N-H Insertion reactions of rhodium carbenoids. Part 4.[1] New chiral dirhodium(II) carboxylate catalysts

Richard T. Buck, Christopher J. Moody*, and Adrian G. Pepper

School of Chemistry, University of Exeter, Stocker Road, Exeter EX4 4QD, UK
E-mail: c.j.moody@exeter.ac.uk

Dedicated to Professor Albert Padwa in recognition of his outstanding contributions to the dirhodium(II) catalysed chemistry of diazocarbonyl compounds

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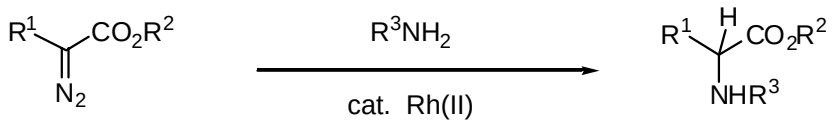
Abstract

The reaction of methyl 2-diazophenylacetate **1** and dimethyl α-diazobenzylphosphonate **2** with various N-H components in the presence of chiral dirhodium(II) catalysts results in N-H insertion in good yield but with little or no stereoselectivity.

Keywords: Diazoester, diazophosphonate, carbene insertion, rhodium, catalyst

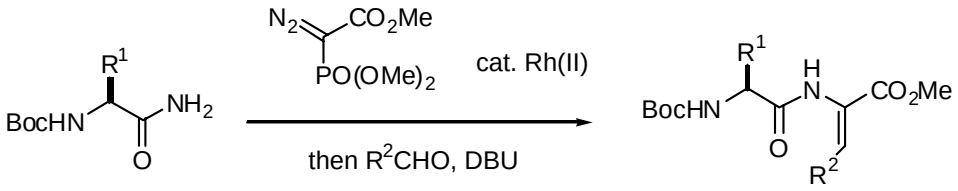
Introduction

The synthesis of α-amino acids and peptides remains a topic of considerable importance and current interest. In previous papers,[2,3] we have reported that diazoesters react with a range of R^3NH_2 compounds in the presence of dirhodium(II) catalysts to give α-amino acid derivatives, the products of N-H insertion of the intermediate rhodium carbene, in high yield (Scheme 1).



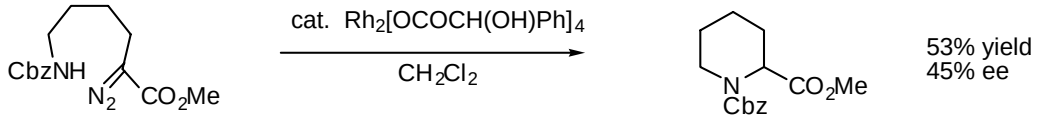
Scheme 1

In an extension to this work,[4] we showed that *N*-protected amino acid amides also underwent N-H insertion reaction, in a new approach to dipeptides (Scheme 2).



Scheme 2

The N-H insertion reactions of metallocarbenes have been known for some time. Early work relied on copper catalysts,[5] but it was the 1974 report that dirhodium(II) acetate was an extremely effective catalyst for such transformations,[6] that stimulated much of the subsequent work in the area.[7] However, the possibility that such N-H insertion reactions could be carried out stereoselectively to give α-amino acid derivatives as single enantiomers at the new stereocentre remains the most attractive aspect. Attempts to use chiral auxiliaries (Scheme 1, R^2 = chiral group) resulted in modest asymmetric induction,[2,8] and little work on the use of chiral catalysts has been reported. Thus McKervey's group reported that intramolecular N-H insertion reactions could be carried out using dirhodium(II) mandelate as catalyst to give the desired piperidine product in 53% yield with 45% *ee* (Scheme 3).[9]

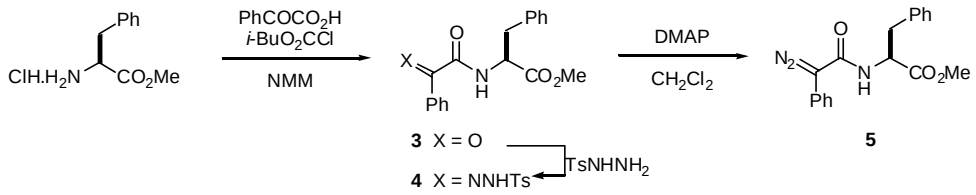


Scheme 3

In view of our own interest in the development of novel chiral dirhodium(II) catalysts,[10–13] we now report the results of our attempts to effect stereoselective N-H insertion reactions of rhodium carbenes derived from diazoesters and diazophosphonates.

Results and Discussion

Diazocarbonyl compounds. Three diazocarbonyl compounds were investigated: the simple diazoester **1,** the diazophosphonate **2** used in our previous work,[2] and the diazoamide **5**. This was prepared from phenylalanine methyl ester by conversion to the α-ketoamide **3**, followed by formation and decomposition of the corresponding tosylhydrazone **4** as outlined in Scheme 4.



Scheme 4

Dirhodium (II) catalysts. A wide range of chiral catalysts was selected for study. These encompassed the known catalysts **6**–**8** derived from mandelic acid,[14] 2-methoxy-2-(trifluoromethyl)phenylacetic acid,[15] and *N*-benzenesulfonylproline,[16] as well as the novel catalysts **9** and **10** reported earlier.[10] We also examined dirhodium(II) camphenate **11**,[17] its related camphenate derivative **12**,[11] Doyle's MEPY catalyst **13**,[18] and our recently developed difluoro-MEPY **14**.[13] Finally, we investigated four catalysts **15**–**18** identified using our parallel synthesis catalyst screen for new Si-H insertion catalysts,[12] and three new catalysts **19**–**21,** also based on *N*-arenesulfonylamino acids (Figure 1). These new catalysts were prepared by reaction of the appropriate *N*-arenesulfonyl amino acid with dirhodium(II) carbonate.[19]

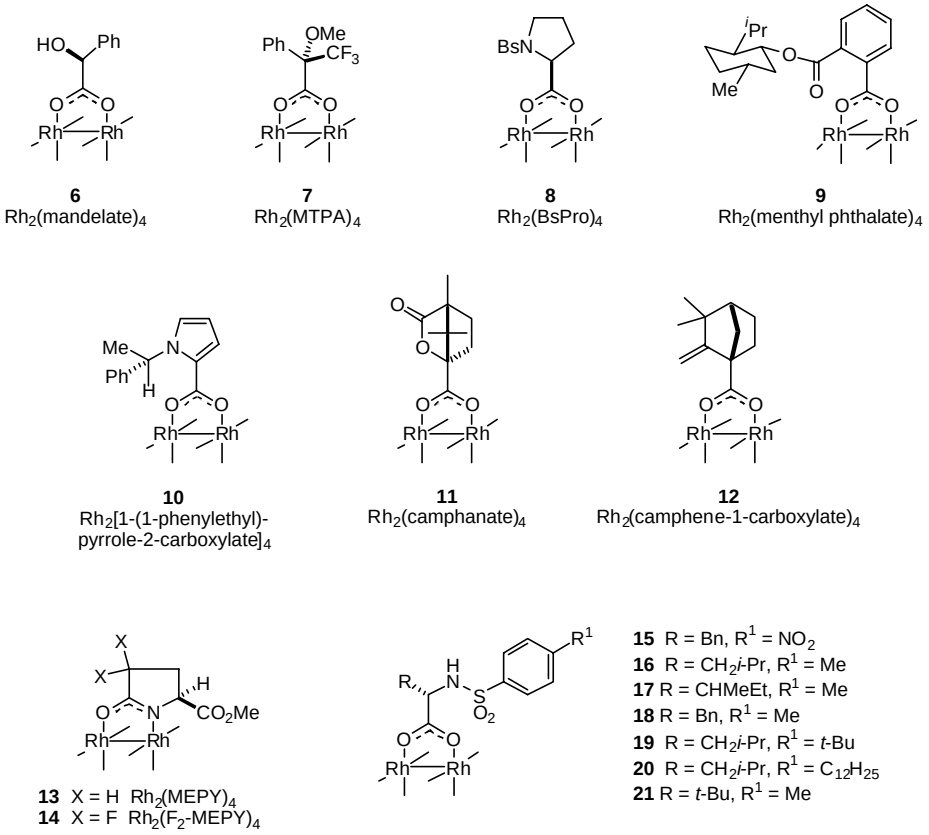
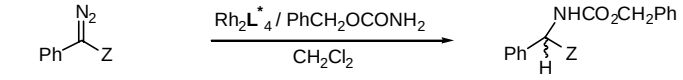


Figure 1. Chiral dirhodium(II) catalysts (only one of the four bridging ligands is shown in each case).

With a range of chiral dirhodium(II) catalysts available, the N-H insertion reactions of both methyl 2-diazophenylacetate **1** and dimethyl α-diazobenzylphosphonate **2** were investigated. Benzyl carbamate was selected as the N-H component since it is known to give high yields of N-H insertion products with achiral dirhodium(II) catalysts.[2] In the event, decomposition of methyl 2-diazophenylacetate, **1,** in the presence of the 16 chiral dirhodium(II) catalysts gave the expected *N*-benzyloxycarbonylphenylglycine methyl ester **22** in good yield (62–92%). However, the enantiomeric excess (ee), as determined by HPLC on a chiral stationary phase, was less than 5% in all cases (Table 1). Likewise, the diazophosphonate **2** gave the aminophosphonate derivative **23** in 63–96% yield but with less than 10% *ee* (Table 1). Therefore, as with the corresponding O-H insertion reactions,[10] there is negligible enantioselectivity in the N-H insertion process when using chiral dirhodium(II) catalysts.

Table 1. Dirhodium(II) catalysed N-H insertion reactions of methyl 2-diazophenylacetate and dimethyl α-diazobenzylphosphonate



1 Z = CO_2Me
2 Z = $PO(OMe)_2$

22 Z = CO_2Me
23 Z = $PO(OMe)_2$

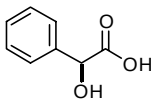
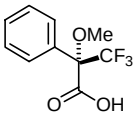
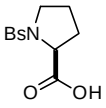
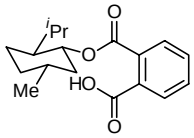
Entry	Chiral Dirhodium(II) Catalyst ($Rh_2L^*_4$)	Z = CO_2Me Yield / %	Z = CO_2Me *ee* / % [a]	Z = $PO(OMe)_2$ Yield / %	Z = $PO(OMe)_2$ *ee* / % [b]
1	 **6**	92	2	96	8
2	 **7**	82	3	63	2
3	 **8**	80	3	94	7
4	 **9**	80	4	92	4

Table 1. Continued

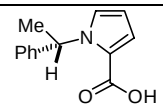
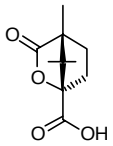
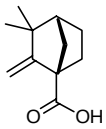
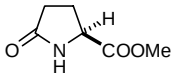
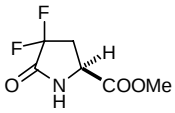
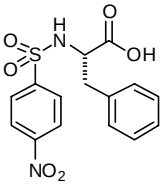
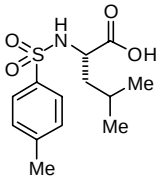
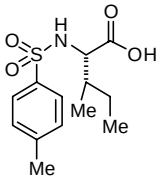
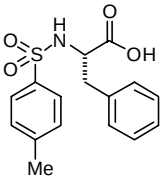
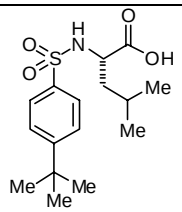
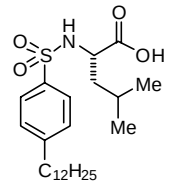
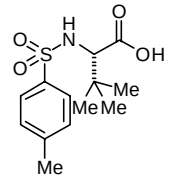
5	 **10**	76	2	94	3
6	 **11**	80	2	88	9
7	 **12**	69	4	95	1
8	 **13**	62	0	-	-
9	 **14**	86	0	-	-
10	 **15**	78	3	69	5
11	 **16**	80	5	81	0
12	 **17**	76	2	79	5
13	 **18**	69	4	72	9

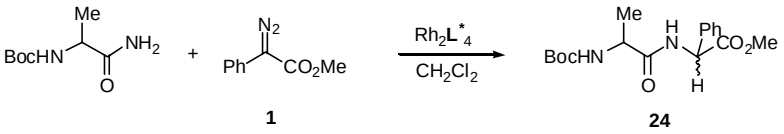
Table 1. Continued

14	 **19**	80	4	76	6
15	 **20**	74	3	71	3
16	 **21**	76	3	73	4

[a] HPLC analysis was carried out on a Chiralcel OD column using 5% 2-propanol in hexane at 1.0 mL/min.
[b] HPLC analysis was carried out on a Chiralcel OD column using 10% 2-propanol in hexane at 1.0 mL/min.

Despite the poor *ee* in the above reactions, we also investigated N-H insertion reactions involving the N-H bond in chiral amides. Earlier studies had shown that both Boc-Ala-NH_2 and Boc-Val-NH_2 underwent N-H insertion with methyl 2-diazophenylacetate **1** in modest diastereomeric excess (de) (20–25%) when using achiral dirhodium(II) acetate.[4] This raises the question of whether the *de* could be raised (or lowered) by the use of an appropriate catalyst whose chirality was matched (or mis-matched) to that of the amino acid amide derivative. To investigate this possibility, methyl 2-diazophenylacetate, **1,** was reacted with both (S)- and (R)-*N*-*tert*-butoxycarbonylalaninamide in the presence of a range of chiral dirhodium(II) catalysts (Table 2). In all cases the *de* of the product dipeptide **24** was less than that observed with dirhodium(II) acetate itself (25%), and there was no significant difference between the (R)- and (S)- enantiomers of the alaninamide derivative, *i.e.,* no evidence of a match/mismatch situation. Similar results were obtained with the corresponding valinamides (Table 3), although in one case (Entry 1) there was some evidence that the chiral catalyst did influence the reaction to a small degree (*ca*. 20% *de* when dirhodium(II) acetate used as catalyst).

Table 2. Dirhodium(II) catalysed N-H insertion reactions of methyl 2-diazophenylacetate with Boc-Ala-NH_2



1 **24**

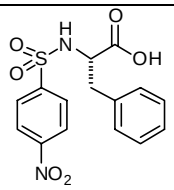
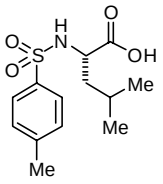
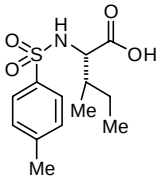
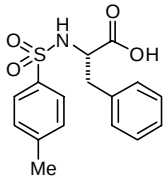
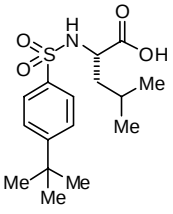
Entry	Chiral Dirhodium(II) Catalyst ($Rh_2\mathbf{L}^*_4$)	(S)-Boc-Ala-NH_2 Yield / %	(S)-Boc-Ala-NH_2 *de* / %	(R)-Boc-Ala-NH_2 Yield / %	(R)-Boc-Ala-NH_2 *de* / %
1	 **15**	47	18	39	15
2	 **16**	49	15	48	13
3	 **17**	51	14	45	17
4	 **18**	56	17	38	20
5	 **19**	47	20	38	14

Table 2. Continued

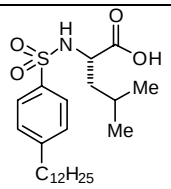
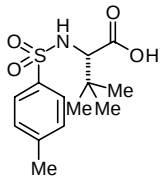
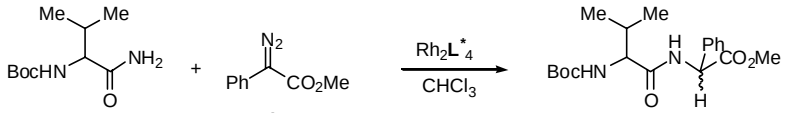
6	 **20**	47	9	41	13
7	 **21**	45	11	34	7

Table 3. Dirhodium(II) catalysed N-H insertion reactions of methyl 2-diazophenylacetate with Boc-Val-NH_2



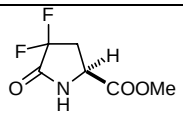
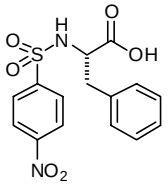
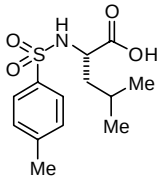
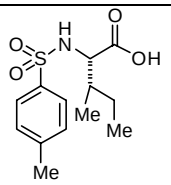
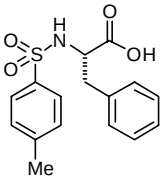
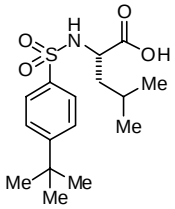
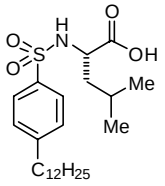
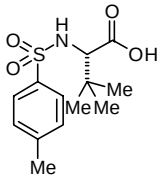
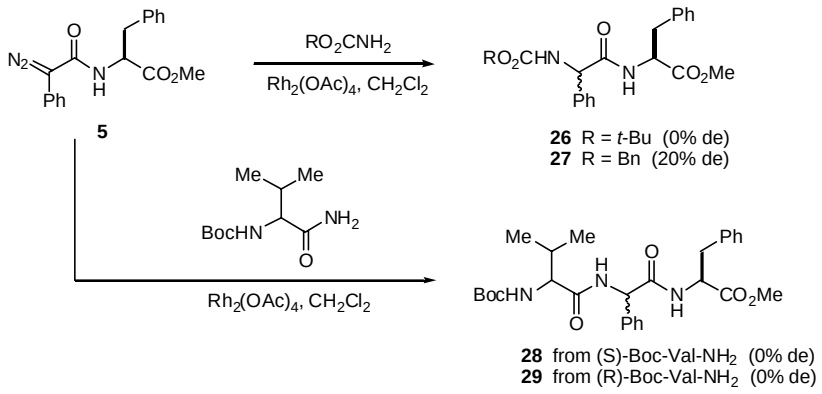
Entry	Chiral Dirhodium(II) Catalyst (Rh_2**L**$^*_4$)	(S)-Boc-Val-NH_2 Yield / %	(S)-Boc-Val-NH_2 *de* / %	(R)-Boc-Val-NH_2 Yield / %	(R)-Boc-Val-NH_2 *de* / %
1	 **14**	23	37	26	10
2	 **15**	56	26	44	28
3	 **16**	61	15	49	12

Table 3. Continued

4	 **17**	64	17	47	14
5	 **18**	59	20	55	17
6	 **19**	58	18	46	18
7	 **20**	53	19	43	23
8	 **21**	48	14	37	4

Finally, the diazophenylacetyl-phenylalanine derivative **5** was investigated. Insertion into both *tert*-butyl- and benzyl carbamate proceeded smoothly and gave the corresponding *N*-protected phenylglycine-phenylalanine dipeptide methyl esters **26** and **27** in 69 and 91% yield, respectively, but with zero- or poor diastereoselectivity (Scheme 5). Attempts to extend the reaction to a stereoselective synthesis of the protected valine–phenylglycine–phenylalanine tripeptides **28** and **29** resulted in modest yields and zero diastereoselectivity.



Scheme 5

Hence, despite the fact that chiral dirhodium(II) catalysts have been used successfully to effect other enantioselective carbene reactions (cyclopropanation, C-H and Si-H insertion), we have found—as have others[20] — that simple chiral catalysts for stereoselective intermolecular carbene N-H insertion reactions remain elusive.

Experimental Section

For general experimental details, see ref. 2.

Diazo Compounds

Methyl 2-diazophenylethanoate (1)

Prepared using the literature method (Bamford–Stevens reaction).[21]

Dimethyl α-diazobenzylphosphonate (2)

Prepared using the literature method (Bamford–Stevens reaction).[22]

***N*-(Diazophenylacetyl)-(*S*)-phenylalanine methyl ester (5)**

(a) To a solution of phenylglyoxylic acid (272 mg, 1.81 mmol) in dry THF (20 mL) under nitrogen at 0 °C was added *N*-methylmorpholine (0.40 mL, 3.63 mmol) followed by *iso*-butyl chloroformate (0.24 mL, 1.84 mmol), and the reaction mixture stirred at 0 °C for a further 30 min. A solution of phenylalanine methyl ester hydrochloride (350 mg, 1.62 mmol) in DMF (5 mL) was then added and the reaction mixture stirred at 0 °C for a further 2 h and at room temperature for a further 17 h. The reaction mixture was then partitioned between EtOAc (50 mL), water (25 mL) and brine (25 mL) and the separated aqueous phase extracted with EtOAc (2 x 25 mL). The combined organic phases were washed with water (20 mL) and brine (20 mL), dried over sodium sulfate, filtered and concentrated *in vacuo* to give the crude product. Flash chromatography (20% ethyl acetate/light petroleum) gave *N*-(phenylglyoxyl)-(*S*)-phenylalanine methyl ester **3** as a colourless oil (lit.,[23] no data given) (517 mg, 92%); $[\alpha]_D^{22}$

+81.6 (*c*=1.03, $CHCl_3$); (Found: MH^+, 312.1237. $C_{18}H_{17}NO_4$ + H requires 312.1236); $\nu_{max.}$(film)/cm^{-1} 3344, 3064, 3030, 2953, 1741, 1668, 1522 and 1205; δ_H(400 MHz; $CDCl_3$) 8.26–8.24 (2H, m, ArH), 7.64–7.60 (1H, m, ArH), 7.48–7.44 (3H, m, ArH), 7.31–7.26 (3H, m, ArH, NH), 7.18–7.16 (2H, m, ArH), 4.99–4.94 (1H, m, NCH), 3.76 (3H, s, OMe), 3.26 (1H, dd, *J* 5.7, 13.9, CHHPh) and 3.17 (1H, dd, *J* 6.6 13.9, CHHPh); δ_C (100 MHz; $CDCl_3$) 186.9 (C), 171.1 (C), 161.3 (C), 135.4 (C), 134.5 (CH), 133.1 (C), 131.1 (CH), 129.3 (CH), 128.8 (CH), 128.5 (CH), 127.3 (CH), 53.3 (CH), 52.6 (Me) and 38.0 (CH_2); *m/z* (CI, NH_3) 312 (MH^+, 100%), 284 (10), 252 (25), 180 (20), 162 (40) and 105 (55).

(b) To a solution of the above ketoester **3** (517 mg, 1.66 mmol) in AcOH (15 mL) under nitrogen was added *para*-toluenesulfonyl hydrazide (303 mg, 1.63 mmol) and the reaction mixture stirred at room temperature for 17 h. The reaction mixture was then concentrated *in vacuo* to give the crude product. Flash chromatography (40% ethyl acetate/light petroleum) gave *N*-(phenylglyoxyl)-(*S*)-phenylalanine methyl ester tosylhydrazone **4** as a mixture of *E*- and *Z*-isomers as a colourless gummy oil (753 mg, 96%); $[\alpha]_D^{25}$ +12.3 (*c*=1.00, $CHCl_3$); (Found: MH^+, 480.1600. $C_{25}H_{25}N_3O_5S$ + H requires 480.1593); $\nu_{max.}$(film)/cm^{-1} 3402, 3180, 3064, 3029, 2954, 2927, 1743, 1675, 1513, 1446, 1361, 1171, 1083 and 733; δ_H (400 MHz; $CDCl_3$) 7.82 and 7.70 (2H, d *J* 8.3 and 8.5, ArH, ratio 3:4), 7.44–7.25 (11H, m, ArH, NH), 7.19–7.17 (3H, m, ArH), 4.89–4.83 (1H, m, NCH), 3.76 and 3.73 (3H, s, OMe, ratio 3:4), 3.23–2.99 (2H, m, CH_2Ph), 2.43 and 2.39 (3H, s, ArMe, ratio 4:3); *m/z* (FAB) 502 (MNa^+, 30%), 480 (MH^+, 100%), 420, (10), 324 (10), 296 (10), 268 (10), 209 (10), 120 (10) and 105 (15).

(c) To a solution of the above tosylhydrazone, **4** (846 mg, 1.77 mmol), in dichloromethane (50 mL) under nitrogen was added DMAP (584 mg, 4.78 mmol) and the reaction mixture stirred at room temperature for 2 days. The reaction mixture was then concentrated *in vacuo* to give the crude product. Flash chromatography (25% ethyl acetate/light petroleum) gave the *title compound* **5** as an orange oil (195 mg, 34%); $[\alpha]_D^{21}$ +22.1 (*c*=1.01, $CHCl_3$); (Found: MH^+, 324.1345. $C_{18}H_{17}N_3O_3$ +H requires 324.1348); $\nu_{max.}$(film)/cm^{-1} 3413, 3307, 3061, 3030, 2953, 2931, 2085, 1743, 1645, 1497, 1203, 758 and 700; δ_H(400 MHz; $CDCl_3$) 7.39–7.34 (2H, m, ArH) 7.31–24 (4H, m, ArH), 7.20–7.17 (2H, m, ArH), 7.11–7.07 (2H, m, ArH), 5.82 (1H, d, *J* 7.6, NH), 4.97 (1H, app, dt, *J* 7.6, 6.1, NCH), 3.74 (3H, s, OMe), 3.22 (1H, dd, *J* 5.8, 13.9, CHHPh) and 3.09 (1H, dd, *J* 6.6 13.9, CHHPh); δ_C (100 MHz; $CDCl_3$) 172.2 (C), 164.4 (C) , 135.8 (C), 129.7 (CH), 129.2 (CH), 128.7 (CH), 127.6 (CH), 127.3 (CH), 127.2 (CH), 125.9 (C), 77.3 (C), 53.7 (CH), 52.5 (Me), 37.8 (CH_2); *m/z* (CI, NH_3) 324 ($[M+H]^+$, 60%), 298 (40), 248 (40), 226 (45), 182 (100), 150 (90), 108 (50), and 100 (60).

Catalysts

Dirhodium(II) tetrakis(*N*-(4-tert-butylphenylsulfonyl)-(*S*)-leucinate) (19)

(a) To a stirred solution of (S)-(-)-leucine (1.00 g, 7.62 mmol) and sodium carbonate (2.42 g, 22.87 mmol) in water (100 mL) was added 4-*tert*-butylbenzenesulfonyl chloride (2.13 g, 9.15 mmol). After rapid stirring overnight the aqueous phase was extracted with ether (2 x 50 mL) and the organic extracts were then removed. The remaining aqueous phase was then

acidified to pH 1.5 with concentrated hydrochloric acid, saturated with sodium chloride and extracted with dichloromethane (3 x 50 mL). The organic extracts were combined, dried (Na_2SO_4) and the solvent was then removed under reduced pressure to yield a colourless solid. Recrystallization from ethyl acetate and light petroleum yielded *N-(4-tert-butylphenylsulfonyl)-(S)-leucine* as colourless crystals (1.40 g, 4.28 mmol, 56%), m.p. 140–141 °C; $[\alpha]_D^{21}$ –18.0 (*c*=1.0, $CHCl_3$); (Found: C, 58.9; H, 7.6; N, 4.3. $C_{16}H_{25}NO_4S$ requires C, 58.7; H, 7.7; N, 4.3%); (Found: M^+, 327.1506. $C_{16}H_{25}NO_4S$ requires 327.1504); $\nu_{max.}$ ($CHCl_3$)/cm^{-1} 3500–3000, 3226, 3060, 2964, 1725, 1597, 1451, 1334, 1166, 1088 and 738; δ_H (400 MHz; $CDCl_3$) 7.77 (2H, d, *J* 8.8, ArH), 7.50 (2H, d, *J* 8.8, ArH), 5.22 (1H, d, *J* 9.5, NH), 3.91 (1H, m, CH), 1.73 (1H, m, C<u>H</u>Me_2), 1.50 (2H, m, CH_2), 1.33 (9H, s, CMe_3), 0.87 (3H, d, *J* 6.7, Me) and 0.77 (3H, d, *J* 6.5, Me), OH not observed; δ_C (100 MHz; $CDCl_3$) 177.3 (C=O), 156.9 (C), 136.5 (C), 127.1 (ArC), 126.0 (ArC), 54.0 (CH), 42.1 (CH_2), 35.1 (<u>C</u>Me_3), 31.0 (CMe_3), 24.3 (<u>C</u>HMe_2), 22.7 (Me) and 21.1 (Me); *m/z* 327 (M^+, 1%), 282 (37), 197 (31), 133 (36), 118 (19), 83 (100), 74 (22) and 51 (72).

(b) A stirred suspension of dirhodium(II) tetrakis(carbonate)[19] (50 mg, 0.08 mmol) and *N*-(4-*tert*-butylphenylsulfonyl)-(*S*)-leucine (212 mg, 0.64 mmol) in water (5 mL) was heated at 85 °C for 1 h. During this time the initial deep blue colour faded and the green product precipitated out. Cooling and filtration gave a green solid which was subsequently washed with water (10 mL) and dried under vacuum to yield the *title compound* as a green powdery solid (120 mg, 0.08 mmol, 98%), m.p. 250 °C (dec.); $[\alpha]_D^{23}$ -80.0 (*c*=0.1, $CHCl_3$); (Found: C, 50.6; H, 6.5; N, 3.7. $C_{64}H_{96}N_4O_{16}Rh_2S_4$ requires C, 50.8; H, 6.4; N, 3.7%); (Found: MH^+, 1511.3982. $C_{64}H_{97}N_4O_{16}S_4Rh_2$ requires 1511.3983); $\nu_{max.}$ ($CHCl_3$)/cm^{-1} 3268, 3055, 2965, 1726, 1597, 1448, 1336, 1112, 1087 and 740; δ_H (400 MHz; $CDCl_3$) 7.81 (8H, d, *J* 8.8, ArH), 7.54 (8H, d, *J* 8.8, ArH), 5.20 (4H, bs, NH), 3.87 (4H, m, CH), 1.72 (4H, m, C<u>H</u>Me_2), 1.55 (8H, m, CH_2), 1.31 (36H, s, CMe_3), 0.86 (12H, d, *J* 6.7, Me) and 0.76 (12H, d, *J* 6.5, Me); δ_C (100 MHz; $CDCl_3$) 178.3 (C=O), 156.4 (C), 136.2 (C), 127.0 (ArC), 126.3 (ArC), 53.7 (CH), 42.6 (CH_2), 35.9 (<u>C</u>Me_3), 31.1 (CMe_3), 24.9 (<u>C</u>HMe_2), 22.6 (Me) and 21.1 (Me); *m/z* (FAB) 1511 (MH^+, 1%), 1463 (14), 1229 (19), 1136 (17), 984 (16), 899 (20), 855 (30), 799 (39), 721 (100), 675 (31) and 574 (61).

Dirhodium(II) tetrakis(*N*-(4-dodecylphenylsulfonyl)-(S)-leucinate) (20)

(a) To a stirred solution of 4-dodecylphenylsulfonyl chloride (1.00 g, 2.90 mmol) in dry tetrahydrofuran (20 mL) under a nitrogen atmosphere was added (S)-(-)-leucine methyl ester hydrochloride (0.53 g, 2.90 mmol) followed by triethylamine (0.73 g, 7.25 mmol) dropwise. After stirring overnight the solvent was removed under reduced pressure and the remaining colourless solid was partitioned between water (100 mL) and ethyl acetate (100 mL). The aqueous phase was then extracted with further ethyl acetate (2 x 100 mL). The organic extracts were combined, dried (Na_2SO_4) and the solvent removed under reduced pressure to yield yellow oil. This crude product was then subjected to flash silica gel chromatography using light petroleum and ethyl acetate (9:1) as eluent to yield *N-(4-dodecylphenylsulfonyl)-(S)-leucine methyl ester* as a colourless oil (1.01 g, 2.23 mmol, 77%), $[\alpha]_D^{20}$ +6.0 (*c*=1.0, $CHCl_3$); (Found:

MH^+, 454.2989. $C_{25}H_{44}NO_4S$ requires 454.2991); $\nu_{max.}$ (film) /cm^{-1} 3274, 3028, 2957, 1745, 1598, 1457, 1339, 1165, 1093 and 757; δ_H (400 MHz; $CDCl_3$) 7.75 (2H, d, *J* 8.5, ArH), 7.23 (2H, d, *J* 8.3, ArH), 5.00 (1H, d, *J* 10.1, NH), 3.93 (1H, m, CH), 3.45 (3H, s, OMe), 1.77 (1H, m, C<u>H</u>Me_2), 1.65 (2H, m, CH_2), 1.55 (2H, m, CH_2), 1.48 (2H, m, C<u>H_2</u>$CHMe_2$), 1.23 (14H, m, CH_2), 0.88 (3H, d, *J* 6.7, $CHMe_2$), 0.84 (3H, d, *J* 6.6, $CHMe_2$), 0.83 (4H, m, CH_2) and 0.82 (3H, m, Me); δ_C (100 MHz; $CDCl_3$) 172.7 (C=O), 152.3 (C), 136.9 (C), 128.2 (ArC), 127.4 (ArC), 54.3 (CH), 52.1 (OMe), 42.4 (<u>C</u>H_2CHMe_2), 36.7 (CH_2), 31.8 (CH_2), 31.7 (CH_2), 29.64 (CH_2), 29.60 (CH_2), 29.54 (CH_2), 29.52 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 29.1 (CH_2), 27.5 (CH_2), 24.3 (<u>C</u>HMe_2), 22.7 ($CHMe_2$), 21.3 ($CHMe_2$) and 14.0 (Me); *m/z* 454 (MH^+, 1%), 394 (58), 380 (100), 366 (36), 295 (15), 105 (18), 91 (91) and 57 (12).

(b) To a stirred solution of the above ester (0.50 g, 1.10 mmol) in tetrahydrofuran / water (5:1) (18 mL) was added lithium hydroxide monohydrate (0.23 g, 5.51 mmol). After stirring overnight the solvent was removed under reduced pressure and water (50 mL) was added to the remaining colourless solid. The reaction mixture was acidified to pH 1 with aqueous hydrochloric acid (2*M*) and extracted with ether (3 x 100 mL). The organic extracts were combined, dried ($MgSO_4$), and the solvent removed under reduced pressure to yield *N-(4-dodecylphenylsulfonyl)-(S)-leucine* as a colourless oil (0.46 g, 1.05 mmol, 96%), $[\alpha]_D^{24}$ –7.0 (*c*=1.0, $CHCl_3$); (Found: M^+, 439.2730. $C_{24}H_{41}NO_4S$ requires 439.2756); $\nu_{max.}$ (film)/cm^{-1} 3500–2500, 3268, 3027, 2958, 1724, 1598, 1466, 1334, 1162, 1094 and 759; δ_H (400 MHz; $CDCl_3$) 7.79 (2H, d, *J* 8.4, ArH), 7.26 (2H, d, *J* 8.4, ArH), 6.51 (1H, bs, OH), 5.18 (1H, d, *J* 9.8, NH), 3.89 (1H, m, CH), 1.65 (1H, m, C<u>H</u>Me_2), 1.64 (2H, m, CH_2), 1.55 (2H, m, CH_2), 1.54 (2H, m, C<u>H_2</u>$CHMe_2$), 1.22 (14H, m, CH_2), 0.86 (3H, d, *J* 6.8, $CHMe_2$, 0.84 (3H, d, *J* 6.7, $CHMe_2$), 0.82 (4H, m, CH_2) and 0.71 (3H, t, *J* 4.8, Me); δ_C (100 MHz; $CDCl_3$) 176.9 (C=O), 152.6 (C), 136.8 (C), 128.4 (ArC), 127.4 (ArC), 53.9 (CH), 42.0 (<u>C</u>H_2CHMe_2), 36.69 (CH_2), 36.66 (CH_2), 36.4 (CH_2), 36.3 (CH_2), 31.7 (CH_2), 29.62 (CH_2), 29.59 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 27.5 (CH_2), 24.3 (<u>C</u>HMe_2), 22.7 ($CHMe_2$), 21.1 ($CHMe_2$) and 14.0 (Me); *m/z* 439 (M^+, 1%), 380 (6), 309 (22), 263 (19), 235 (18), 118 (12), 83 (100) and 51 (74).

(c) A stirred suspension of dirhodium(II) tetrakis(carbonate)[19] (50 mg, 0.08 mmol) and *N*-(4-dodecylphenylsulfonyl)-(*S*)-leucine (284 mg, 0.64 mmol) in water (5 mL) was heated at 85 °C for 1 h. During this time the initial deep blue colour faded and the green product precipitated out. Cooling and filtration gave a green solid which was subsequently washed with water (10 mL) and dried under vacuum to yield the *title compound* as a green solid (34 mg, 0.02 mmol, 21%), m.p. 250 °C (dec.); $[\alpha]_D^{23}$ -60.0 (c=0.1, $CHCl_3$); (Found: C, 58.9; H, 8.2; N, 2.9. $C_{96}H_{160}N_4O_{16}Rh_2S_4$ requires C, 58.8; H, 8.4; N, 2.9%); (Found: M^+, 1958.8826. $C_{96}H_{160}N_4O_{16}Rh_2S_4$ requires 1958.8822); ν_{Max} ($CHCl_3$)/cm^{-1} 3271, 3060, 2957, 1716, 1598, 1466, 1328, 1160, 1095 and 739; δ_H (400 MHz; $CDCl_3$) 7.82 (8H, d, *J* 8.3, ArH), 7.23 (8H, d, *J* 8.3, ArH), 5.20 (4H, bs, NH), 3.90 (4H, m, CH), 1.67 (4H, m, C<u>H</u>Me_2), 1.62 (8H, m, CH_2), 1.56 (8H, m, CH_2), 1.54 (8H, m, C<u>H_2</u>$CHMe_2$), 1.21 (56H, m, CH_2), 0.88 (12H, d, *J* 6.8, $CHMe_2$, 0.86 (12H, d, *J* 6.7, $CHMe_2$), 0.81 (16H, m, CH_2) and 0.73 (12H, t, *J* 4.8, Me); δ_C (100 MHz; $CDCl_3$) 177.1 (C=O), 151.9 (C), 137.0 (C), 128.0 (ArC), 127.9 (ArC), 54.5 (CH), 42.0 (<u>C</u>H_2CHMe_2),

36.69 (CH_2), 36.66 (CH_2), 36.4 (CH_2), 36.3 (CH_2), 31.7 (CH_2), 29.67 (CH_2), 29.61 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 27.9 (CH_2), 23.9 ($\underline{C}HMe_2$), 22.9 ($CHMe_2$), 21.1 ($CHMe_2$) and 15.0 (Me); *m/z* (FAB) 1959 (M^+, 1%), 1445 (4), 990 (9), 484 (100) and 342 (21).

Dirhodium(II) tetrakis(*N*-(4-toluenesulfonyl)-(S)-tert-leucinate) 21. A stirred suspension of dirhodium(II) tetrakis(carbonate)[19] (50 mg, 0.08 mmol) and *N*-(4-toluenesulfonyl)-(*S*)-*tert*-leucine (185 mg, 0.64 mmol) in water (5 mL) was heated at 85 °C for 1 h. During this time the initial deep blue colour faded and the green product precipitated out. Cooling and filtration gave a green solid which was subsequently washed with water (10 mL) and dried under vacuum to yield the *title compound* as a green powdery solid (99 mg, 0.07 mmol, 91%), m.p. 250 °C (dec.); $[\alpha]_D^{23}$ -90.0 (*c*=0.1, $CHCl_3$); (Found: C, 46.8; H, 5.6; N, 4.3. $C_{52}H_{72}N_4O_{16}Rh_2S_4$ requires C, 46.5; H, 5.4; N, 4.0%); (Found: MH^+, 1343.2013. $C_{52}H_{73}N_4O_{16}S_4Rh_2$ requires 1343.2015); $\nu_{max.}$ ($CHCl_3$)/cm^{-1} 3296, 3054, 2968, 1706, 1599, 1470, 1330, 1158, 1093 and 738; δ_H (400 MHz; $CDCl_3$) 7.75 (8H, d, *J* 8.1, ArH), 7.37 (8H, d, *J* 8.0, ArH), 3.50 (4H, s, CH), 2.44 (12H, s, Me) and 0.98 (36H, s, CMe_3), NH not observed; δ_C (100 MHz; $CDCl_3$) 173.1 (C=O), 143.6 (C), 137.1 (C), 129.0 (ArC), 127.2 (ArC), 64.6 (CH), 33.3 ($\underline{C}Me_3$), 25.8 (CMe_3) and 19.7 (Me); *m/z* (FAB) 1343 (MH^+, 1%), 1285 (10), 1131 (11), 1058 (30), 729 (49), 389 (37), 295 (36) and 240 (100).

Insertion Reactions

Methyl 2-(benzyloxycarbonylamino)phenylethanoate (22). To a stirred solution of methyl 2-diazophenylethanoate **1** (100 mg, 0.57 mmol) in dry dichloromethane (2 mL) under a nitrogen atmosphere was added benzyl carbamate (94.4 mg, 0.63 mmol) followed by a chiral dirhodium(II) carboxylate catalyst (2 mol %). After stirring for 30 min the solvent was removed under reduced pressure to yield a green oil. This crude product was then subjected to flash silica gel chromatography using light petroleum and ethyl acetate (4:1) as eluent to yield the *title compound* as a colourless solid, m.p. 74–75 °C, data as before.[2]

Dimethyl α-*N*-(benzyloxycarbonylamino)benzylphosphonate (23). To a stirred solution of dimethyl α-diazobenzylphosphonate **2** (100 mg, 0.44 mmol) in dry toluene (2 mL) was added benzyl carbamate (334 mg, 2.20 mmol) followed by a chiral dirhodium(II) carboxylate catalyst (2 mol %). After heating under reflux for 2 h, the solvent was removed under reduced pressure to yield a pale yellow solid. This crude product was then subjected to flash silica gel chromatography using light petroleum and ethyl acetate (1:2) as eluent to yield a colourless solid, m.p. 117–118 °C, data as before.[2]

(*R*- or *S*-)-*N*-(*tert*-Butoxycarbonyl)alanyl-(*R*,*S*)-phenylglycine methyl ester (24). To a stirred solution of methyl 2-diazophenylethanoate **1** (50 mg, 0.28 mmol) in dry dichloromethane (4 mL) under a nitrogen atmosphere was added (*R- or S*-)-*N*-(*tert*-butoxycarbonyl)alaninamide (58.8 mg, 0.31 mmol) followed by a chiral dirhodium(II) carboxylate catalyst (2 mol %). After stirring for 1 h the solvent was removed under reduced pressure to yield a green oil. This crude product was then subjected to flash silica gel chromatography using light petroleum and ethyl acetate (7:3) as

eluent to yield an inseparable diastereomeric mixture of the *title compound* as a colourless oil; data as before.[4]

(*R*- or *S*-)-*N*-(*tert*-Butoxycarbonyl)valinyl-(*R*,*S*)-phenylglycine methyl ester (25). To a stirred solution of methyl 2-diazophenylethanoate **1** (50 mg, 0.28 mmol) in dry chloroform (4 mL) under a nitrogen atmosphere was added (R or S)-*N*-(*tert*-butoxycarbonyl)valinamide (67.5 mg, 0.31 mmol) followed by a chiral dirhodium(II) catalyst (2 mol.%). After stirring for 1 h the solvent was removed under reduced pressure to yield a green oil. This crude product was then subjected to flash silica gel chromatography using light petroleum and ethyl acetate (4:1) as eluent to yield an inseparable diastereomeric mixture of the *title compound* as a colourless oil; data as before.[4]

Boc-(*R*,*S*-)-Phg-(*S*)-Phe-OMe (26). To a stirred solution of *tert*-butyl carbamate (45 mg, 0.38 mmol) and *N*-(diazophenylacetyl)-(*S*)-phenylalanine methyl ester **5** (51 mg, 0.16 mmol) in dry dichloromethane (3 mL) under nitrogen was added dirhodium(II) acetate (2 mg, 4.5 μmol). The reaction mixture was then stirred for 2 h, concentrated *in vacuo* to give the crude product. Flash chromatography (25% ethyl acetate/light petroleum) gave an inseparable diastereoisomeric mixture (0% *de* by NMR) of the *title compound* as a colourless solid (44 mg, 69%), m.p. 119–25 °C (lit.,[24] m.p. not given); $\nu_{max.}$ (KBr)/cm^{-1} 3336, 3028, 3003, 2972, 2953, 1738, 1687, 1655, 1522, 1250, 1169 and 702; δ_H(400 MHz; $CDCl_3$) 7.35–7.24 (7H, m, ArH), 7.15–7.11 (1H, m, ArH), 7.08–7.04 (2H, m, ArH), 6.65 (1H, d, *J* 6.6, NH), 5.85 and 5.72 (1H, br s, NH, ratio 1:1), 5.15 (1H, br s, CHPh), 4.89 and 4.80 (1H, app dt, *J* 8.0, 5.4 and 8.1, 6.0, CHBn, ratio 1:1), 3.70 and 3.63 (3H, s, OMe, ratio 1:1), 3.15, 3.04 and 2.96 (2H, dd, dd and d, *J* 5.7, 13.9 and 6.3, 13.9 and 5.6, CH_2Ph, ratio 1:1:2), 1.44 and 1.40 (9H, s, Boc, ratio 1:1).

Cbz-(*R*,*S*)-Phg-(*S*)-Phe-OMe (27). To a stirred solution of benzyl carbamate (37 mg, 0.25 mmol) and *N*-(diazophenylacetyl)-(*S*)-phenylalanine methyl ester **5** (48 mg, 0.15 mmol) in dry dichloromethane (3 mL) under nitrogen was added dirhodium(II) acetate (2 mg, 4.5 μmol). The reaction mixture was then stirred for 2 h, concentrated *in vacuo* to give the crude product. Flash chromatography (33% ethyl acetate/light petroleum) gave an inseparable diastereoisomeric mixture (20% *de* by NMR) of the *title compound* as a colourless solid (60 mg, 91%), m.p. 161–166 °C (lit.,[24] (R,S) m.p. 168–170 °C; (S,S-) m.p. 153–155 °C); $\nu_{max.}$ (KBr)/cm^{-1} 3404, 3331, 3061, 3032, 2947, 1736, 1687, 1649, 1525, 1238, 1049 and 700; δ_H(400 MHz; $CDCl_3$) 7.38–7.25 (12H, m, ArH), 7.16–12 (1H, m, ArH), 7.07–7.03 (2H, m, ArH), 6.62 (1H, d, *J* 6.1, NH), 5.21 (1H, br s, NH), 5.11 (2H, br s, OCH_2Ph), 4.93–4.89 (1H, m, CHPh), 4.81–4.78 (1H, m, CHBn), 3.72 and 3.63 (3H, s, OMe, ratio 3:2), 3.16, 3.05 and 2.97 (2H, dd, dd and d, *J* 5.8, 14.0 and 5.7, 14.0 and 5.0, CH_2Ph, ratio 1:1:3).

Boc-(*S*)-Val-(*R*,*S*)-Phg-(*S*)-Phe-OMe (28). To a solution of (S)-*tert*-butoxycarbonyl valinamide (135 mg, 0.63 mmol) and dirhodium(II) acetate (7 mg, 0.016 mmol) in dry dichloromethane (7 mL) stirred at reflux under nitrogen was added dropwise a solution of *N*-(diazophenylacetyl)-(*S*)-phenylalanine methyl ester **5** (82 mg, 0.25 mmol) in dry dichloromethane (3 mL) over 1 h. The reaction mixture was then stirred at reflux for a further 17 h before being allowed to cool to room temperature and concentrated *in vacuo* to give the crude product. Flash chromatography

(50% ethyl acetate/light petroleum) gave an inseparable diastereoisomeric mixture (0% *de* by NMR) of the *title compound* as a colourless solid (36 mg, 27%), m.p. 165–173 °C; (Found: MH^+, 511.2763; $C_{28}H_{37}N_3O_6$ + H requires 511.2760); $\nu_{max.}$ (KBr)/cm^{-1} 3323, 3064, 3032, 2966, 2929, 1740, 1689, 1641, 1522, 1173, 1024 and 698; δ_H(400 MHz; $CDCl_3$, -20 °C) 7.33–7.22 (7H, m, ArH), 7.12–7.09 (1H, m, ArH), 7.02–6.97 (2H, m, ArH), 6.47 (1H, d, *J* 7.5, NH), 5.71 and 5.58 (1H, s, NH, ratio 1:1), 5.44 and 5.36 (1H, d, *J* 8.8 and 10.1, NH, ratio 1:1), 4.91 and 4.74 (1H, app d, *J* 5.3 and 5.7, CHPh, ratio 1:1), 4.06–4.01 (2H, m, CHBn and CH^iPr), 3.72 and 3.63 (3H, s. OMe, ratio 1:1), 3.11 and 3.00–2.86 (2H, dd and m, *J* 5.4 and 13.9, CH_2Ph, ratio 1:3), 2.06–2.01 and 1.94–1.89 (1H, m, $CHMe_2$, ratio 1:1), 1.41 and 1.39 (9H, s, Boc, ratio 1:1), 0.94, 0.84, 0.80 and 0.76 (6H, d, *J* 6.6, 6.7, 6.7 and 6.6, CMe_2, ratio 1:1:1:1); δ_C (100 MHz; $CDCl_3$, -20 °C) 171.5 (C), 171.4 (C), 171.3 (C), 171.2 (C), 169.4 (C), 169.2 (C), 156.0 (C), 155.9 (C), 137.5 (C), 136.9 (C), 135.5 (C), 134.9 (C), 130.2 (CH), 129.3 (CH), 129.2 (CH), 129.1 (CH), 128.7 (CH), 128.54 (CH), 128.49 (CH), 128.45 (CH), 127.32 (CH), 127.25 (CH), 127.1 (CH), 126.9 (CH), 80.0 (C), 79.9 (C), 59.6 (CH), 59.4 (CH), 56.8 (CH), 56.6 (CH), 53.6 (CH), 53.1 (CH), 52.8 (Me), 52.7 (Me), 37.53 (CH_2), 37.48 (CH_2), 31.43 (CH), 31.37 (CH), 28.4 (Me), 28.3 (Me), 19.4 (Me), 19.3 (Me), 17.73 (Me), 17.68 (Me).

Boc-(*R*)-Val-(*R*,*S*-)-Phg-(*S*)-Phe-OMe (29). To a solution of (R)-*tert*-butoxycarbonyl valinamide (136 mg, 0.63 mmol) and dirhodium(II) acetate (7 mg, 0.016 mmol) in dry dichloromethane (7 mL) stirred at reflux under nitrogen was added dropwise a solution of *N*-(diazophenylacetyl)-(*S*)-phenylalanine methyl ester **5** (90 mg, 0.28 mmol) in dry dichloromethane (3 mL) over 1 h. The reaction mixture was then stirred at reflux for a further 17 h before being allowed to cool to room temperature and concentrated *in vacuo* to give the crude product. Flash chromatography (50% ethyl acetate/light petroleum) gave an inseparable diastereoisomeric mixture (0% *de* by NMR) of the *title compound* as a colourless solid (48 mg, 34%), m.p. 192–199 °C; (Found: $M+NH_4^+$, 529.3030; $C_{28}H_{37}N_3O_6$ + NH_4 requires 529.3026); $\nu_{max.}$ (KBr)/cm^{-1} 3325, 3064, 3032, 2968, 2929, 1740, 1687, 1641, 1521, 1367, 1173, 1024 and 700; δ_H(400 MHz; $CDCl_3$) 7.29–7.25 (10H, m, ArH), 7.07 (2H, app d, *J* 6.6, NH), 6.29 and 5.07 (1H, br s, NH, ratio 1:1), 5.41 (1H, br s, CHPh), 4.79 (1H, br s, CHBn), 3.99 (1H, br s, CH^iPr), 3.64 (3H, br s, OMe), 3.17 (1H, app dd, *J* 5.1, 13.3, C<u>H</u>HPh), 3.05 (1H, app dd, *J* 6.1, 13.6, CH<u>H</u>Ph), 2.12–2.18 (1H, m, $CHMe_2$), 1.43 (9H, br s, Boc), 0.88 (3H, d, *J* 6.4, Me), 0.84 (3H, d, *J* 6.6, Me); δ_C (100 MHz; $CDCl_3$) 171.2 (C), 171.1 (C), 171.0 (C), 169.27 (C), 169.25 (C), 169.2 (C), 155.8 (C), 137.1 (C), 135.6 (C), 129.2 (CH), 129.1 (CH), 129.0 (CH), 128.6 (CH), 128.5 (CH), 127.3 (CH), 127.2 (CH), 79.9 (C), 59.80 (CH), 59.75 (CH), 57.2 (CH), 53.6 (CH), 53.5 (CH), 52.3 (Me), 37.7 (CH_2), 31.0 (CH), 30.9 (CH), 28.3 (Me), 19.2 (Me), 17.5 (Me).

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