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ASYMMETRIC HYDROFORMYLATION OF N-ACYL 1-AMINOACRYLIC ACID DERIVATIVES BY RHODIUM/CHIRAL DIPHOSPHINE CATALYSTS

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Abstract: The asymmetric hydroformylation of N-acylaminoacrylic acid esters **1** is efficiently catalysed by $HRh(CO)(PPh_3)_3$ in the presence of DIOP and related diphosphines as chiral ligands. The reaction is completely regioselective and affords in high yield the more branched aldehyde with the formyl group linked to a quaternary stereocenter. Irrespective of the structure of **1**, preferential insertion of carbon monoxide always occurs onto the Re face of the substrate giving the (R)-antipodes in up to 60% enantioselectivity. Due to self enrichment during crystallisation, aldehyde **2b** is readily isolated in 70-75% e.e.

In a recent paper we have reported that the asymmetric hydroformylation of methyl N-acetamidoacrylate **1a** is efficiently catalysed by $HRh(CO)(PPh_3)_3$ in the presence of a chiral chelating diphosphine[1]. A remarkable feature of this reaction is that the insertion of carbon monoxide, when it occurs, takes place with complete positional selectivity onto the more substituted carbon atom of the substrate. Thus, the reaction affords, as the exclusive aldehydic product, the more branched isomer **2a**, where the formyl group is bound to a chiral quaternary carbon. In all the catalytic experiments we have carried out, the isomeric aldehyde **3a**, if formed, was not present in detectable amounts and the only by-product formed in variable extent was the alanine derivative **4a** arising from hydrogenation of the substrate. Since under optimum conditions chemoselectivities up to 95% are attained for the aldehyde, the reaction deserves particular interest from the preparative viewpoint as compound **2a** can be obtained by simple distillation in isolated yields as high as 90%.

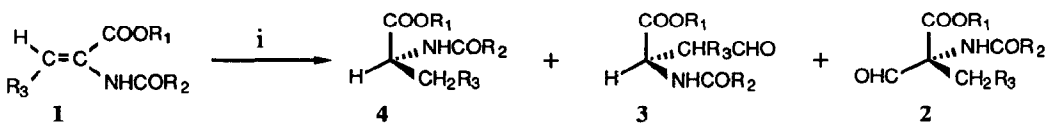
Operating at 30°C under 110 atm (H_2:CO = 10:1) in the presence of (-)-DIOP as chiral ligand, a 60% e.e. was recorded for compound **2a** (R configuration). Even if not exceptional, this is the highest enantioselectivity so far attained in the asymmetric hydroformylation with rhodium catalysts. Curiously, the hydrogenated by-product **4a** contextually formed is almost racemic (S configuration prevailing).

These results stimulated us to extend the rhodium catalysed hydroformylation to some other derivative of α-aminoacrylic acid. It was our hope that the well known bidentate coordination of this kind of substrates to rhodium(I) derivatives[2] could synergically match with a particular pattern of substituents in the substrate resulting in an increased enantioselectivity of the process.

Three different substrates **1b**, **1c** and **1d** were investigated in this work. With respect to the parent olefin **1a**, they introduce a variation of the substitution pattern at the carboxylic group, at the amino group and at the vinylidenic carbon atom, respectively. Compounds **1b** and **1c** contain easily removable functionalities and have been appositely chosen since they are particularly well suited for a further elaboration of the hydroformylation products to synthetic purposes.

The esters **1a**, **1b** and **1d** have been prepared following a literature procedure[3] by reaction of the corresponding acids with methyl iodide (**1a** and **1d**) or benzyl bromide (**1b**) in acetone in the presence of excess potassium carbonate. The preparation of the Boc-derivative **1c** was accomplished through acid catalysed condensation of *t*.butylurethane with methyl pyruvate. In this reaction, using a two fold excess of pyruvate rather than a deficiency and trichloroethylene as the solvent resulted in a sharp increase of the yields (65-70%) with respect to the ones obtained previously (47%)[4].

SCHEME 1



	a	b	c	d	e	
R_1	CH_3	$PhCH_2$	CH_3	CH_3	H	i) CO/H_2 (1:1) 100 atm; 80°;
R_2	CH_3	CH_3	*t*.BuO	CH_3	CH_3	70 h; $HRh(CO)(PPh_3)_3$;
R_3	H	H	H	Ph	H	chelating diphosphine.

The asymmetric hydroformylation experiments were carried out in the presence of $HRh(CO)(PPh_3)_3$ as procatalyst and (-)-DIOP as chiral ligand at a substrate-to-metal ratio 100 (Scheme 1). Following the results obtained with **1a** [1], no other chiral phosphine except DIOP and the closely related DIOCOL[5] were employed in this study. The two ligands gave comparable results.

Both the substrates hydroformylated smoothly at 80°C under 100-120 atm of an equimolar mixture of hydrogen and carbon monoxide. Almost quantitative conversions were obtained with **1b** in 70 h, whereas **1c** was slightly less reactive (80-85%). This difference almost vanished when methyl ethyl ketone instead of benzene was used as solvent. Selected results obtained in the hydroformylation of **1b** and **1c** are summarized in Tables 1 and 2, respectively.

On the whole, the results obtained in the hydroformylation of **1b** and **1c** are comparable with those recorded with **1a**. Like the previous case, the reaction is highly chemoselective (90-97%) and the insertion of carbon monoxide occurs with complete positional selectivity on the more substituted carbon atom of the substrate. Thus, compounds **2b** and **2c** are the exclusive aldehydic products that could be detected in the crude

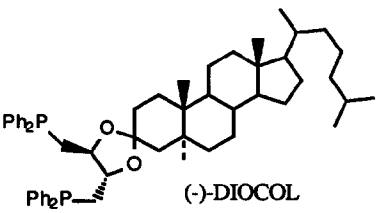
reaction mixtures and can be obtained in 80-90% isolated yields. Both of them contain a quaternary stereocentre originated through the formation of a new carbon-carbon bond.

TABLE 1

ASYMMETRIC HYDROFORMYLATION OF **1b** CATALYSED BY $HRh(CO)(PPh_3)_3$/ (-)-DIOP. (**1b**: 10 mmol; $HRh(CO)(PPh_3)_3$: 0.1 mmol; benzene: 30 ml; initial pressure: 100 atm)

L/Rh	T (°C)	H_2/CO	t (h)	Conv [a]	e.e.[a]
4	100	1	68	99	32
2	80	1	70	99	32
4	80	1	70	99	32
4	80	1	70	99	33[b]
4	80	1	70	99	31[c]
4	80	4	69	99	34
4	60	4	70	93	36
4	40	4	480	nd	46

a) Determined by GLC analysis. Prevailing configuration (R).
b) Ligand: (-)-DIOCOL[5]
c) Ligand: (+)-DIOCOL[5]. Prevailing configuration (S).



(-)-DIOCOL

Polymerization of the substrates occurred to some extent, but it was of some significance only in low temperature hydroformylations, likely as a consequence of the long reaction times necessary. In all the other runs, only small amounts (3-10%) of the alanine derivatives **4b** and **4c**, arising from competitive hydrogenation of the relevant substrates, could be detected besides aldehydes **2b** and **2c**. The free acid **1e** was not hydroformylated even in the presence of triethylamine.

Under the conditions reported above, the phenyl substituted derivative **1d** was unreactive and was quantitatively recovered at the end of the experiment. Neither hydrogenation took place on this substrate, even when the reaction was carried out with a hydrogen rich (3:1) gas mixture. This result is in keeping with the behaviour displayed by N-alkenylphtalimides under hydrocarbonylation conditions[6] and seems to configure a general trend of reactivity for alkenyl nitrogen compounds containing a trisubstituted double bond in rhodium catalysed hydroformylation.

With both the substrates **1b** and **1c**, the dextrorotatory isomers were prevailing when (-)-DIOP was employed as chiral ligand. In standard conditions, however, the enantioselectivities of the process were modest (~30%) and lower than with **1a** (38%). Definite improvements in the asymmetric induction could be achieved either by using a solvent of low polarity or a relatively high phosphine to Rh ratio. An increase in the hydrogen content of the gas mixture and a decrease in the reaction temperature displayed also a beneficial effect on the enantioselectivity of the reaction. Under optimum conditions, the highest e.e.'s recorded for **2b** and **2c** were

equal (46%) and lower than in the case of **1a** (59%). The hydrogenated by-products **4b** and **4c** had preferential S configuration and were invariably almost racemic, even when the corresponding aldehydes showed significative e. e's.

TABLE 2

ASYMMETRIC HYDROFORMYLATION OF **1c** CATALYSED BY $HRh(CO)(PPh_3)_3$/ (-)-DIOP.(**1c**: 10 mmol; $HRh(CO)(PPh_3)_3$: 0.1 mmol; benzene: 30 ml; initial pressure: 100 atm)

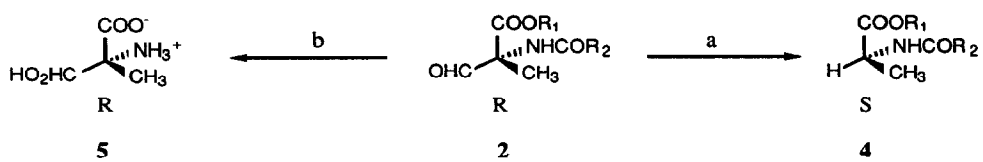
L/Rh	T (°C)	H_2/CO	t (h)	Conv [a]	e.e.[a]
2	80	1	65	99	17[b,c]
2	80	1	68	85	20[b]
4	80	1	70	97	28[b]
4	80	1	70	80	32
4	60	4	188	80	40
4	40	4	525	30	46

a) Determined by GLC analysis. Prevailing configuration (R).
b) Solvent: methyl ethyl ketone.
c) Ligand: (+)-DIOCOL[5]. Prevailing configuration (S).

Crystallization of **2b** from ether-hexane occurred with preferential separation of a racemic conglomerate, resulting in a consistent enrichment of the R enantiomer in the mother liquors. Taking advantage from this fact, the aldehyde **2b** could be easily obtained in high enantiomeric purity (70-75%) after two fractional crystallizations of a sample at 32% e. e.

Right handed samples of **2b** and **2c** were catalytically decarbonylated with $[Rh(DPP)_2]Cl$[7] to give the corresponding derivatives of (S)-alanine **4** (Scheme 2), as determined by comparison with authentic samples prepared from the natural aminoacid with standard procedures. Although both the reactions were markedly affected by racemization, the (R) configuration for the prevailing enantiomer could be thus established for both the aldehydes and the specific rotations of the optically pure enantiomers could be extrapolated.

SCHEME 2

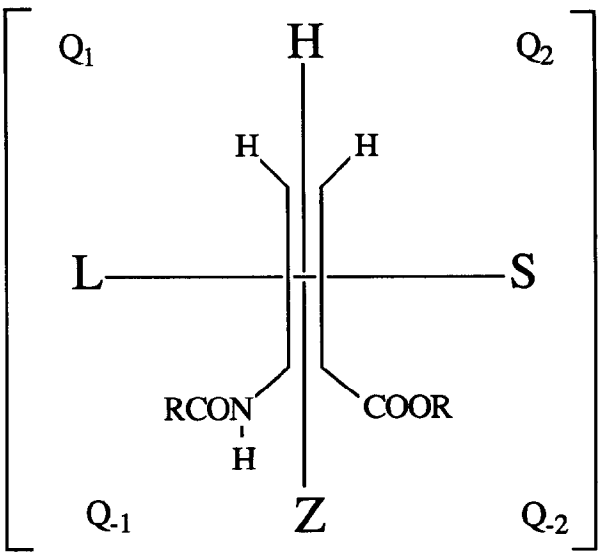


a) $Rh(DPP)_2Cl$, xylene, reflux

b) $NaBH_4$/ THF, 25°C, overnight; then HCl 1:1, reflux 6 h.

Since (-)-DIOP promotes the preferential formation of the (R) enantiomer also in the case of **1a**, this result demonstrates that, irrespective of the structural modification introduced into the substrates, the direction of the asymmetric induction in the hydroformylation of α-aminoacrylic acid derivatives is always the same and that formyl group and hydrogen addition occurs preferentially onto the Re enantioface of each substrate.

If we may assume, as it seems reasonable [8], that the enantioselectivity-determining step in the catalytic cycle is the formation of diastereomeric metal alkyl complexes, the relevant transition state can be represented in a simplified way according to the model proposed by Consiglio and Pino for olefinic hydrocarbons [9]. In the figure the four quadrants are listed in decreasing order of steric crowding for the complex containing (-)-DIOP, L (large) and S (small) representing the relative steric hindrance of the ligand.



$$Q_2 > Q_1 >> Q_{-2} > Q_{-1}$$

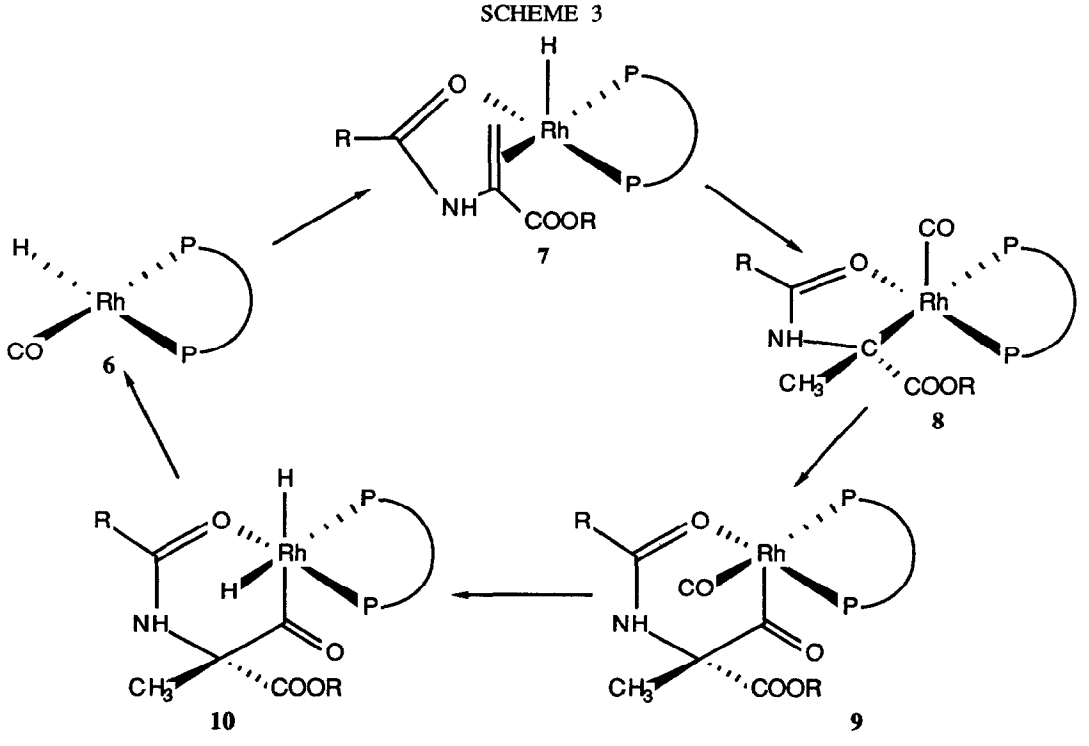
Within the frame of the validity of this model, the observed enantioselectivity is in keeping with the one predicted if we assume that the carboalkoxy substituent is always exerting a steric hindrance higher than the acylamido group. This should be the case if in these substrates coordination to rhodium through the oxygen of the acylamido group occurs under hydroformylation conditions.

On the contrary, the regioselectivity of the reaction is opposite to the one expected on steric considerations and should then rest on different grounds. Electronic effects undoubtedly play a significant role since preferential formation of the more substituted aldehyde is not uncommon in rhodium catalysed hydroformylation of electron deficient olefins. A remarkable example of this trend is the hydroformylation of styrene where, at room temperature, branched/linear (B/L) aldehyde ratios up to 61.5 and 49 can be obtained in the presence[10] or not[11] of phosphine ligands, respectively. The branched isomer usually predominates also when an electron withdrawing substituent is attached to the C=C bond. 3,3,3-Trifluoropropene is a significant

example of this behaviour, affording a B/L ratio as high as 33 to be compared with 0.4-1 for propene[12]. High selectivities for the branched aldehyde have been obtained in the presence of rhodium catalysts from both acrylonitrile (97%)[13] and enamides (more than 99%)[6,14]. The hydroformylation of α,β-unsaturated esters consistently affords α-formyl derivatives in more than 90% selectivities[15]. This regioselectivity is unchanged by the presence of an additional substituent on the olefinic carbon: methyl methacrylate[16] and dimethyl itaconate[7] can be hydroformylated in up to 99% and 95% α-selectivity, respectively. Both these substrates afford an aldehyde where the formyl group is attached to a quaternary carbon.

Preferential or even exclusive formation of the branched isomer can be obtained in rhodium catalysed hydroformylation when a heteroatom which can coordinate to the metal is incorporated into the alkene. This "chelation control" of the regioselectivity can be very efficient. For example, 4-alkyl-4-diphenylphosphino-1-butenes[17] and phosphite esters of homoallylic alcohols[18] give in high yield the branched derivative as a single product, whereas a terminal alkene like 1-hexene affords preferentially the straight chain isomer in about 70% selectivity under identical reaction conditions. Temporary introduction of a phosphinated arm has been used to govern the direction of CO insertion in a key step of the total synthesis of (+)-phyllanthocin[19]. Six-membered ring chelate alkyl-rhodium complexes have been suggested as key intermediates in the intramolecular amidocarbonylation of alkenamides[20] and the hydrocarbonylation of N-allylamides apparently occurs under amide-directed chelation control[21].

SCHEME 3



In the hydroformylation of α-aminoacrylic acid derivatives electronic and chelation effects should be cooperative and the complete positional selectivity of the insertion of carbon monoxide should be substantially ascribed to this synergism. According to the widely accepted mechanism proposed for the phosphine-rhodium complex catalysed hydroformylation[22], a plausible catalytic cycle leading to aldehyde **2** can be envisaged as reported in Scheme 3.

Bidentate coordination of the substrate to a rhodium(I) carbonyl hydride complex like **6** should be assumed to occur preferentially to the Re enantioface leading to the adduct **7** (diastereomeric mixture). Hydride migration should then take place selectively to the β carbon of the coordinated C=C bond affording exclusively (or predominantly) the more substituted σ-alkyl rhodium complex which, upon CO coordination, should give the diastereomeric carbonyl derivatives **8**. Making allowance for the different catalytic precursor, these two steps are identical to the rhodium catalysed hydrogenation of **2a**[2]. Insertion of carbon monoxide into the carbon-rhodium bond converts the five-membered alkyl chelate into the six-membered acyl complex **9**. Oxidative addition of hydrogen, followed by reductive elimination of aldehyde **2**, should then complete the catalytic cycle, restoring the intermediate **6**.

The CO insertion step is critical for the chemoselectivity of the entire process and occurs easily only when flexible diphosphines like DIOP or 1,4-diphenylphosphinobutane are used as chelating ligands. CO insertion is almost completely inhibited when more rigid chelating diphosphines like 1,2-diphenylphosphinoethane or (S,S)-CHIRAPHOS are employed[1]. It is our feeling that this may be a consequence of the steric constraints involved in ring expansion of the chelating substrate, that would require a higher degree of conformational mobility to be accommodated. A similar reason may account for the prevalence of the branched isomer (75-95%) in the hydroformylation of vinyl acetate[23], where both the aldehydes may be formed under chelation control and electronic factors should favour the linear isomer.

Aldehydes **2** are valuable intermediates in the enantioselective synthesis of several classes of organic compounds of biological interest. Conversion of (+)-(R)-**2a** into (-)-(R)-α-methyl serine **5** (Scheme 2) has been already accomplished (see Experimental). Further applications of aldehydes **2b** and **2c** to the stereodivergent synthesis of β-hydroxy-α-methyl aminoacids are currently under investigation and will be reported in the due course.

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EXPERIMENTAL

Melting points were determined on a Büchi melting point apparatus and are uncorrected. GLC analyses were performed on a Hewlett Packard 5890A instrument equipped with a 50 m Alltech Chirasil-Val capillary column using a FID detector and helium (80 KPa) as carrier. ^{1}H NMR spectra were recorded on a Varian VXR 300 spectrometer at 300 MHz in deuterochloroform solution with tetramethylsilane as internal standard (δ=0). Optical rotations were determined with a Perkin Elmer 241 polarimeter. Elemental analyses were performed with a Perkin Elmer Elemental Analyzer 240B. Mass spectra were recorded on a Hewlett Packard HP 5988 mass spectrometer linked to a gas chromatograph HP 5890. IR spectra were recorded on a Perkin Elmer 983 instrument.

Commercial chemical reagents were used as received. $HRh(CO)(PPh_3)_3$[24] and $Rh(DPP)_2Cl$[25] were prepared according to literature procedures.

Preparation of acetamido esters 1a, 1b, 1d.

Following a literature procedure [3], the acid (0.1 mol) and anhydrous potassium carbonate (0.2 mol) were refluxed in acetone (600 ml) with mechanical stirring, while the appropriate alkyl halide (0.1 mol) was added slowly. After 6 h, the products were recovered and crystallized from diethyl ether/hexane.

1a: m.p. 51 °C (lit.[26] 52-54 °C). ^{1}H NMR (d, $CDCl_3$): 2.1 (s, CH_3CO-); 3.8 (s, -$COOCH_3$); 5.9 (d, CH_2=); 6.6 (s, CH_2=). IR (Nujol, cm^{-1}): 3360 (NH); 1705 (CO); 1675 (CO). MS: m/z 143 (45.16%, M^+). (Found: C, 50.21; H, 6.33; N, 9.70. $C_6H_9NO_3$ requires: C, 50.35; H, 6.34; N, 9.79).

1b: m.p. 53 °C. ^{1}H NMR (d, $CDCl_3$): 2.1 (s, CH_3CO-); 5.3 (s, -CH_2-); 6.0 (d, CH_2=); 6.6 (s, CH_2=); 7.4 (s, C_6H_5-). IR (Nujol, cm^{-1}): 3362 (NH); 1709 (CO); 1675 (CO). MS: m/z 219 (1.67%, M^+). (Found: C, 65.80; H, 6.02; N, 6.35. $C_{12}H_{13}NO_3$ requires: C, 65.74; H, 5.98; N, 6.39).

1d: m.p. 124 °C (lit.[27] 122-123 °C). ^{1}H NMR (d, $CDCl_3$): 2.0 (s, -$COCH_3$); 3.8 (s, -$COOCH_3$); 7.2 (d, CH=); 7.4 (s, -C_6H_5). IR (Nujol, cm^{-1}): 3421 (NH); 1718 (CO); 1675 (CO).

Preparation of Methyl N-[(tert.butyloxy)carbonyl]dehydroalaninate (1c).

Methyl piruvate (0.1 mol), *tert.*-butylcarbamate (0.05 mol) and a few milligrams of *p*-toluensulfonic acid in trichloroethylene (50 ml) were refluxed in a Soxlet apparatus equipped with activated 4Å molecular sieves. After 8 h, the solvent was removed, the residue was chromatographed on silica gel (100 g., CH_2Cl_2 as eluant) and distilled: 65-70% yield; b.p. 100 °C at 50 Pa. ^{1}H NMR (d, $CDCl_3$): 1.5 (s, -$C(CH_3)_3$); 3.9 (s, -$COOCH_3$); 5.9 (d, CH_2=); 6.3 (s, CH_2=); 7.2 (b, -NH-). IR (Nujol, cm^{-1}): 3421 (NH); 1718 (CO); 1675 (CO).

Hydroformylation experiments: general procedure.

The substrate (10 mmol), $HRh(CO)(PPh_3)_3$ (0.1 mmol) and the required amount of phosphine were introduced in a 250 ml stainless steel autoclave. The air was evacuated, benzene (30 ml) was introduced by suction and the vessel was pressurized with CO/H_2 at room temperature (10 MPa). After 70 h at 80 °C the solvent was removed, the residue was chromatographed on silica (25 g, ether as eluant) and purified by distillation or crystallisation.

2a: b.p.140-150°C at 10 Pa. Abs. config.: R. $[\alpha]_D^{25}$ +21.2 (c 2; acetone) for a 60% enantiomerically pure sample. GLC retention times (149 °C, m): 18.5 (S); 19.0 (R). ^{1}H NMR (d, $CDCl_3$): 1.7 (s, $-CH_3$); 2.2 (s, CH_3CO-); 4.0 (s, $-COOCH_3$); 7.3 (b, -NH-); 9.8 (s, -CHO). IR (nujol, cm^{-1}) 3283 (NH); 1729 (CO); 1656 (CO). MS: m/z 173 (0.60%, M^+). (Found: C, 48.78; H, 6.29; N, 8.18. $C_7H_{11}NO_4$ requires: C, 48.55; H, 6.40; N, 8.09).

2b: m.p. 72 °C (ether/hexane). Abs. config.: R. $[\alpha]_D^{25}$ +20.6 (c 2; acetone) for a 42% enantiomerically pure sample. GLC retention times (190 °C, m): 46.8 (S); 47.5 (R). ^{1}H NMR (d, $CDCl_3$): 1.7 (s, CH_3-); 2.1 (s, CH_3CO-); 5.4 (s, $-CH_2$-); 7.2 (b, -NH-); 7.6 (s, C_6H_5-); 9.8 (s, -CHO). IR (Nujol, cm^{-1}): 3249 (NH); 1726 (CO); 1643 (CO). MS: m/z 249 (4.2%, M^+). (Found: C, 62.70; H, 6.09; N, 5.48. $C_{13}H_{15}NO_4$ requires: C, 62.64; H, 6.07; N, 5.62).

2c: b.p. 120 °C at 2 Pa. Abs. config.: R. $[\alpha]_D^{25}$ +44.5 (c 2; acetone) for a 73% enantiomerically pure sample. GLC retention times (120 °C, m): 53.2 (S); 54.2 (R). ^{1}H NMR (d, $CDCl_3$): 1.5 (s, $-C(CH_3)_3$); 1.7 (s, $-CH_3$); 4.0 (s, $-COOCH_3$); 6.0 (b, -NH-); 9.6 (s, -CHO). IR (Nujol, cm^{-1}): 3369 (NH); 1729 (CO). (Found: C, 52.16; H, 7.30; N, 5.78. $C_{10}H_{17}NO_5$ requires: C, 51.94; H, 7.41; N, 6.06).

Decarbonylation experiments.

2a [100 mg, $[\alpha]_D^{25}$ +15.5 (c 2; acetone)] and $Rh(DPP)_2Cl$ (30 mg) in dry xylene (2ml) were refluxed for 4 h under nitrogen atmosphere. The solvent was removed under reduced pressure and the residue was distilled (150 °C at 40 Pa) affording (-)-(S)-methyl N-acetylalaninate (6% e.e. by GLC) [52 mg, $[\alpha]_D^{25}$ -5.6 (c 2; water)]. (lit.[28] $[\alpha]_D^{25}$ -91.7 for (S) enantiomer).

2b [200 mg, $[\alpha]_D^{25}$ +3.5 (c 2; acetone)] by an analogous procedure afforded benzyl (-)-(S)-N-acetylalaninate (3% e.e. by GLC) [124 mg, $[\alpha]_D^{25}$ -1.8 (c 1; ethanol)]. A sample of pure (S)-enantiomer was prepared from natural alanine and showed $[\alpha]_D^{25}$ -59.5.

2c [223 mg, $[\alpha]_D^{25}$ +13.8 (c 2; acetone)] by an analogous procedure afforded methyl (-)-(S)-N-BOC-alaninate (6% e.e. by GLC) [102 mg, $[\alpha]_D^{25}$ -2.7 (c 1; ethanol)]. A sample of pure (S)-enantiomer was prepared from natural alanine and showed $[\alpha]_D^{25}$ -40.7.

Preparation of α-methylserine 5

2a [48 mmol, $[\alpha]_D^{25}$ +7.4 (c 2; acetone); 21% e.e. by GLC] and $NaBH_4$ (48 mmol) were stirred overnight in tetrahydrofuran (125 ml). The crude reaction product was then refluxed 6 h with a solution of HCl/H_2O 1:1. The residue obtained after neutralization (NH_4OH) and evaporation of the aqueous phase was chromatographed on Amberlite IR 120 with a 3% solution of NH_4OH and the eluted (R)-2-methylserine was crystalised from ethanol-water: m.p. 265-267 °C (lit.[29] 245 °C); $[\alpha]_D^{20}$ -1.01 (c 1; water) [lit.[30] $[\alpha]_D^{20}$ -5.4 (c 1; water) for (R) enantiomer]

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