The solvent is removed in vacuum and the oily residue is dissolved in 25 mL of water and extracted with 4 × 20 mL of chloroform. The combined organic layers are dried and evaporated to leave yellow oil. The oil is triturated with 30 mL of hexane to give (*S*)-(−)-methyl 2-benzamido-3-(4,5-dihydro-1*H*-imidazol-5-yl)propanoate as a white solid (PM = 273, 1.9 mmol, yield 21%).

Elemental Anal. Calcd for $C_{14}H_{15}N_3O_3$: C, 61.53; H, 5.53; N, 15.38. Found: C, 61.30; H, 5.51; N, 15.64. ^{1}H NMR: ppm 3.2 (d, 2H), 3.65 (s, 3H), 4.8 (q, 1H), 6.8 (s, 1H), 7.5 (m, 4H), 7.8 (d, 2H), 8.8 (d, 1H). For (*S*)-(−)-methyl 2-benzamido-3-(4,5-dihydro-1*H*-imidazol-5-yl)propanoate $[\alpha]_D^{25} = -70.7$ (*c* 0.5 in HBF_4 1.6 M in CH_3OH).

Acknowledgments

This work has been funded by the FIRST, Università degli Studi di Milano and by Flamma s.p.a. Via Bedeschi, 22-24040 Chignolo D'Isola-BG-Italy. We also wish to thank Johnson Matthey Plc; indeed this work has been realized by using their generous loan of $RhCl_3 \cdot 3H_2O$.

References

1. *Asymmetric Catalysis on Industrial Scale*; Blaser, H. U., Schmidt, E., Eds.; Wiley-VCH, 2003.
2. Vineyard, B. D.; Knowles, W. S.; Sabaky, M. J.; Bachman, G. L.; Weinkauff, D. J. J. *J. Am. Chem. Soc.* **1977**, *99*, 5946.
3. Knowles, W. S. *Acc. Chem. Res.* **1983**, *16*, 106.
4. Kagan, H. B.; Dang, T. P. *J. Chem. Soc., Chem. Commun.* **1971**, 481.
5. *The Handbook of Homogeneous Hydrogenation*; de Vries, J. G., Elsevier, C. J., Eds.; Willey-VCH: Weinheim, 2007; Vol. 1–3.
6. *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999.
7. Fenselau, C. *J. Chromatogr. B: Anal. Technol. Biomed. Life Sci.* **2007**, *855*, 14–20.
8. Aldini, G.; Facino, R. M.; Beretta, G.; Carini, M. *Biofactors* **2005**, *24*, 77–87.
9. Aldini, G.; Dalle Donne, I.; Colombo, R.; Maffei Facino, R.; Milzani, A.; Carini, M. *Chem. Med. Chem.* **2006**, *1*, 1045–1058.
10. *Redox Proteomics: From Protein Modifications to Cellular Dysfunction and Diseases*; Carini, M., Aldini, G., Maffei Facino, R., Dalle-Donne, I., Scaloni, A., Butterfield, D. A., Eds.; Wiley, 2006.
11. Vistoli, G.; Pedretti, A.; Cattaneo, M.; Aldini, G.; Testa, B. *J. Med. Chem.* **2006**, *49*, 3269–3277.
12. Erlenmeyer, E.; Halsey, J. T. *Justus Liebig's Ann. Chem.* **1899**, *307*, 138.
13. Masquelin, T.; Broger, E.; Müller, K.; Schmid, R.; Obrecht, D. *Helv. Chim. Acta* **1994**, *77*, 1395.
14. Schmidt, U.; Langer, B.; Kirschbaum, B.; Braun, C. *Synthesis* **1994**, 1138.
15. Cesarotti, E.; Chiesa, A. *Tetrahedron Lett.* **1982**, *43*, 275.
16. Cativela, C.; Mayoral, J.; Melendes, E.; Oro, L.; Pinillos, M.; Uson, R. *J. Org. Chem.* **1984**, *49*, 2502.
17. Döbler, C.; Kreuzfeld, H. J.; Michalik, M.; Krause, H. W. *Tetrahedron: Asymmetry* **1996**, *7*, 117.
18. Bozell, J. J.; Voght, C. E.; Gozum, J. J. *J. Org. Chem.* **1991**, *56*, 2584.
19. Halpern, J.. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: Orlando, FL, 1985; Vol. 5, and references cited therein.
20. Feldgus, S.; Landis, C. R. *J. Am. Chem. Soc.* **2000**, *122*, 12714.
21. Genet, J. P. *Acc. Chem. Res.* **2003**, *36*, 908–918.
22. Erlenmeyer, E.; Halsey, J. T. *Justus Liebig's Ann. Chem.* **1899**, *307*, 138.