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Synthesis of non-proteinogenic (D)- or (L)-amino acids by asymmetric hydrogenation

Review Article

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Summary. Non-proteinogenic amino acids play an increasing role in oligopeptide chemistry. Their pharmacological and chemical properties, caused by D-configuration and "unnatural" residues, are more and more used for drug design. Different methods of asymmetric synthesis have been developed during the last decade to prepare "unusual" amino acids. One of them, the asymmetric hydrogenation of dehydroamino aids catalyzed by chiral rhodium (I) complexes, will be described. A series of examples, D- and L-configured, like naphthyl-, thienyl-, furyl-, and pyridylalanines, as well as phenylalanines substituted by chlorine, fluorine, p-nitro, p-methyl, p-trifluoromethyl, p-isopropyl, and p-tert-butyl have been prepared and characterized. Some analytical data like melting points and values of optical rotation are summarized in tables.

Keywords: Amino acids – Non-proteinogenic optically active amino acids – D- and L-enantiomers – Dehydroamino acids – Chiral rhodium catalysts – Asymmetric hydrogenation

Abbreviations: (−) - DIOP; (4R,5R) - 4,5 - Bis(diphenylphosphinomethyl) - 2,2 - dimethyl - 1,3 - dioxolane; (−) - BPPM: (2S,4S) - N - tert - Butoxycarbonyl - 4 - diphenylphosphino - 2 - diphenylphosphinomethyl - pyrrolidine; Ph - β - glup: Phenyl 4,6 - O - (R) - benzylidene - 2,3 - O - bis(diphenylphosphino) - β - D - glucopyranoside, DuPHOS: 1,2-bis-(phospholano)benzene; PROPRAPHOS: 2,3-O,N-bis(diphenylphosphino)-1-(naphthoxy)-2-hydroxy-3-isopropylamino propane; PINDOPHOS: 2,3-O,N-bis(diphenylphosphino)-1-(4-indolyloxy)-2-hydroxy-3-isopropylamino propane

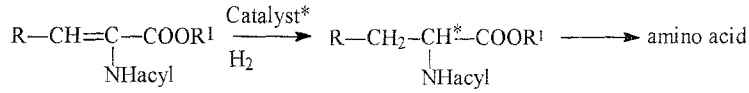
Introduction

Non-proteinogenic amino acids have attracted the interest of many chemists since it is known that significant modifications of biological activity in a peptide can be effected by inversion of configuration at one or more chiral centers, or by replacement of one or more "natural" amino acids by "unnatural" amino acids. Different denotations like non-proteinogenic, non-protein, non-coded, unnatural, and unusual have been introduced in the literature to underline that this type of amino acids differs from the 20 "standard" amino acids, the building stones of life. Today about 700 unnatural amino acids are known, most of them are recognized as secondary metabolites and therefore it is often very difficult to find out their origin (see Lubec and Rosenthal, 1990; Wagner and Musso, 1983; Seebach et al., 1989, 1991; Williams, 1989; Hunt, 1991). As a representative of a natural product may be mentioned Cyclosporin A, a cyclic undecapeptide, produced as the main metabolite by the fungus Beauveria nivea. This peptide contains D-alanine at position 8 and is successfully applied particularly to prevent graft rejection in organ transplantation (Wenger, 1986).

During the last years other unnatural amino acids have received much interest because of their anticipated pharmacological and chemical properties and their incorporation into synthetic peptides. Recently the ASTA-Medica AG published the LH-RH antagonist Cetrorelix to be a high effective antitumor agent in human hormon sensitive breast cancer and prostatic cancer. The decapeptide contains five D-configured non-coded amino acids (Reissmann et al., 1994). Last results of a clinical study showed a clear superiority of the D-Cit^6 diastereomer over the L- and D,L-Cit^6 analogues (Pinski et al., 1995). D-Amino acids have been also used in enkephalin agonists (Morgan et al., 1977), somatostatin analogues (Wynants et al., 1988) and others. The role of structure modifications to conformational constrains has been reviewed (Hruby et al., 1990).

Besides the enzymatic synthesis of non-proteinogenic amino acids, today used in many cases in an industrial scale, also the enantioselective synthesis offers a broad access to natural as well as unnatural amino acids. D. Seebach and coworkers (1989) offered a just as original as general entry to higher amino acids starting from chiral glycine building blocks, the so-called (R)- and (S)-BMI (tert-butyl 2-(tert-butyl)-3-methyl-4-oxo-1-imidazolidine carboxylate). Both enantiomers are commercially available on a kg scale and have been used for the preparation of phenylalanine analogues, deuterated, carbocyclic and heterocyclic amino acids. Corey and Link (1992) published a very general approach to α-amino acids based on the enantioselective reduction of trichloromethyl ketones, the conversion of the resulting carbinols to (S)-azido acids and (S)-α-amino acids.

Apart from generally known synthetic routes to natural and unnatural amino acids, the asymmetric hydrogenation of dehydroamino acids according to reaction 1 catalyzed by heterogeneous and more favorably by homogeneous catalysts proved to be an efficient way to achieve amino acids in high optical purity.



R = H, alkyl, aryl, heteroaryl; acyl = MeCO, PhCO, tert.BuOCO, $PhCH_2OCO$;
R^1 = H, CH_3

Reaction 1

The catalytic asymmetric hydrogenation is one of the most investigated reactions in the field of asymmetric synthesis and several reviews have been published (Halpern, 1985; Koenig, 1985; Fryzuk, et al., 1977; Takaya et al., 1993; Noyori, 1994). For an excellent comprehensive work see H. Brunner and W. Zettlmeier (1993).

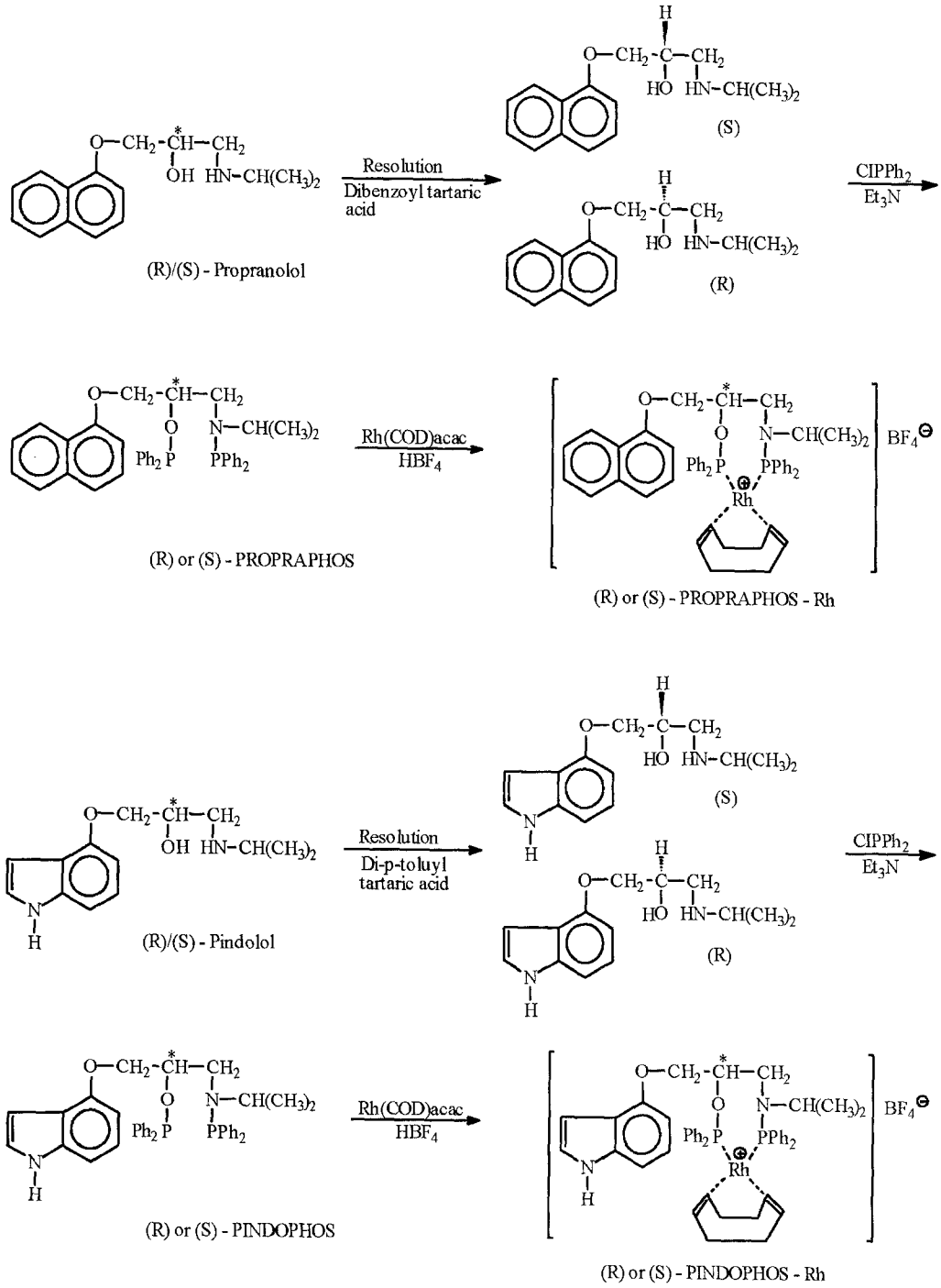
Relatively few papers have been published dealing with the enantioselective catalytic hydrogenation to prepare non-proteinogenic amino acids (see Cativiela et al., 1982, 1984; Miyazawa et al., 1982; Nagel et al., 1986; Bozell et al., 1991; Schmidt et al., 1992b). In 1993 a new type of chiral ligand, DuPHOS, was created, which displayed the highest enantioselectivities yet reported for the rhodium-catalyzed asymmetric hydrogenation of unsaturated amino acid precursors (Burk and coworkers, 1993, 1995).

We would like to describe here our experiences in the application of two chiral rhodium complexes, both in the (R)- and (S)-configuration, for the synthesis of unnatural amino acids by asymmetric hydrogenation. The ligands presented here are based on industrial products and therefore readily available.

The catalyst synthesis

Among the great number of chiral ligands designed for the rhodium-catalyzed asymmetric hydrogenation of unsaturated amino acid precursors, aminophosphine phosphinites have been established (Cesarotti et al., 1983; Pracejus, 1984; Mortreux et al., 1986; Karim et al., 1986; Pracejus et al., 1987; Döbler et al., 1988). Based on the corresponding optically active amino alcohols only one additional step, the reaction with P-chlorodiphenylphosphine, is necessary to prepare the ligands. In all cases, when the natural amino acid pool has been used as starting material, the stereogenic center of the amino alcohols is situated at the carbon atom bearing the amino group, and only the (S)-enantiomer is available.

Some years ago we looked for an additional source of chiral 1.2-amino alcohols and found propranolol, well known as β-adrenoreceptor antagonist (β-blocker), to be suitable. In contrast to such amino alcohols derived from natural amino acids the chiral center is bonded to the OH-function. After resolution of the commercially available racemate the ligand synthesis of PROPRAPHOS (Krause et al., 1989) was readily realized as shown in Scheme 1.



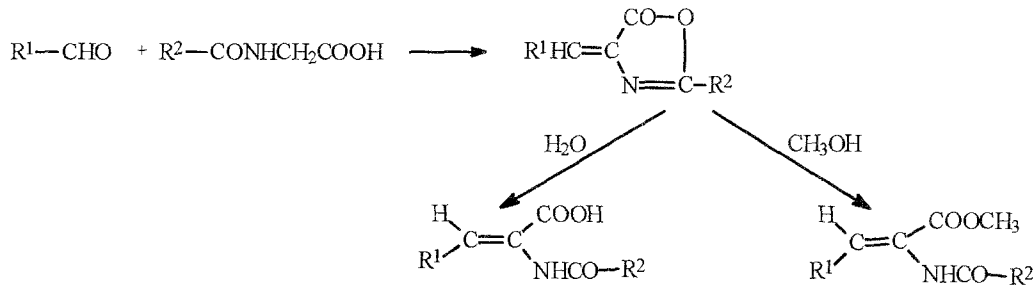
Scheme 1

The good experiences made with PROPRAPHOS-Rh prompted us to look for a further 1.2-amino alcohol in the series of β-blockers. We selected Pindolol, which offers the possibility for additional derivatization at the nitrogen atom of the indol unit, a target to be investigated in future. Following the

procedure for PROPRAPHOS, the enantiomers of PINDOPHOS could be isolated in a highly pure state (Kreuzfeld et al., 1996) and hence the rhodium complexes also (see Scheme 1).

The dehydroamino acid synthesis

For the preparation of the appropriate prochiral precursors, needed in the (Z)-configuration, excellent reviews have been published (Rao et al., 1975; Noda et al., 1983; Schmidt et al., 1979, 1988). Often the classical Erlenmeyer synthesis is used to obtain the N-acyl dehydroamino acids or their esters (Cativiela et al., 1982, 1983, 1984, 1985; Crawford et al., 1959; see Scheme 2). The condensation of aldehydes with alkyl acetamidomalonates has also been applied successfully (Hellmann et al., 1960; Hengartner et al., 1979).

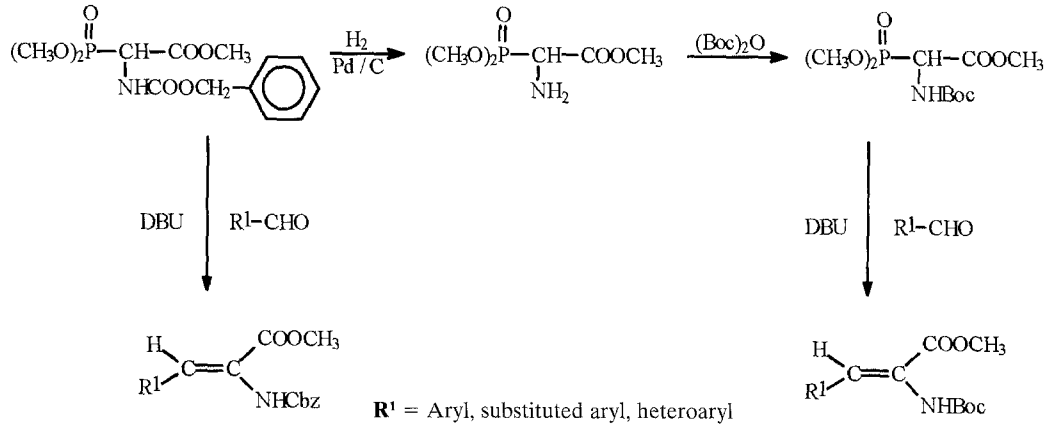


R¹ = Aryl, substituted aryl, heteroaryl; **R²** = CH_3, C_6H_5 (Z)

Scheme 2

During the last years the interest in synthetic, non-proteinogenic α-amino acids has increased sharply because of the emerging therapeutic possibilities. The incorporation into peptides required smoothly removable protecting groups in order to exclude partial racemization or splitting of the peptide bonds in the deprotection step. Therefore, we checked in a comparative investigation the N-Cbz and N-Boc protected derivatives of α-aminocinnamic acid in the rhodium-catalyzed asymmetric hydrogenation applying PROPRAPHOS, BPPM, DIOP, and Ph-β-GLUP as chiral ligands. Activity as well as enantioselectivity can be strongly dependent on the catalyst used. Only BPPM, PROPRAPHOS, and PINDOPHOS did tolerate the Cbz-and Boc-group without significant loss of efficiency. However, a retarding influence on the hydrogenation rate was observed in all cases, especially when Cbz-protected substrates were used (Kreuzfeld et al., 1993).

To prepare the substrates we applied a very effective and general procedure (Schmidt et al., 1992a; see Scheme 3).



Scheme 3

Thus the way was free to prepare a series of non-proteinogenic amino acids in both the D- or L-configuration, bearing Ac, Bz, Cbz or Boc protective groups, and different residues like naphthyl, heteroaryl (thiophene, furane, pyridine) or phenylalanines substituted by fluorine, chlorine, p-nitro, p-methyl, p-trifluoromethyl, p-isopropyl, and p-tert-butyl, often incorporated into oligopeptides instead of natural amino acids, (e.g. Reissmann et al., 1994; Pinski et al., 1995).

The asymmetric hydrogenation

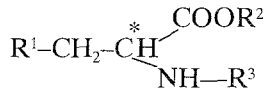
The hydrogenations were performed in a standard apparatus described by H. B. Kagan (Kagan et al., 1972) under normal pressure at 25°C in methanolic solution. After the reaction was finished the solvent was evaporated under reduced pressure. The resulting oily or solid products were dissolved in some milliliters of benzene and filtered on a small column of silica (Kieselgel 60, Merck) to remove the catalyst. After evaporation of the solvent solid, sometimes oily, compounds were isolated. The described method to separate the catalyst fails, when amino acids were used instead of the esters. Therefore, when the carboxylic acids were needed in a preparative scale, they were isolated after saponification of the corresponding optically pure esters. The activity of the catalysts is in general given as t/2 (min.) a rough measure for comparison. That means the time needed for the uptake of 50% of the theoretical amount of hydrogen. We observed a strong dependence on the substrates and found 1–4 minutes for the acetyl- and benzoyl-derivatives and 5–35 minutes for the Boc- and Cbz protected substrates. Generally 1.0 mmol of substrate and 0.01 mmol of catalyst were used. The (R)-configured catalyst induces (S)-configuration in the hydrogenation product and vice versa.

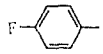
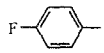
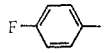
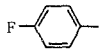
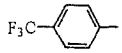
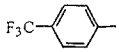
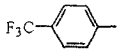
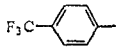
To check the productivity of the catalysts the substrate: catalyst ratio was enlarged using the standard substrate (Z)-α-acetamidocinnamic acid. Up to a ratio of 3000:1 (0.01 mmol of catalyst) the enantioselectivity and conversion are not significantly influenced. But, the hydrogenation rate drops to 1.0 mmol H_2 per minute (Kreuzfeld et al., 1996).

The enantiomeric excesses determined after the catalytic asymmetric hydrogenation were between 86 and 95% ee, depending on the substrates used. Higher optical purities are the result of further enrichment by fractionated crystallization.

In conclusion, each method has advantages and limitations. We believe that the presented approach to non-proteinogenic amino acids by asymmetric

Table 1. Phenylalanine derivatives I



R^1	R^2	R^3	m.p. (°C)	$[\alpha]_D^{25}$	ee (D, L)
	H	COC_6H_5	147–149	61.1 (c 1, MeOH)	99% (D) (GLC)
	CH_3	COC_6H_5	111–112	64.6 (c 1, MeOH)	89% (D) (GLC)
	CH_3	Cbz	64–66	21.1 (c 1, EtOH)	99.5% (D) (HPLC)
	CH_3	Boc	41–42	6.8 (c 1, EtOH)	95% (D) (HPLC)
	H	COC_6H_5	135–137	43.0 (c 1, MeOH)	99% (D) (GLC)
	CH_3	COC_6H_5	79–80	56.5 (c 1, MeOH)	99% (D) (GLC)
	CH_3	Cbz	42–47	18.2 (c 1, EtOH)	90% (D) (HPLC)
	H	COC_6H_5	158–161	38.1 (c 1, MeOH)	99% (D) (GLC)
	CH_3	COC_6H_5	96–97	50.1 (c 1, MeOH)	88% (D) (GLC)
	CH_3	Cbz	40–48	13.7 (c 1, EtOH)	89% (D) (HPLC)
	CH_3	Boc	67–69	3.2 (c 1, EtOH)	97% (D) (HPLC)
	H	COC_6H_5	167–168	41.8 (c 1, MeOH)	92% (D) (GLC)
	CH_3	Cbz	81–83	21.3 (c 1, EtOH)	95% (D) (HPLC)
	CH_3	Boc	77–79	8.1 (c 1, MeOH)	99% (D) (HPLC)
	H	Boc	132–135	−12.2 (c 1, EtOH)	97% (D) (HPLC)

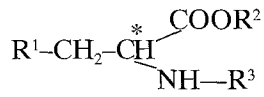
For further experimental and analytical details see Krause et al. (1992a, 1996), Kreuzfeld et al. (1996).

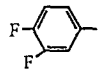
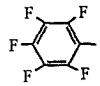
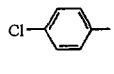
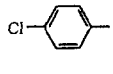
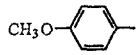
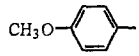
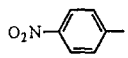
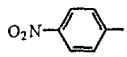
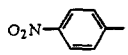
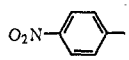
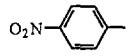
hydrogenation can be a helpful completion, when the catalyst acts highly active and enantioselective and can be readily synthesized in the (R)- as well as in the (S)-configuration.

Analytical methods

The optical rotation was measured on a GYROMAT-HP polarimeter (Fa. Dr. Kernchen, Seelze). The enantiomeric excess (% ee) was determined by GLC on a Hewlett-Packard chromatograph HP 5880 A fitted with a 4.3 m capillary column XE-60 (N-L-valin-tert-butylamide) FID, split 1:60, 175°C, for the

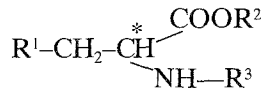
Table 2. Phenylalanine derivatives II

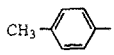
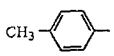
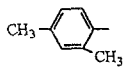
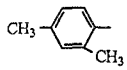
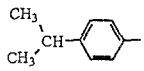
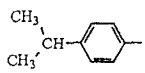
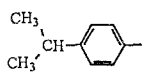
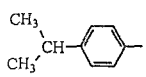
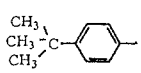
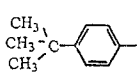
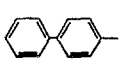
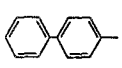
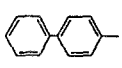


R^1	R^2	R^3	m.p. (°C)	$[\alpha]_D^{25}$	ee (D, L)
	CH_3	Cbz	58–60	25.4 (c 1, EtOH)	97% (D) (HPLC)
	CH_3	Boc	50–51	8.4 (c 1, EtOH)	99% (D) (HPLC)
	H	COC_6H_5	193–196	−56.1 (c 1, MeOH)	86% (L) (GLC)
	H	COC_6H_5	159–161	31.6 (c 1, MeOH)	99% (D) (GLC)
	CH_3	COC_6H_5	98–99	51.9 (c 1, MeOH)	96% (D) (GLC)
	H	COC_6H_5	128–130	33.4 (c 1, MeOH)	97% (D) (GLC)
	CH_3	COC_6H_5	82–84	37.3 (c 1, MeOH)	93% (D) (GLC)
	H	COC_6H_5	196–198	58.4 (c 1, MeOH)	91% (D) (GLC)
	CH_3	COC_6H_5	154–155	73.2 (c 1, MeOH)	91% (D) (GLC)
	H	Cbz	118–120	5.8 (c 0,5, EtOH)	92.5% (D) (HPLC)
	CH_3	Cbz	86–88	26.7 (c 1, EtOH)	93% (D) (HPLC)
	CH_3	Boc	96–97	7.8 (c 1, EtOH)	92.5% (D) (HPLC)

Further details see Krause et al. (1992a, 1996), Taudien et al. (1993).

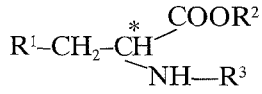
Table 3. Phenylalanine derivatives III

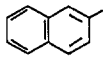
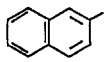
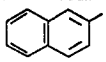
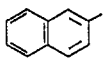
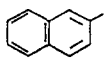
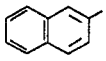


R^1	R^2	R^3	m.p. (°C)	$[\alpha]_D^{25}$	ee (D, L)
	H	COC_6H_5	133–136	35.8 (c 1, MeOH)	92% (D) (GLC)
	CH_3	Boc	27–29	52.1 (c 1, $CHCl_3$)	99% (L) (HPLC)
	H	COC_6H_5	164–166	69.7 (c 1, MeOH)	92% (L) (GLC)
	CH_3	COC_6H_5	94–96	−58.1 (c 1, MeOH)	82% (L) (GLC)
	H	COC_6H_5	192–194	35.2 (c 1, MeOH)	92% (D) (GLC)
	CH_3	COC_6H_5	104	−49.2 (c 1, MeOH)	99% (L) (GLC)
	H	Boc	80–83	−26.5 (c 1, EtOH)	>99% (D) (HPLC)
	CH_3	Boc	Oil	−42.1 (c 1, $CHCl_3$)	99% (D) (HPLC)
	H	Boc	50–53	−24.7 (c 1, EtOH)	>99% (D) (HPLC)
	CH_3	Boc	Oil	−43.0 (c 1, $CHCL_3$)	99% (D) (HPLC)
	CH_3	Cbz	Oil	12.2 (c 1, MeOH)	88% (D) (HPLC)
	CH_3	Boc	48–53	4.8 (c 1, MeOH)	93% (D) (HPLC)
	H	Cbz	145–152	−11.2 (c 1, EtOH)	98% (D) (HPLC)
	CH_3	Cbz	84–89	8.3 (c 1, EtOH)	88% (D) (HPLC)
	CH_3	Boc	60–68	−6.4 (c 1, $CHCl_3$)	89% (D) (HPLC)

Further details see Kreuzfeld et al. (1993, 1996), Taudien et al. (1993), Krause et al. (1996).

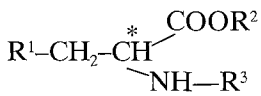
Table 4. Naphthylalanine derivatives



R^1	R^2	R^3	m.p. (°C)	$[\alpha]_D^{25}$	ee (D, L)
	H	COC_6H_5	155–157	140.6 (c 1, MeOH)	98% (D) (GLC)
	H	COC_6H_5	153–155	32.0 (c 1, MeOH)	97% (D) (GLC)
	CH_3	COC_6H_5	102–103	44.2 (c 1, MeOH)	87% (D) (GLC)
	H	Cbz	106–110	−18.7 (c 1, EtOH)	91% (D) (HPLC)
	CH_3	Cbz	84–86	−1.24 (c 1, MeOH)	92% (D) (HPLC)
	H	Boc	98–102	−30.9 (c 0.5, EtOH)	92% (D) (HPLC)
	CH_3	Boc	83–85	−16.3 (c 1, EtOH)	91% (D) (HPLC)

Further details see Taudien et al. (1993), Krause et al. (1996).

Table 5. Thienylalanine derivatives



R^1	R^2	R^3	m.p. (°C)	$[\alpha]_D^{25}$	ee (D, L)
	H	$COCH_3$	164–165	−42.3 (c 1, EtOH)	>99% (D) (GLC)
	H	COC_6H_5	100–102	−13.3 (c 1, EtOH)	91% (L) (GLC)
	CH_3	$COCH_3$	112–114	−16.7 (c 1, EtOH)	>99% (D) (GLC)
	CH_3	COC_6H_5	72–74	−39.7 (c 1, EtOH)	90% (L) (GLC)
	H	$COCH_3$	176–178	−46.2 (c 1, EtOH)	>99% (D) (GLC)
	H	COC_6H_5	135	4.1 (c 1, EtOH)	96% (D) (GLC)
	CH_3	$COCH_3$	106–108	−14,6 (c 1, EtOH)	98% (D) (GLC)
	CH_3	COC_6H_5	85–86	35.2 (c 1, EtOH)	93% (D) (GLC)
	H	H	246–258	31.8 (c 1, H_2O)	>99% (D) (HPLC)
	H	H	239–242	42.6 (c 1, H_2O)	>99% (D) (HPLC)

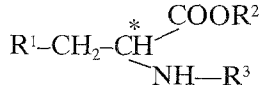
Further details see Döbler et al. (1993), Furylalanine derivatives see Krause et al. (1992b).

acetyl- and benzoyl derivatives, by HPLC on a Hewlett-Packard 1090 chromatograph Series II, fitted with 50 × 4.6mm CHIRACEL OD and 250 × 4.6mm CHIRACEL OD columns (eluent: n-hexane/isopropanol) for the Cbz- and Boc-derivatives and also for the deprotected compounds. Melting points were determined on a Galen™ III (Cambridge Instruments).

Results

The results of our investigations to prepare non-proteinogenic amino acids by catalytic asymmetric hydrogenation are summarized in the Tables 1–6. For more experimental details the corresponding references are given at the bottom of each table. For comparison see also references cited therein.

Table 6. Pyridylalanine derivatives



R^1	R^2	R^3	m.p.(°C)	$[\alpha]^{25}_D$	ee (D, L)
	NH_4^+	$COCH_3$	181–183	−87.1 (c 1, EtOH)	92% (D) (GLC)
	CH_3	$COCH_3$	101–103	−103.4 (c 1, $CHCl_3$)	>99% (D) (GLC)
	CH_3	COC_6H_5	108–109	75.9 (c 1, MeOH)	>99% (D) (GLC)
	NH_4^+	$COCH_3$	199–201	−92.4 (c 1, EtOH)	>99% (D) (GLC)
	H	COC_6H_5	246–248	98.6 (c 1, 1N HCl)	84% (D) (GLC)
	CH_3	$COCH_3$	77–79	−99.8 (c 1, $CHCl_3$)	>99% (D) (GLC)
	CH_3	COC_6H_5	Oil	−84.3 (c 1, $CHCl_3$)	86% (D) (GLC)
	H	H	250–253	−24.6 (c 1, 1N, HCl)	>99% (D) (HPLC)
	H	H	246–248	−34.5 (c 1, 1N HCl)	>99% (D) (HPLC)

Further details see Döbler et al. (1996).

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