

N-H Insertion reactions of rhodium carbenoids. Part 1. Preparation of α -amino acid and α -aminophosphonic acid derivatives

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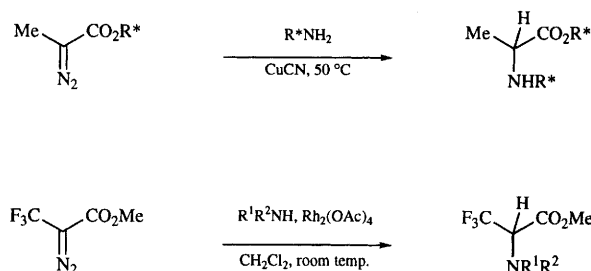
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Rhodium(II) acetate-catalysed decomposition of diazophenylacetates 1 and 3 in the presence of a range of N-H compounds results in an N-H insertion reaction of the intermediate carbenoids and formation of N-substituted phenylglycine derivatives 2 and 4. The corresponding reactions of dimethyl α -diazobenzylphosphonate 5 constitute a simple route to aminophosphonates 6.

The synthesis of α -hydroxy and α -amino carboxylic acid derivatives and the corresponding phosphonates remains a topic of considerable importance and current interest. We have recently reported a new approach to α -hydroxy carboxylic acid derivatives based on the O-H insertion reaction of rhodium carbenoids¹⁻¹⁰ derived from diazo esters containing chiral auxiliaries.¹¹ We now describe the corresponding N-H insertion reactions of diazo esters and diazophosphonates as a route to α -amino acid and α -aminophosphonic acid derivatives.

The N-H insertion reaction of a metalocarbenoid intermediate was first described by Yates in the copper bronze-catalysed decomposition of diazoacetophenone in the presence of aniline or piperidine to give α -anilinoacetophenone and α -piperidinoacetophenone in 33 and 80% yield respectively.¹² Further copper-mediated intermolecular N-H carbenoid insertion reactions were subsequently reported,¹³⁻¹⁹ along with photochemical²⁰ and protic and Lewis acid-catalysed²¹⁻²³ reactions of diazo compounds leading to N-H insertion products. However, it was the 1974 report by Paulissen and co-workers that rhodium(II) acetate was an effective catalyst for N-H insertion reactions of carbenoids that has stimulated much of the subsequent work in this area.²⁴ Although a number of other intermolecular N-H insertion reactions of rhodium carbenoids have been reported,²⁵⁻³¹ including work from our own group,^{32,33} it is the intramolecular reaction that has found the widest use in synthesis. Since the original report from the Merck group in 1978,³⁴ the intramolecular rhodium carbenoid insertion into a β -lactam N-H bond has become a standard synthetic route to a range of bicyclic β -lactams and is widely used.³⁵⁻³⁸ The intramolecular reaction is not limited to insertion into the β -lactam N-H, and many other examples leading to 4-, 5- and 6-membered rings have been reported.³⁹⁻⁴⁶

Hence, the insertion of metalocarbenoids derived from diazocarbonyl compounds into the N-H bond of a variety of nitrogen compounds (amines, amides, carbamates, lactams) is apparently a facile reaction, although in cases where competing pathways exist, then O-H insertion often supervenes over insertion into the N-H bond of amides and carbamates.⁴⁷⁻⁴⁹ Therefore, it is surprising that the reaction has not been extensively



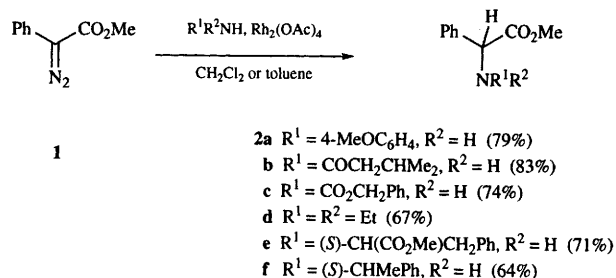
Scheme 1

investigated as a route to α -amino acids and their derivatives, although some work with this express aim in mind has been published (Scheme 1). Thus Kagan reported a new synthesis of alanine derivatives based on the copper(I) cyanide-catalysed decomposition of diazopropionates, including chiral menthyl esters, in the presence of chiral amines, R^*NH_2 , although the observed asymmetric induction was modest,¹⁴ and very recently a related rhodium(II)-catalysed N-H insertion reaction has been used as a route to α,α,α -trifluoroalanine derivatives (Scheme 1).³¹

Results and discussion

The diazo esters selected for study were the 2-diazo-2-phenylacetates 1 and 3, which were readily prepared from phenylglyoxylic acid by esterification followed by the Bamford-Stevens reaction.^{11,50} A range of N-H compounds was investigated: amines, anilines, amides and carbamates. Rhodium(II) acetate-catalysed decomposition of methyl 2-diazo-2-phenylacetate 1 in dichloromethane in the presence of 4-methoxyaniline, isovaleramide, benzyl carbamate or diethylamine gave the corresponding products 2a-2d of carbenoid N-H insertion in good yield (Scheme 2), thereby extending the work of Nicoud and Kagan¹⁴ and Osipov *et al.*³¹ in the alanine series to the preparation of N-substituted phenylglycine derivatives. The nucleophilic amines clearly coordinate to the metal (colour change from green to red-brown) and to a certain extent poison the catalyst. In the case of diethylamine, the reaction did

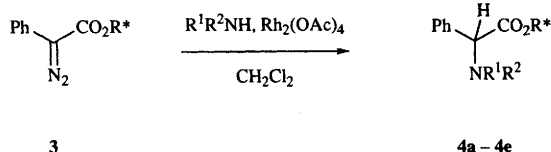
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Scheme 2

proceed in the absence of the rhodium catalyst, although the yield was lower (30–40%) and a number of unidentified by-products were formed. In an attempt to effect some asymmetric induction in such reactions, the N–H insertion reactions of (*S*)-phenylalanine methyl ester and of (*S*)-1-phenylethylamine were investigated. Both reactions gave the desired phenylglycine derivative **2e** and **2f** in reasonable yield (Scheme 2), but in both cases the induction was negligible (*ca.* 6 and 10% respectively as measured from the ^1H NMR spectrum of the mixture of diastereomers). This result is similar to that reported by Nicoud and Kagan, where only modest induction was observed in related copper-catalysed processes.¹⁴

In order to investigate further the possibility of diastereoselectivity in the N–H insertion reactions of rhodium carbenoids, the 2-diazo-2-phenylacetates **3** of (–)-borneol, (+)-menthol and (–)-8-phenylmenthol were studied.¹¹ Rhodium(II) acetate-catalysed decomposition in the presence of diethylamine, acetamide or methyl carbamate gave the corresponding *N*-substituted phenylglycine esters **4** in reasonable yield (Scheme 3), but in all cases the diastereoselectivity was



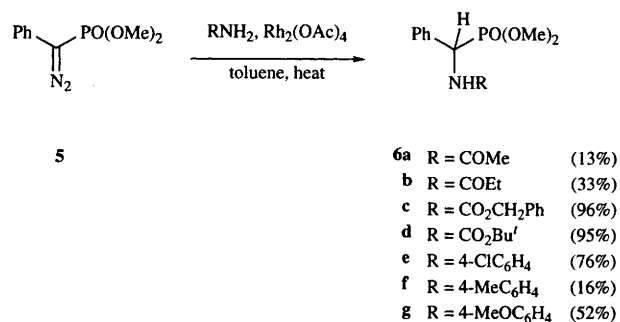
Scheme 3

very low (13% *de* maximum) (Table 1). This is in contrast to the closely related O–H insertion reactions of the rhodium carbenoids derived from the same diazo esters **3**, where *des* of over 50% could be obtained in some cases.¹¹

Having established the N–H insertion reactions of rhodium carbenoids derived from diazo esters as a simple route to amino acid derivatives, we next investigated the corresponding reaction of diazophosphonates as a route to aminophosphonate derivatives. Diazophosphonates are readily available⁵⁰ and the derived rhodium carbenoids undergo a range of reactions including intramolecular C–H insertion^{51,52} and O–H insertion.¹⁰ However, apart from our own work,^{32,33} there are only two reports of N–H insertion reactions of carbenoids from diazophosphonates and both of these involve the ubiquitous intramolecular insertion into the β -lactam N–H.^{53,54} Therefore we investigated the simple intermolecular N–H insertion reactions of dimethyl α -diazobenzylphosphonate **5**, readily prepared by the literature method,^{55,56} as a route to aminophosphonates. Diazophosphonates are more stable thermally and towards rhodium(II) catalysts than diazo esters and higher reaction temperatures are often needed.⁵⁷ Therefore, the rhodium(II) acetate-catalysed decomposition of diazophosphonate **5** in the presence of various NH compounds was carried out in boiling toluene and gave the corresponding N–H insertion products **6** (Scheme 4). The reaction with simple amides was low-yielding and the acetamide derived product **6a** could never be obtained

Table 1 Synthesis of compounds 4a–4e

Diazo ester	R*	R ¹	R ²	Product	Yield (%)	De (%)
3a		Et	Et	4a	49	4
3b		Et	Et	4b	42	3
		COMe	H	4c	71	10
		CO ₂ Me	H	4d	68	13
3c		COMe	H	4e	37	0



Scheme 4

completely pure. On the other hand, reaction with benzyl and *tert*-butyl carbamates gave the known^{58–60} *N*-protected aminobenzylphosphonates **6c** and **6d** in excellent yield. Reaction with anilines to give anilino-benzylphosphonates⁶¹ was more variable; 4-chloroaniline gave a good yield of the N–H insertion product **6e**, whereas 4-toluidine was less satisfactory. The anilino-benzylphosphonates **6e–6g** have been reported previously⁶² and although we were never able to obtain the latter two as crystalline solids, the spectroscopic data closely matched those described in the literature.

There is considerable current interest in aminophosphonates and a number of methods have been developed for their synthesis.^{63–78} The above route based on diazophosphonates complements existing methods and efforts are in hand to develop an asymmetric synthesis of aminophosphonates using diazophosphonate chemistry.

Experimental

Commercially available reagents were used throughout without further purification; solvents were dried by standard procedures. Analytical thin layer chromatography was carried out using aluminium-backed plates coated with Merck Kieselgel 60 GF₂₅₄. Plates were visualised under UV light (at 254 and/or 360 nm). Flash chromatography was carried out using Merck Kieselgel 60 H silica or Matrex silica 60. Pressure was applied at the column head with hand bellows. Samples were applied pre-adsorbed on silica.

Fully characterised compounds were chromatographically homogeneous. IR spectra were recorded in the range 4000–600 cm^{-1} using a Nicolet FT-205 spectrometer, with internal calibration. ^1H , ^{13}C and ^{31}P NMR spectra were recorded in deuteriochloroform (unless otherwise stated) using Bruker AC-250 and Bruker DPX-400 instruments; *J* values are given in Hz. High- and low-resolution mass spectra were recorded on a Kratos MS80 instrument.

Ether refers to diethyl ether and light petroleum refers to the fraction of bp 40–60 °C.

Methyl 2-(4-methoxyphenylamino)-2-phenylacetate 2a

A stirred solution of methyl 2-diazo-2-phenylacetate **1** (200 mg, 1.13 mmol) and 4-methoxyaniline (280 mg, 2.3 mmol) in dry dichloromethane (5 ml) was treated with rhodium(II) acetate (2 mol%). The mixture was heated under reflux for 12 h, the solvent evaporated and the residue chromatographed on silica gel (light petroleum–ether; gradient elution) to give the title compound (243 mg, 79%) as a colourless crystalline solid, mp 107–108 °C (lit.,⁷⁹ no mp given) (Found: M^+ , 271.1212. $C_{16}H_{17}NO_3$ requires M , 271.1208); $\nu_{\max}(\text{CHCl}_3)/\text{cm}^{-1}$ 3405, 1736, 1513 and 1238; $\delta_{\text{H}}(360 \text{ MHz})$ 7.50–7.49 (2 H, m, ArH), 7.47–7.28 (3 H, m, ArH), 6.72 (2 H, d, J 6.8, ArH), 6.53 (2 H, d, J 6.8, ArH), 5.02 (1 H, s, CH), 3.72 (3 H, s, OMe) and 3.71 (3 H, s, OMe); $\delta_{\text{C}}(62.9 \text{ MHz})$ 172.5, 152.5, 140.2, 137.8, 128.8, 128.2, 127.2, 114.8, 114.7, 61.6, 55.6 and 52.6; m/z (EI) 271 (M^+ , 20%), 212 (100), 196 (8), 168 (9), 151 (5), 134 (8), 122 (7), 107 (6), 91 (7), 77 (11), 64 (6), 51 (6) and 39 (4).

Methyl 2-(3-methylbutanoylamino)-2-phenylacetate 2b

A stirred solution of methyl 2-diazo-2-phenylacetate **1** (200 mg, 1.13 mmol) and isovaleramide (230 mg, 2.3 mmol) in dry dichloromethane (5 ml) was treated with rhodium(II) acetate (2 mol%). The mixture was stirred at room temperature for 24 h, the solvent evaporated and the residue chromatographed on silica gel (light petroleum–ether; gradient elution) to give the title compound (235 mg, 83%) as a colourless crystalline solid, mp 106–107 °C (Found: M^+ , 249.1365. $C_{14}H_{19}NO_3$ requires M , 249.1365); $\nu_{\max}(\text{CHCl}_3)/\text{cm}^{-1}$ 3271, 2956, 1747, 1690, 1262; $\delta_{\text{H}}(400 \text{ MHz})$ 7.29–7.23 (5 H, m, ArH), 6.43 (1 H, br d, J 6.4, exch D_2O , NH), 5.52 (1 H, d, J 7.20, CH), 3.64 (3 H, s, OMe), 2.01–2.05 (3 H, m, $CHCH_2$), 0.89 (3 H, d, J 6.48, Me) and 0.84 (3 H, d, J 6.48, Me); $\delta_{\text{C}}(100.6 \text{ MHz})$ 170.3, 170.0, 135.1, 128.4, 127.4, 126.9, 54.7, 51.2, 44.0, 24.5, 20.7 and 20.4; m/z (EI) 250 (MH^+ , 15%), 217 (6), 190 (36), 164 (40), 149 (8), 121 (9), 106 (100), 85 (9), 77 (12), 57 (23), 51 (4) and 41 (16).

Methyl 2-benzyloxycarbonylamino-2-phenylacetate 2c

A stirred solution of methyl 2-diazo-2-phenylacetate **1** (200 mg, 1.13 mmol) and benzyl carbamate (343 mg, 2.3 mmol) in dry dichloromethane (5 ml) was treated with rhodium(II) acetate (2 mol%). The mixture was stirred at room temperature for 24 h, the solvent evaporated and the residue chromatographed on silica gel (light petroleum–ether; gradient elution) to give the title compound (251 mg, 74%) as a colourless crystalline solid, mp 74–75 °C (lit.,⁸⁰ mp 76–77 °C) (Found: M^+ , 299.1162. Calc. for $C_{14}H_{19}NO_3$, 299.1158); $\nu_{\max}(\text{CHCl}_3)/\text{cm}^{-1}$ 3368, 1745, 1710, 1514 and 1215; $\delta_{\text{H}}(400 \text{ MHz})$ 7.39–7.34 (10 H, m, ArH), 5.90 (1 H, br d, J 6.0, exch D_2O , NH), 5.42 (1 H, d, J 7.20, CH), 5.13 (2 H, d, J 6.80, OCH_2) and 3.75 (3 H, s, OMe); $\delta_{\text{C}}(100.6 \text{ MHz})$ 172.6, 156.7, 137.9, 137.5, 130.3, 130.0, 129.9, 129.8, 129.4, 128.5, 68.4, 59.3 and 54.1; m/z (EI) 299 (M^+ , 1%), 240 (29), 196 (20), 163 (3), 132 (6), 104 (8), 91 (100), 77 (11), 65 (10) and 51 (7).

Methyl 2-(diethylamino)-2-phenylacetate 2d

Methyl 2-diazo-2-phenylacetate **1** (200 mg, 1.14 mmol) and diethylamine (83 mg, 1.14 mmol) were dissolved in toluene (5 ml), rhodium acetate (2 mol%) was added and the mixture was heated to reflux for 12 h. The solvent was removed *in vacuo* to yield a brown oil. Purification by flash chromatography (light petroleum–ether; gradient elution) afforded the title compound as a colourless oil (168 mg, 67%) (lit.,⁸¹ oil) (Found: M^+ , 221.1416. $C_{13}H_{19}NO_2$ requires M , 221.1417); $\nu_{\max}(\text{CHCl}_3)/\text{cm}^{-1}$ 2971, 1740 and 1202; $\delta_{\text{H}}(400 \text{ MHz})$ 7.44–7.43 (2 H, m, ArH), 7.33–7.28 (3 H, m, ArH), 4.49 (1 H, s, CH), 3.70 (3 H, s, OMe), 2.65–2.60 (4 H, m, CH_2) and 1.01–0.98 (6 H, t, J 6.7, Me); $\delta_{\text{C}}(100.6 \text{ MHz})$ 173.6, 137.1, 129.3, 128.7, 127.6, 69.3, 51.7, 43.7 and 12.0; m/z (EI) 221 (M^+ , 4%), 162 (100), 146 (5), 134 (10), 121 (9), 105 (19), 91 (17) and 77 (22).

Methyl 2-[(1*S*)-1-methoxycarbonyl-2-phenylamino]-2-phenylacetate 2e

Methyl 2-diazo-2-phenylacetate **1** (200 mg, 1.14 mmol) and (*S*)-(–)-phenylalanine methyl ester (238 mg, 1.14 mmol) were dissolved in toluene (5 ml), rhodium(II) acetate (2 mol%) was added and the mixture was heated to reflux for 12 h. The solvent was removed *in vacuo* to yield a yellow oil. Purification by flash chromatography (light petroleum–ether; gradient elution) afforded the title compound as a colourless oil as a mixture of diastereomers (264 mg, 71%) (Found: MH^+ , 328.1549. $C_{19}H_{21}NO_4$ requires MH , 328.1548); $\nu_{\max}(\text{CHCl}_3)/\text{cm}^{-1}$ 2952, 1738, 1732 and 1203; $\delta_{\text{H}}(400 \text{ MHz})$ 7.30–7.12 (10 H, m, ArH), 4.37 (1 H, s, CH), 3.65 (3 H, s, OMe), 3.60 (3 H, s, OMe), 3.31 (1 H, m, CH), 3.01 (2 H, m, CH_2) and 2.72 (1 H, br s, exch D_2O , NH); $\delta_{\text{C}}(100.6 \text{ MHz})$ 175.2, 173.5, 138.1, 138.3, 130.2, 129.5, 129.4, 128.8, 127.6, 65.0, 64.4, 61.8, 60.6, 53.2, 52.6, 40.65 and 40.57; m/z (CI) 328 (MH^+ , 100%).

Methyl 2-[(1*S*)-1-phenylethylamino]-2-phenylacetate 2f

Methyl 2-diazo-2-phenylacetate **1** (300 mg, 1.70 mmol) and (*S*)-2-phenylethylamine (206 mg, 1.70 mmol) were dissolved in toluene (5 ml), rhodium(II) acetate (2 mol%) was added and the mixture was heated to reflux for 12 h. The solvent was removed *in vacuo* to yield an orange oil. Purification by flash chromatography (light petroleum–ether; gradient elution) afforded the title compound, a colourless oil (293 mg, 64%), as a mixture of diastereomers. The faster running diastereomer was obtained pure whereas the lower running diastereomer contained a trace impurity that could not be removed (Found: M^+ , 269.1403. $C_{17}H_{19}NO_2$ requires M , 269.1415); $\nu_{\max}(\text{CHCl}_3)/\text{cm}^{-1}$ 2955, 1737 and 1206; $\delta_{\text{H}}(400 \text{ MHz})$ (faster-running diastereomer) 7.33–7.29 (10 H, m, ArH), 4.22 (1 H, s, CH), 3.79 (1 H, q, J 6.5, $CHMe$), 3.70 (3 H, s, OMe) and 1.83 (3 H, d, J 6.5, Me); $\delta_{\text{C}}(100.6 \text{ MHz})$ 172.5, 144.8, 138.5, 128.2, 128.0, 127.7, 127.4, 127.2, 126.9, 62.9, 56.7, 52.2 and 24.6; m/z (EI) 270 (MH^+ , 100%), 265 (6), 210 (97), 194 (11), 166 (12), 149 (8), 121 (19), 105 (88), 91 (12) and 77 (20). The slower-running diastereomer shows the following signals: $\delta_{\text{H}}(400 \text{ MHz})$ 4.19 (1 H, s, CH), 3.59 (3 H, s, OMe), 3.54 (1 H, q, J 6.4, CH) and 1.33 (3 H, d, J 6.4, Me); $\delta_{\text{C}}(100.6 \text{ MHz})$ 174.2, 144.6, 138.4, 128.7, 128.5, 128.4, 127.9, 127.6, 126.9, 62.9, 52.0, 50.4 and 24.4.

(1*S*)-2-endo-Bornyl 2-diethylamino-2-phenylacetate 4a

A stirred solution of bornyl 2-diazo-2-phenylacetate **3a** (100 mg, 0.33 mmol) and diethylamine (49 mg, 0.66 mmol) in dry dichloromethane (5 ml) was treated with rhodium(II) acetate (2 mol%). The mixture was stirred at room temperature for 7 days, the solvent evaporated and the residue chromatographed on silica gel (dichloromethane) to give the title compound (56 mg, 49%) as a mixture of diastereomers (*ca.* 4% de) as a colourless oil (Found: M^+ , 343.2514. $C_{22}H_{33}NO_2$ requires M , 343.2511); $\nu_{\max}(\text{neat})/\text{cm}^{-1}$ 2961, 1732, 1454, 1198 and 1152; $\delta_{\text{H}}(250 \text{ MHz})^\ddagger$ 7.45 (4 H, m, ArH), 7.29 (6 H, m, ArH), 4.92 (2 H, m, bornyl H-2), 4.51 (1 H, s, $CHNEt_2$), 4.50 (1 H, s, $CHNEt_2$), 2.64 (8 H, q, J 7.1, NCH_2Me), 1.89 (2 H, m), 2.34 (2 H, m), 1.15 (5 H, m), 1.67 (4 H, m), 1.01 (12 H, t, J 7.1, NCH_2Me), 0.88 (6 H, s, Me), 0.85 (3 H, s, Me), 0.84 (3 H, s, Me), 0.82 (3 H, s, Me), 0.81 (1 H, m) and 0.70 (3 H, s, Me); $\delta_{\text{C}}(62.9 \text{ MHz})^\ddagger$ 172.7, 172.6, 137.8, 137.7, 128.7, 128.5, 128.3, 127.8, 80.3, 69.7, 69.5, 48.9, 48.8, 47.9, 44.9, 44.9, 43.8, 43.7, 36.9, 36.6, 28.1, 28.0, 27.3, 27.2, 19.7, 18.9, 13.6, 13.4, 12.1 and 12.0; m/z (EI) 344 (MH^+ , 13%), 343 (M^+ , 0.7), 162 (100), 91 (12) and 81 (11).

(1*S*,3*S*,4*R*)-3-Menthyl 2-diethylamino-2-phenylacetate 4b

A stirred solution of menthyl 2-diazo-2-phenylacetate **3b** (100 mg, 0.33 mmol) and diethylamine (49 mg, 0.66 mmol) in dry

[†] NMR data for both diastereomers given.

dichloromethane (5 ml) was treated with rhodium(II) acetate (2 mol%). The mixture was stirred at room temperature for 24 h, the solvent evaporated and the residue chromatographed on silica gel (dichloromethane) to give the *title compound* (46 mg, 42%) as a mixture of diastereomers (ca. 3% de) as a colourless oil (Found: M^+ , 345.2660. $C_{22}H_{35}NO_2$ requires M , 345.2688); $\nu_{\max}(\text{neat})/\text{cm}^{-1}$ 1733, 1455, 1198 and 1164; $\delta_H(250 \text{ MHz})\dagger$ 7.43 (4 H, m, ArH), 7.31 (6 H, m, ArH), 4.72 (1 H, dt, J 10.9 and 4.4, menthyl H-3), 4.67 (1 H, dt, J 10.9 and 4.4, menthyl H-3), 4.46 (1 H, s, $CHNEt_2$), 4.41 (1 H, s, $CHNEt_2$), 2.64 (8 H, m), 1.85 (1 H, m), 1.80 (2 H, m), 1.65 (3 H, m), 1.35 (6 H, m), 0.99 (12 H, t, J 7.2, Me), 0.89 (3 H, d, J 6.5, Me), 0.86 (3 H, d, J 6.5, Me), 0.85 (3 H, d, J 6.5, Me), 0.85 (6 H, m), 0.70 (3 H, d, J 7.0, Me), 0.69 (3 H, d, J 7.0 Me) and 0.51 (3 H, d, J 6.9, Me); $\delta_C(62.9 \text{ MHz})$ 172.0, 137.4, 137.3, 128.7, 128.7, 128.2, 127.8, 127.7, 74.7, 74.5, 69.6, 69.6, 47.0, 46.8, 43.5, 43.4, 40.9, 40.3, 34.2, 31.4, 31.3, 25.9, 25.5, 23.0, 22.0, 21.9, 20.7, 20.6, 15.8, 15.6, 11.8 and 11.6; m/z (EI) 345 (M^+ , 0.2%), 162 (100), 91 (13) and 81 (11).

(1S,3S,4R)-3-Menthyl 2-acetylamino-2-phenylacetate 4c

A stirred solution of menthyl 2-diazo-2-phenylacetate **3b** (100 mg, 0.33 mmol) and acetamide (39 mg, 0.66 mmol) in dry dichloromethane (5 ml) was treated with rhodium(II) acetate (2 mol%). The mixture was stirred at room temperature for 1 h, the solvent evaporated and the residue chromatographed on silica gel (ethyl acetate–light petroleum, 1:3) to give the *title compound* (78 mg, 71%) as a mixture of diastereomers (10% de) as colourless crystals, mp 68–70 °C (Found: M^+ , 331.2142. $C_{20}H_{29}NO_3$ requires M , 331.2147); $\nu_{\max}(\text{Nujol})/\text{cm}^{-1}$ 3341, 1729, 1709, 1680, 1655, 1273, 1178 and 728; $\delta_H(250 \text{ MHz})\dagger$ 7.29 (10 H, m, ArH), 6.88 (1 H, d, J 7.2, NH), 6.79 (1 H, d, J 7.5, NH), 5.56 (1 H, d, J 7.5, CHNH), 5.52 (1 H, d, J 7.2, CHNH), 4.71 (1 H, dt, J 10.9 and 4.4, menthyl H-3), 4.59 (1 H, dt, J 10.9 and 4.4, menthyl H-3), 1.98 (6 H, s, Me), 1.95 (2 H, m), 1.47 (10 H, m), 0.95 (6 H, m), 0.88 (3 H, d, J 6.4, Me), 0.88 (3 H, d, J 6.5, Me), 0.80 (3 H, d, J 6.5, Me), 0.75 (3 H, d, J 7.0, Me), 0.57 (3 H, d, J 6.9, Me) and 0.38 (3 H, d, J 6.8, Me); $\delta_C(62.9 \text{ MHz})$ 170.7, 170.5, 169.3, 136.9, 136.8, 128.6, 128.5, 128.2, 128.1, 127.2, 127.0, 76.0, 75.9, 56.6, 56.3, 46.8, 46.6, 40.6, 39.8, 34.0, 33.9, 31.3, 31.2, 26.0, 25.2, 23.2, 22.9, 22.8, 21.8, 21.8, 20.5, 20.3, 16.1 and 15.5; m/z (EI) 332 (MH^+ , 19%), 331 (M^+ , 0.4), 194 (30), 148 (100), 106 (97) and 83 (59).

(1S,3S,4R)-3-Menthyl 2-methoxycarbonylamino-2-phenylacetate 4d

A stirred solution of menthyl 2-diazo-2-phenylacetate **3b** (100 mg, 0.33 mmol) and methyl carbamate (25 mg, 0.33 mmol) in dry dichloromethane (6 ml) was treated with rhodium(II) acetate (2 mol%). The mixture was stirred at room temperature, the solvent evaporated and the residue chromatographed on silica gel (dichloromethane) to give the *title compound* (78 mg, 68%), an oil, as a mixture of diastereomers (13% de) (Found: M^+ , 347.2093. $C_{20}H_{29}NO_4$ requires M , 347.2096); $\nu_{\max}(\text{neat})/\text{cm}^{-1}$ 3436, 3364, 1728, 1499, 1179, 1054 and 698; $\delta_H(250 \text{ MHz})\dagger$ 7.32 (10 H, m, ArH), 5.91 (2 H, m, NH), 5.34 (1 H, d, J 7.4, NHCH), 5.28 (1 H, d, J 7.4, NHCH), 4.73 (1 H, dt, J 10.9 and 4.4, menthyl H-3), 4.62 (1 H, dt, J 10.9 and 4.4, menthyl H-3), 3.66 (3 H, s, OMe), 3.65 (3 H, s, OMe), 2.30 (1 H, m), 1.28 (17 H, m), 0.90 (3 H, d, J 6.5, Me), 0.89 (3 H, d, J 7.1, Me), 0.82 (3 H, d, J 6.5, Me), 0.76 (3 H, d, J 6.8, Me), 0.60 (3 H, d, J 6.9, Me) and 0.40 (3 H, d, J 7.0, Me); $\delta_C(62.9 \text{ MHz})$ 170.4, 170.3, 155.9, 137.1, 128.7, 128.6, 128.3, 128.2, 127.1, 126.9, 76.1, 75.9, 58.2, 57.8, 52.2, 46.9, 46.7, 40.6, 39.8, 34.0, 33.8, 31.3, 31.2, 26.1, 25.2, 23.2, 22.9, 21.8, 21.8, 20.6, 20.4, 15.5 and 15.2; m/z (EI) 347 (M^+ , 0.1%), 210 (27), 164 (100), 121 (18), 95 (22) and 83 (35).

(1R,3R,4S)-8-Phenyl-3-menthyl 2-acetylamino-2-phenylacetate 4e

A stirred solution of 8-phenyl-3-menthyl 2-diazo-2-phenylacetate **3c** (100 mg, 0.26 mmol) and acetamide (32 mg, 0.66

mmol) in dry dichloromethane (8 ml) was treated with rhodium(II) acetate (2 mol%). The mixture was stirred at room temperature for 3 h, the solvent evaporated and the residue chromatographed on silica gel (ethyl acetate–light petroleum, 1:1) to give the *title compound* (39 mg, 37%) as a mixture of diastereomers (ca. 0% de) as a colourless oil (Found: M^+ , 407.2453. $C_{26}H_{33}NO_3$ requires M , 407.2460); $\nu_{\max}(\text{neat})/\text{cm}^{-1}$ 3299, 1735, 1719, 1655, 1175 and 698; $\delta_H(250 \text{ MHz})\dagger$ 7.22 (20 H, m, ArH), 6.50 (1 H, d, J 6.9, NH), 6.34 (1 H, d, J 6.9, NH), 5.39 (1 H, d, J 6.9, CHNH), 4.78 (2 H, m, menthyl H-3), 4.68 (1 H, d, J 6.9, CHNH), 2.00 (2 H, m), 1.99 (3 H, s, MeCO), 1.99 (3 H, s, MeCO), 1.81 (3 H, m), 0.50–1.70 (11 H, m), 1.28 (3 H, s, Me), 1.22 (3 H, s, Me), 0.99 (3 H, s, Me), 0.84 (3 H, d, J 6.4, Me), 0.78 (3 H, s, Me) and 0.77 (3 H, d, J 6.4, Me); $\delta_C(62.9 \text{ MHz})$ 170.0, 169.9, 169.2, 168.8, 151.5, 149.9, 136.8, 136.0, 128.6, 128.6, 128.4, 128.0, 127.9, 127.8, 127.8, 127.0, 125.6, 125.31, 125.27, 77.5, 76.0, 57.3, 56.0, 50.4, 50.2, 41.5, 40.4, 39.9, 39.4, 34.3, 31.3, 31.1, 29.4, 28.8, 27.2, 26.3, 23.6, 23.1, 21.6 and 21.6; m/z (EI) 408 (MH^+ , 7%), 407 (M^+ , 2), 214 (18), 194 (91), 148 (70), 119 (100), 105 (95), 91 (59) and 77 (37).

Dimethyl α -acetylaminobenzylphosphonate 6a

To a stirred solution of dimethyl α -diazobenzylphosphonate **5** (100 mg, 0.44 mmol) in dry toluene (2 ml) was added acetamide (261 mg, 4.40 mmol). After the addition of rhodium(II) acetate (2 mol%) the reaction mixture was stirred at reflux for 2 h. Removal of the solvent under reduced pressure and purification of the reaction mixture by flash chromatography (ether–ethyl acetate, 7:3) yielded the *title compound* as a pale yellow oil (15 mg, 13%) (lit.,⁸² mp 138–139.5 °C); $\nu_{\max}(\text{film})/\text{cm}^{-1}$ 3471br, 2957, 1757, 1263 and 1030; $\delta_H(400 \text{ MHz})$ 7.51–7.36 (5 H, m, ArH), 6.17 (1 H, d, J 13.5, CHP), 3.73 [3 H, d, J 10.6, P(OMe)₂], 3.65 [3 H, d, J 10.6, P(OMe)₂], 2.19 (3 H, s, Me), NH was not observed; $\delta_C(100.6 \text{ MHz})$ 169.3 (d), 133.1, 130.0, 128.9, 127.8, 70.9 (d), 53.9 (d), 53.8 (d) and 20.9; $\delta_P(101.3 \text{ MHz})$ 19.04; satisfactory mass spectrum could not be obtained.

Dimethyl α -propionylaminobenzylphosphonate 6b

To a stirred solution of dimethyl α -diazobenzylphosphonate **5** (100 mg, 0.44 mmol) in dry toluene (2 ml) was added propionamide (162 mg, 4.40 mmol). After the addition of rhodium(II) acetate (2 mol%) the reaction mixture was stirred at reflux for 1 h. Removal of the solvent under reduced pressure and purification of the reaction mixture by flash chromatography (ether–ethyl acetate, 7:3) yielded the *title compound* as a pale yellow oil (39 mg, 33%) (Found: M^+ , 272.0814. $C_{12}H_{19}NO_4P$ requires M , 272.1052); $\nu_{\max}(\text{film})/\text{cm}^{-1}$ 3496, 2958, 1752, 1464, 1378 and 1038; $\delta_H(250 \text{ MHz})$ 7.48–7.35 (5 H, m, ArH), 6.19 (1 H, d, J 13.6, CHP), 3.72 [3 H, d, J 10.9, P(OMe)₂], 3.66 [3 H, d, J 10.5, P(OMe)₂], 2.46 (2 H, m, CH₂), 1.18 (3 H, t, J 7.4, Me), NH was not observed; $\delta_C(62.9 \text{ MHz})$ 161.1 (d), 140.2, 128.8, 128.5, 127.6, 69.8 (d), 53.9 (d), 53.8 (d), 27.4 and 8.9; $\delta_P(101.3 \text{ MHz})$ 19.15; m/z 272 (MH^+ , 10%), 216 (15), 166 (10), 138 (15), 110 (30), 105 (20) and 57 (100).

Dimethyl α -benzyloxycarbonylamino- α -benzylphosphonate 6c

To a stirred solution of dimethyl α -diazobenzylphosphonate **5** (100 mg, 0.44 mmol) in dry toluene (2 ml) was added benzyl carbamate (334 mg, 2.20 mmol). After the addition of rhodium(II) acetate (2 mol%) the reaction mixture was stirred at 80 °C for 1 h. Removal of the solvent under reduced pressure and purification of the reaction mixture by flash chromatography (ether–ethyl acetate, 7:3) yielded the *title compound* as a colourless solid (149 mg, 96%), mp 117–118 °C (lit.,⁵⁸ mp 117–118.5 °C; lit.,⁵⁹ mp 120–121 °C) (Found: C, 58.6; H, 5.8; N, 4.2. Calc. for $C_{17}H_{20}NO_5P$: C, 58.5; H, 5.8; N, 4.0%); $\nu_{\max}(\text{Nujol})/\text{cm}^{-1}$ 3250, 3018, 2956, 1716, 1490, 1256, 1216 and 1041; $\delta_H(250 \text{ MHz})$ 7.46–7.30 (10 H, m, ArH), 6.41 (1 H, dd, J 9.2, 3.4, NH), 5.24 (1 H, dd, J 21.7, 9.7, CHP), 5.12 (1 H, d, J 18.0, OCH₂), 5.05 (1 H, d, J 18.0, OCH₂), 3.71 [3 H, d, J 10.6,

P(OMe)₂] and 3.44 [3 H, d, *J* 10.5, P(OMe)₂]; δ_{C} (62.9 MHz) 155.6, 136.0, 134.8, 128.7, 128.4, 128.2, 128.1, 127.9, 127.8, 67.2, 53.8, (d), 53.5 (d) and 50.8 (d); δ_{P} (101.3 MHz) 22.67; *m/z* 349 (M⁺, 3%), 240 (40), 196 (36), 132 (20), 104 (20), 91 (100) and 77 (25).

Dimethyl α -*tert*-butoxycarbonylaminobenzylphosphonate 6d

To a stirred solution of dimethyl α -diazobenzylphosphonate **5** (100 mg, 0.44 mmol) in dry toluene (2 ml) was added *tert*-butyl carbamate (259 mg, 2.20 mmol). After the addition of rhodium(II) acetate (2 mol%) the reaction mixture was stirred at reflux for 1 h. Removal of the solvent under reduced pressure and purification of the reaction mixture by flash chromatography (ether–ethyl acetate, 4:1) yielded the title compound as a colourless solid (132 mg, 95%), mp 115–116 °C (lit.⁶⁰ mp 110–111 °C) (Found: C, 53.6; H, 7.25; N, 4.6. Calc. for C₁₄H₂₂NO₃P: C, 53.3; H, 7.0; N, 4.4%; ν_{max} (CHCl₃)/cm⁻¹ 3261, 3011, 2954, 1712, 1496, 1252, 1217 and 1040; δ_{H} (250 MHz) 7.45–7.32 (5 H, m, ArH), 5.81 (1 H, dd, *J* 5.5, 9.3, NH), 5.16 (1 H, dd, *J* 21.5, 9.3, CHP), 3.76 [3 H, d, *J* 10.6, P(OMe)₂], 3.50 [3 H, d, *J* 10.5, P(OMe)₂] and 1.42 (9 H, s, Bu^t); δ_{C} (62.9 MHz) 154.9, 135.2, 128.5, 128.0, 127.7, 80.2, 53.6 (d), 53.4 (d), 51.4 (d) and 28.1; δ_{P} (101.3 MHz) 23.12; *m/z* 315 (M⁺, 3%), 242 (8), 206 (40), 150 (85), 106 (90) and 57 (100).

Dimethyl α -(4-chlorophenylamino)benzylphosphonate 6e

To a stirred solution of dimethyl α -diazobenzylphosphonate **5** (100 mg, 0.44 mmol) in dry toluene (2 ml) was added 4-chloroaniline (282 mg, 2.20 mmol). After the addition of rhodium(II) acetate (2 mol%) the reaction mixture was stirred at reflux for a period of 3 h. Removal of the solvent under reduced pressure and purification of the reaction mixture by flash chromatography (ethyl acetate–light petroleum, 1:1) yielded the title compound as a pale brown solid (110 mg, 76%) which was recrystallised from ethyl acetate–light petroleum to give the title compound as colourless crystals (80 mg, 56%), mp 101–102 °C (lit.⁶² mp 101–102 °C) (Found: M⁺, 325.0639. Calc. for C₁₅H₁₇ClNO₃P, 325.0635); ν_{max} (film)/cm⁻¹ 3301, 3029, 2955, 1494, 1454, 1241, 1183 and 737; δ_{H} (250 MHz) 7.45–7.30 (5 H, m, ArH), 7.04 (2 H, m, ArH), 6.52 (2 H, m, ArH), 4.95 (1 H, br s, NH), 4.74 (1 H, d, *J* 24.2, CHP), 3.76 [3 H, d, *J* 10.6, P(OMe)₂] and 3.46 [3 H, d, *J* 10.5, P(OMe)₂]; δ_{C} (62.9 MHz) 141.1, 135.0, 129.0, 128.2, 127.7, 127.6, 121.9, 115.0, 56.9 (d), 54.5 (d) and 53.8 (d); δ_{P} (101.3 MHz) 23.56; *m/z* 325 (M⁺, 5%), 216 (100), 138 (12), 111 (16), 77 (9) and 43 (21).

Dimethyl α -(4-methylphenylamino)benzylphosphonate 6f

To a stirred solution of dimethyl α -diazobenzylphosphonate **5** (100 mg, 0.44 mmol) in dry toluene (2 ml) was added 4-methylaniline (237 mg, 2.20 mmol). After the addition of rhodium(II) acetate (2 mol%) the reaction mixture was stirred at reflux for 3 h. Removal of the solvent under reduced pressure and purification of the reaction mixture by flash chromatography (ethyl acetate–light petroleum, 1:1) yielded the title compound as a brown oil (22 mg, 16%) (lit.⁶² mp 89–90 °C) (Found: M⁺, 305.1179. Calc. for C₁₆H₂₀NO₃P, 305.1180); ν_{max} (film)/cm⁻¹ 3311, 3028, 2954, 1493, 1454, 1240, 1183 and 733; δ_{H} (250 MHz) 7.48–7.33 (5 H, m, ArH), 6.91 (2 H, m, ArH), 6.52 (2 H, m, ArH), 4.77 (1 H, d, *J* 24.5, CHP), 4.72 (1 H, br s, NH), 3.76 [3 H, d, *J* 10.7 P(OMe)₂], 3.47 [3 H, d, *J* 10.5, P(OMe)₂] and 2.17 (3 H, s, ArMe); δ_{C} (62.9 MHz) 142.1, 142.0, 135.7, 129.6, 128.6, 128.0, 127.8, 114.0, 57.0 (d), 54.7 (d), 53.7 (d) and 20.3; δ_{P} (101.3 MHz) 24.05; *m/z* 305 (M⁺, 6%), 196 (100), 91 (18) and 69 (53).

Dimethyl α -(4-methoxyphenylamino)benzylphosphonate 6g

To a stirred solution of dimethyl α -diazobenzylphosphonate **5** (100 mg, 0.44 mmol) in dry toluene (2 ml) was added 4-methoxyaniline (272 mg, 2.20 mmol). After the addition of rhodium(II) acetate (2 mol%) the reaction mixture was stirred at reflux for 3

h. Removal of the solvent under reduced pressure and purification of the reaction mixture by flash chromatography (ether) yielded the title compound as a brown oil (74 mg, 52%) (lit.⁶² mp 100–101 °C) (Found: M⁺, 321.1133. Calc. for C₁₆H₂₀NO₃P, 321.1130); ν_{max} (film)/cm⁻¹ 3311, 3021, 2954, 1494, 1453, 1238, 1181 and 1033; δ_{H} (250 MHz) 7.47–7.29 (5 H, m, ArH), 6.69 (2 H, m, ArH), 6.55 (2 H, m, ArH), 4.88 (1 H, d, *J* 24.1, CHP), 4.58 (1 H, br s, NH), 3.76 [3 H, d, *J* 10.6, P(OMe)₂], 3.68 (3 H, s, OMe) and 3.46 [3 H, d, *J* 10.5, P(OMe)₂]; δ_{C} (62.9 MHz) 154.6, 152.8, 140.1, 136.5, 128.6, 127.8, 115.2, 114.7, 57.0 (d), 56.5, 53.7 (d) and 53.5 (d); δ_{P} (101.3 MHz; CDCl₃) 24.08; *m/z* 321 (M⁺, 12%), 290 (10), 212 (100), 180 (47), 108 (13), 91 (21) and 77 (17).

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