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Preparation of enantioselective enriched α-(dialkoxyphosphoryl) lactams via intramolecular C–H insertion with chiral dirhodium(II) catalysts

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Abstract

The intramolecular C─H insertion on α-diazoacetamides is an extremely useful procedure for the preparation of a wide variety of heterocyclic compounds. In this work is presented a strategy for the preparation of enantioselective enriched α-(dialkoxyphosphoryl)lactams via dirhodium(II) catalyzed C─H insertion on α-diazo-α-(dialkoxyphosphoryl)acetamides, in which enantiomeric excess up to 40% is reported. Moreover, a systematic study was undertaken on the chiral dirhodium(II) catalyst and the α-diazo-α-(dialkoxyphosphoryl)acetamides influence on enantioselectivity.

Keywords: Phosphonates; Diazo compounds; Rhodium catalysts; C─H insertion; Lactams

1. Introduction

As part of the exciting field on the activation of unfunctionalized C–H bonds, the use of dirhodium(II) stabilised carbenes generated from α-diazo compounds stands as a synthetic powerful methodology for the preparation of highly valuable compounds [1]. In recent years the use of these versatile intermediates in intramolecular cyclisations, has emerged as, a standard method for the construction of numerous cyclic and heterocyclic compounds, among which the β- and γ-lactams are especially noteworthy [2].

The usefulness of this approach is deeply related with the level of regio and stereoselective obtained on the C–H insertion process (Scheme 1) [3]. In a recent work, we reported the dirhodium(II) catalysed intramolecular C–H insertion on α-diazo-α-(dialkoxyphosphoryl)acetamides, as a straightforward strategy for the preparation of α-(dialkoxyphosphoryl)lactams [4]. Nonetheless, the success achieved on the racemic cyclisation of α-diazo-α-(dialkoxyphosphoryl)acetamides, the possible biological relevance of these lactams [5], as well as, their suitable application on the Horner–Wadsworth–Emmons (EWH) reaction [6], drew our attention towards the enantioselective preparation of these α-(dialkoxyphosphoryl)lactams (Scheme 2).

The enantioselective version of the dirhodium(II) catalysed intramolecular C–H insertion is a defying challenge, namely because all the steric, conformational and electronic effects (Scheme 1) which are widely recognised to have a crucial influence on the insertion process [1–3], have to be taken together with the additional effort of finding the right chiral dirhodium catalyst for each family of α-diazoacetamides [7].

Hashimoto and co-workers achieved considerable success on the enantioselective cyclisation of α-diazo-α-

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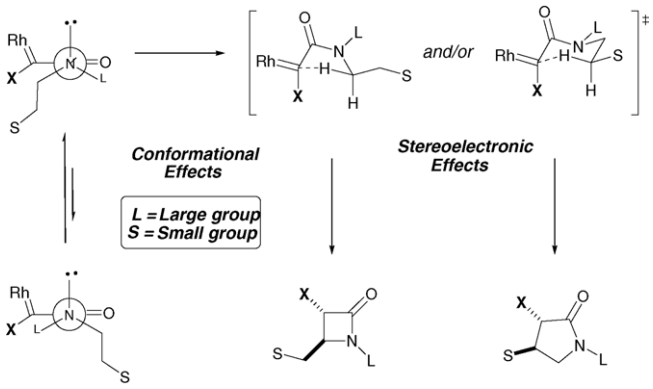
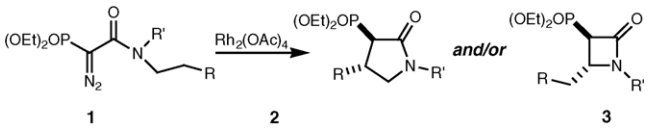


Scheme 1.



Scheme 2.

(methoxycarbonyl)acetamides, using dirhodium(II) carboxylates incorporating *N*-phthaloyl-(*S*)-amino acids [8]. Using dirhodium(II) catalysts with pyrrolidinones and oxazolidinones as bridging ligands, Doyle and co-workers performed the cyclisation of α-diazoacetamides, with high degree of enantioselectivity [9]. Here is presented our results on the enantioselective C–H insertion on α-diazo-α-(dialkoxyphosphoryl)acetamides.

2. Experimental

2.1. General remarks

Tetrahydrofuran (THF) was distilled over calcium hydride immediately prior to use, while triethylamine, and dichloroethane were freshly distilled over calcium hydride. Ethyl acetate was distilled over potassium carbonate. *p*-Toluenesulfonylazide was prepared from *p*-toluenesulfonylchloride and sodium azide. Sodium hydride was used as a 55% dispersion in mineral oil. All reactions were performed in oven-dried glassware under an atmosphere of argon. The diazo substrates **10**, **12**, **14** and **16** and the racemic lactams **11**, **13**, **15** and **17** has been reported by us elsewere [4]. The chiral catalysts **4**–**6** were purchased from Aldrich and **7**–**20** were prepared according to reported procedure [10], catalysts **8**–**20** were further purified on a preparative TLC. Flash chromatography was carried out on silica gel 60M from MN (Ref. 815381) or on aluminium oxide basic from MN (Ref. 815010, Brockmann activity 1). Reaction mixtures were analysed by TLC using ALUGRAM® SIL G/UV$_{254}$ from MN (Ref. 818133, silica gel 60) and aluminiumoxide 60F$_{254}$ neutral plates (type E) from Merck (Ref. 5550). Infrared spectra (IR) spectra were recorded on a Mattson Instruments model Satellite FTIR as thinly dispersed films. High and low resolution mass spectra (EI, FAB) were carried out by mass spectrometry service of University of Santiago de Compostela (Spain). NMR spectra were recorded in a Bruker AMX 400 using $CDCl_3$ as solvent and $(CH_3)_4Si$ (^{1}H) as internal standard. ^{31}P chemical shifts are reported in ppm relative to H_3PO_4 (external standard). All coupling constants are expressed in Hz.

HPLC analysis were carried out on a Chiralpak AD or Chiralpak OD (l = 25 cm and diameter = 0.46 cm) columns with pre-column at 25 °C using 10% or 20% of 2-propanol in hexane at 1 ml/min. Observed retention times (t_R) for each lactam enantiomer: **11** (AD Column), 12.18 and 21.18 min; **13** (OD Column), 11.63 and 13.11 min; **15** (AD Column), 15.78 and 28.67 min; **17** (AD Column), 12.91 and 16.76 min; **24** (AD Column 20% of 2-propanol in hexane at 1 ml/min.), 10.34 and 14.30 min.

2.2. General procedure for the synthesis of α-(diethoxyphosphoryl)acetamides

To a stirring solution of α-bromoacetylamide (5.00 mmol) in anhydrous dichloroethane (2 ml) was added thriethylphosphite (6.00 mmol) under argon atmosphere. The resulting mixture was refluxed until all α-bromoacetylamide was consumed. Then the volatile compounds were evaporated. The residue was purified by distillation under reduce pressure or by flash chromatography.

2.2.1. Preparation of *N*-1,2,3,4-tetrahydroquinoline-α-(diethoxyphosphoryl)acetamide **22**

To a stirred solution of 1,2,3,4-tetrahydroquinoline (3.00 g, 22.00 mmol) and triethylamine (3.62 ml, 26.00 mmol) in anhydrous CH_2Cl_2 (44 ml), was slowly added α-bromoacetylbromide (4.84 g, 24.00 mmol) at 0 °C. the mixture was briefly stirred at 0 °C and then at room temperature for 1 h. The reaction mixture was washed with 5% HCl (30 ml) and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with saturated $NaHCO_3$ solution, followed by brine and then dried over Na_2SO_4. The α-bromoacetylbromide **21** was used without further purification. The *N*-1,2,3,4-tetrahydroquinoline-α-(diethoxyphosphoryl)acetamide **22** was prepared according with general procedure using α-bromoacetylamide **21** (4.50 g, 17.70 mmol). The reaction was refluxed for 6 h. After distillation at 190–200 °C/0.01–0.005 mm Hg the desired phosphonate **22** (4.30 g, 78%) was obtained as a viscous yellow oil, R_f = 0.28 (AcOEt/Hex 1:9); ν_{max} (film): 2983, 1648, 1382, 1252 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$, 25 °C, TMS): 1.29 (6H, t, J 7.0, OCH_2CH_3), 1.95 (2H, m, $NCH_2CH_2CH_2Ar$), 2.70 (2H, m, $NCH_2CH_2CH_2Ar$), 3.21 (2H, d, J_{H-P} 21.9, $POCH_2CO$), 3.81 (2H, t, J 6.6, $NCH_2CH_2CH_2Ar$), 4.12–4.20 (4H, m, J 7.1, OCH_2CH_3), 7.14–7.32 (4H, m, Ar); ^{13}C-NMR (100 MHz, $CDCl_3$, 25 °C): 16.38 (OCH_2CH_3), 24.05 ($NCH_2CH_2CH_2Ar$), 24.66 ($NCH_2CH_2CH_2Ar$), 33.40 (d,

J_{C-P} 137.0, POCH_2CO), 42.96 (NCH_2CH_2CH_2Ar), 62.53 (OCH_2CH$_3$), 124.70; 125.98; 126.57; 128.51; 164.62 (*C*=O); ^{31}P-NMR (160 MHz, $CDCl_3$, 25 °C): 22.31; MS (EI) *m*/*e* 311, 132, 109, 81; HMRS (EI) *m*/*e* calculated $[M]^+$ 311.128647, found $[M]^+$ 311.129791.

2.2.2. Preparation of (R)-(+)-N-(phenylethylamine)-N-[3-(ethoxycarbonyl)-propyl]-α-(diethoxyphosphoryl) acetamide **26**

To a solution of (*R*)-(+)-α-phenylethylamine (3.00 g, 25.00 mmol), sodium carbonate (3.10 g, 27.00 mmol), and sodium iodine (0.20 g) in 50.0 ml of freshly distilled dimethylformamide (DMF) at room temperature was added ethyl-4-bromobutyrate (5.27 g, 27.00 mmol) in 10.0 ml of DMF during a 20 min period. The reaction mixture was heated to 65 °C, maintained at that temperature, with constant stirring, for 4 h, and then left over night at room temperature. After addition of 50 ml of water, the reaction was extracted three times with 50 ml of CH_2Cl_2 and washed with brine. The combined organic layers were then dried over anhydrous $MgSO_4$, and the solvent was removed under reduce pressure. The residue was distilled at 110 °C/0.05 mm Hg yielding the (*R*)-(+)-*N*-(phenylethylamine)-*N*-[3-(ethoxycarbonyl)-propyl]amine (2.45 g, 40%) as a colourless liquid; ν_{max} (film) 3432, 2975, 1730, 1680 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$, 25 °C, TMS): 1.21 (3H, t, *J* 7.1, OCH$_2$C*H*$_3$), 1.32 (3H, d, *J* 6.5, NCH(C*H*$_3$)Ar), 1.70–1.79 (2H, m, NCH$_2$C*H*$_2$), 2.24–2.38 (2H, m, NCH$_2$CH$_2$C*H*$_2$CO$_2$Et), 2.40–2.44 (1H, m, NC*H*$_2$CH$_2$CH$_2$CO$_2$Et), 2.50–2.56 (1H, m, NC*H*$_2$CH$_2$CH$_2$CO$_2$Et), 3.72 (1H, q, *J* 6.5, NC*H*(CH$_3$)Ar), 4.08 (3H, t, *J* 7.2, OC*H*$_2$CH$_3$); ^{13}C-NMR (100 MHz, $CDCl_3$, 25 °C): 14.11 (OCH$_2$*C*H$_3$), 24.36 (NCH(*C*H$_3$)Ar), 25.45 (NCH$_2$*C*H$_2$CH$_2$CO$_2$Et), 32.13 (NCH$_2$CH$_2$*C*H$_2$CO$_2$Et), 46.82 (N*C*H$_2$), 58.10 (N*C*H(CH$_3$)Ar), 60.11 (CO$_2$*C*H$_2$CH$_3$), 126.41, 126.72, 128.27, 145.67 (q), 173.51 (*C*O$_2$CH$_2$CH$_3$); MS (EI) *m*/*e* 235, 220, 207, 105; HMRS (EI) *m*/*e* calculated $[M]^+$ 235.157229, found $[M]^+$ 235.156725.

To a stirred solution of the (*R*)-(+)-*N*-(phenylethylamine)-*N*-[3-(ethoxycarbonyl)-propyl]amine (2.04 g, 8.70 mmol) and anhydrous triethylamine (1.45 ml, 10.4 mmol) in anhydrous CH_2Cl_2 (20 ml), was slowly added α-bromoacetylbromide (1.92 g, 15.40 mmol) at 0 °C. The mixture was briefly stirred at 0 °C and then at room temperature for 1 h. The reaction mixture was washed with 5% HCl (20 ml) and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with saturated $NaHCO_3$ solution, followed by brine and then dried over Na_2SO_4. The α-bromoacetylamide **25** was used without further purification. The (*R*)-(+)-*N*-(phenylethylamine)-*N*-[3-(ethoxycarbonyl)-propyl]-α-(diethoxyphosphoryl)acetamide **26** was prepared according with general procedure using α-bromoacetylamide **25** (3.06 g, 8.60 mmol). The reaction was refluxed for 4 h, purified by flash chromatography (SiO_2, AcOEt/Hex 3:7) yielding the desired phosphonate **26** (1.93 g, 54%) as a viscous yellow oil, R_f = 0.55 (AcOEt/Hex 8:2); ν_{max} (film): 1728, 1640, 1265, 1051 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$, 25 °C, TMS): 1.17 (3H, q, *J* 7.2, CO$_2$CH$_2$C*H*$_3$), 1.28–1.34 (6H, m, OCH$_2$C*H*$_3$), 1.40–1.48 (m, NCH$_2$C*H*$_2$CH$_2$CO$_2$Et), 1.52, 1.66 (3H, rotamers, d, *J* 7.1 and 6.8, NCH(C*H*$_3$)Ar), 1.68–1.74 (m, NCH$_2$C*H*$_2$CH$_2$CO$_2$Et), 2.10–2.25 (m, NCH$_2$CH$_2$C*H*$_2$CO$_2$Et), 2.85–3.36 (overlapped signals, m, POC*H*$_2$CO and NC*H*$_2$), 4.00–4.09 (m, *J* 7.1, CO$_2$C*H*$_2$CH$_3$), 4.11–4.20 (m, *J* 7.3, OC*H*$_2$CH$_3$), 5.26, 5.95 (1H, rotamers, q, *J* 7.0 and 6.8, NC*H*(CH$_3$)Ar), 7.24–7.34 (5H, m, NCH(CH$_3$)*Ar*); ^{13}C-NMR (100 MHz, $CDCl_3$, 25 °C): 14.14 (CO$_2$CH$_2$*C*H$_3$), 16.30 (OCH$_2$*C*H$_3$), 16.89, 18.56 (NCH(*C*H$_3$)Ar), 24.00, 25.73 (NCH$_2$*C*H$_2$), 31.12, 31.86 (NCH$_2$CH$_2$*C*H$_2$CO$_2$Et), 33.51, 34.04 (d, J_{C-P} 132, POC*H*$_2$CO), 42.80, 43.77 (N*C*H$_2$), 51.57, 56.50 (N*C*H(CH$_3$)Ar), 42.80, 43.77 (CO$_2$*C*H$_2$CH$_3$), 62.58 (OCH_2CH$_3$), 126.73, 127.41, 127.49, 127.63, 128.39, 128.67, 140.26 (q), 140.60 (q), 165.01, 165.37 (*C*=O), 172.47, 173.01 (*C*O$_2$Et); ^{31}P-NMR (160 MHz, $CDCl_3$, 25 °C): 21.54, 22.01; MS (EI) *m*/*e* 413, 234, 179, 105; HMRS (EI) *m*/*e* calculated $[M]^+$ 413.196727, found $[M]^+$ 413.195924.

2.3. General procedure for the synthesis of diazophosphates

A solution of the appropriate phosphonate (1.00 mmol) in THF (1.5 ml) was slowly added to a magnetically stirred mixture of sodium hydride or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (1.2 equiv.) and *p*-toluenesulfonylazide (1.2 equiv.) in THF (6.5 ml) at 0 °C. The mixture was stirred for 1 h at this temperature and then allowed to reach room temperature. After reaction of all phosphonate (confirmed by TLC), the solvent was evaporated and the residue was chromatographed (SiO_2, AcOEt/Hex) to yield the diazo compound as an yellow oil.

2.3.1. Preparation of N-1,2,3,4-tetrahydroquinoline-α-diazo-α-(diethoxyphosphoryl)acetamide **23**

A solution of *N*-1,2,3,4-tetrahydroquinoline-α-(diethoxyphosphoryl)acetamide **22** (1.44 g, 3.50 mmol) in THF (33 ml), was slowly added to a magnetically stirred mixture of NaH and *p*-toluenesulfonylazide at 0 °C. The mixture was stirred 1 h at this temperature and then 3 h at room temperature. The reaction mixture was concentrated and the residue was chromatographed on SiO_2 (AcOEt/Hex gradient) yielding the desired diazophosphonate **23** (2.01 g, 93%) as a viscous yellow oil, R_f = 0.40 (AcOEt/Hex 6:4); ν_{max} (film): 2984, 2106, 1631, 1263, 1020 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$, 25 °C, TMS): 1.36 (6H, t, *J* 7.0, OCH$_2$C*H*$_3$), 1.96 (2H, m, NCH$_2$C*H*$_2$CH$_2$Ar), 2.69 (2H, t, *J* 6.5, NCH$_2$CH$_2$C*H*$_2$Ar), 3.76 (2H, t, *J* 6.7, NC*H*$_2$CH$_2$CH$_2$Ar), 4.16–4.30 (4H, m, OC*H*$_2$CH$_3$), 7.08–7.34 (4H, m, *Ar*); ^{13}C-NMR (100MHz, $CDCl_3$, 25 °C): 16.23 (OCH$_2$*C*H$_3$), 24.06 (NCH$_2$*C*H$_2$CH$_2$Ar), 26.56 (NCH$_2$CH$_2$*C*H$_2$Ar), 44.28 (N*C*H$_2$CH$_2$CH$_2$Ar), 63.63

(OCH_2CH_3), 122.17; 125.24; 127.07; 128.73, 132.20 (q); 138.24 (q); 161.91 (*C*=O); ^{31}P-NMR (160 MHz, $CDCl_3$, 25 °C): 13.52; MS (EI) *m*/*e* 309, 281, 235, 173; HMRS (EI) *m*/*e* calc $[M]^+$ 337.119145, found $[M]^+$ 337.119181.

2.3.2. Preparation of (R)-(+)-N-(phenylethylamine)-N-[3-(ethoxycarbonyl)-propyl]-α-diazo-α-(diethoxyphosphoryl) acetamide **27**

To a solution of (*R*)-(+)-*N*-(phenylethylamine)-*N*-[3-(ethoxycarbonyl)-propyl]-α-(diethoxyphosphoryl)acetamide **26** (1.44 g, 3.50 mmol) in THF (30 ml) and *p*-toluenesulfonylazide at room temperature, was slowly added 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (0.58 g, 3.80 mmol). The mixture was stirred for 24 h at this temperature. The reaction mixture was concentrated and the residue was chromatographed on SiO_2 (AcOEt/Hex 1:1) yielding the desired diazophosphonate **27** (1.44 g, 94%) as a viscous yellow oil, $R_f = 0.38$ (AcOEt/Hex 5:5); ν_{max} (film): 2100, 1728, 1619, 1265, 1021 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$, 25 °C, TMS): 1.19 (3H, t, *J* 7.2, $CO_2CH_2CH_3$), 1.33 (6H, t, *J* 7.0, OCH_2CH_3), 1.63, (3H, d, *J* 6.9, NCH(CH_3)Ar), 1.69–1.80 (2H, m, NCH_2CH_2), 2.09–2.25 (2H, m, $NCH_2CH_2CH_2CO_2Et$), 2.81–2.88 (1H, m, NCH_2), 3.23–3.31 (1H, m, NCH_2), 4.06 (2H, q, *J* 7.1, $CO_2CH_2CH_3$), 4.17–4.25 (4H, m, OCH_2CH_3), 5.40 (1H, q, *J* 6.7, $NCH(CH_3)Ar$), 7.26–7.35 (5H, m, $NCH(CH_3)Ar$); ^{13}C-NMR (100 MHz, $CDCl_3$, 25 °C): 14.14 ($CO_2CH_2CH_3$), 16.30 (OCH_2CH_3), 16.89, 18.56 ($NCH(CH_3)Ar$), 24.00, 25.73 ($NCH_2CH_2CH_2CO_2Et$), 31.12, 31.86 ($NCH_2CH_2CH_2CO_2Et$), 33.51, 34.04 (d, J_{C-P} 132, $POCH_2CO$), 42.80, 43.77 (NCH_2), 51.57, 56.50 ($NCH(CH_3)Ar$), 42.80, 43.77 ($CO_2CH_2CH_3$), 62.58 (OCH_2CH_3), 126.96, 127.66, 128.60, 140.14 (q), 162.85 (*C*=O), 172.83 (CO_2Et); ^{31}P-NMR (160 MHz, $CDCl_3$, 25 °C): 13.75; MS (FAB+) *m*/*e* 234, 179, 105, 87; HMRS (FAB+) *m*/*e* calculated $[M + 1]^+$ 440.195050, found $[M + 1]^+$ 440.195197.

2.3.3. Cyclisation of N-1,2,3,4-tetrahydroquinoline-α-diazo-α-(diethoxyphosphoryl)acetamide **23**

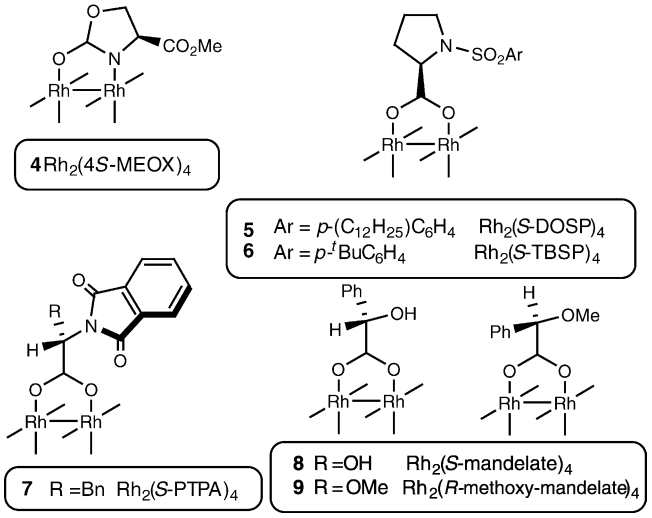
To a refluxing suspension of rhodium(II) tetraacetate (0.0013 g, 0.003 mmol) in 2.50 ml of anhydrous $C_2H_4Cl_2$, was added *N*-1,2,3,4-tetrahydroquinoline-α-diazo-α-(diethoxyphosphoryl)acetamide **23** (0.10 g, 0.30 mmol) in 1 ml of $C_2H_4Cl_2$. After refluxing for 24 h, the mixture was concentrated and the residue was purified by flash chromatography (basic alumina AcOEt/Hex 3:7) yielding the β-lactam **24** (0.07 g, 73%) as a viscous yellow oil, $R_f = 0.50$ (neutral alumina AcOEt/Hex 2:3); ν_{max} (film): 1757, 1633, 1265, 1024 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$, 25 °C, TMS): 1.36 (6H, t, *J* 7.0, OCH_2CH_3), 1.56–1.66 (1H, m, $NCHCH_2CH_2Ar$), 2.37–2.44 (1H, m, $NCHCH_2CH_2Ar$), 2.86–2.88 (2H, m, $NCHCH_2CH_2Ar$), 3.52 (1H, dd, J_{H-P} 16.2 and *J* 2.4, $POCHCO$), 3.92–4.00 (1H, m, $NCHCH_2CH_2Ar$), 4.16–4.30 (4H, m, OCH_2CH_3), 7.01 (1H, t, Ar), 7.10–7.22 (2H, m, Ar), 7.44 (1H, d, Ar); ^{13}C-NMR (100 MHz, $CDCl_3$, 25 °C): 16.32 (OCH_2CH_3), 25.89, 25.92 ($NCHCH_2CH_2Ar$ and $NCHCH_2CH_2Ar$), 49.76 ($NCHCH_2CH_2Ar$), 54.24 (d, J_{C-P} 145.0, $POCHCO$), 62.71, (OCH_2CH_3), 118.58; 123.87; 124.32 (q); 127.14; 129.08; 133.60 (q); 159.18 (*C*=O); ^{31}P-NMR (160 MHz, $CDCl_3$, 25 °C): 19.17; MS (EI) *m*/*e* 309, 280, 130, 91, 77; HMRS (EI) *m*/*e* calculated $[M]^+$ 309.112997, found $[M]^+$ 309.112051.

2.3.4. Cyclisation of (R)-(+)-N-(phenylethylamine)-N-[3-(ethoxycarbonyl)-propyl]-α-diazo-α-(diethoxyphosphoryl) acetamide **27**

To a refluxing suspension of rhodium(II) tetraacetate (0.0024 g, 0.005 mmol) in 4.00 ml of anhydrous $C_2H_4Cl_2$, was added (*R*)-(+)-*N*-(phenylethylamine)-*N*-[3-(ethoxycarbonyl)-propyl]-α-diazo-α-(diethoxyphosphoryl) acetamide **26** (0.24 g, 0.55 mmol) in 2 ml of $C_2H_4Cl_2$. After refluxing for 4 h, the mixture was concentrated and the residue was purified by preparative chromatography (basic alumina AcOEt/Hex 4:6) yielding the γ-lactam **28** (0.08 g, 40%) as a viscous yellow oil, $R_f = 0.33$ (neutral alumina AcOEt/Hex 4:6); ν_{max} (film): 3054, 2984, 1730, 1687, 1265, 1026 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$, 25 °C, TMS): 1.17 (t, *J* 7.2, $CO_2CH_2CH_3$), 1.23 (t, *J* 7.1, $CO_2CH_2CH_3$), 1.31–1.37 (m, OCH_2CH_3), 1.50–1.53 (3H, m, $NCH(CH_3)Ar$), 2.22 (dd, *J* 9.2 and 16.1, $NCH_2CHCH_2CO_2Et$), 2.40–2.46 (m, $NCH_2CHCH_2CO_2Et$), 2.54 (dd, *J* 5.1 and *J* 16.4, $NCH_2CHCH_2CO_2Et$), 2.60–2.66 (m, $NCH_2CHCH_2CO_2Et$ and $NCH_2CHCH_2CO_2Et$), 2.73 (dd, J_{H-P} 22.5 and *J* 4.9, $POCHCO$), 2.98–3.00 (m, NCH_2 and $NCH_2CHCH_2CO_2Et$), 3.32 (t, *J* 8.4, NCH_2), 3.68 (t, *J* 8.0, $NCH_2CHCH_2CO_2Et$), 4.04 (q, *J* 7.0, $CO_2CH_2CH_3$), 4.09–4.27 (m, $CO_2CH_2CH_3$ and OCH_2CH_3), 5.48 (q, *J* 6.7, $NCH(CH_3)Ar$); ^{13}C-NMR (100 MHz, $CDCl_3$, 25 °C): 14.13 ($CO_2CH_2CH_3$), 15.93, 16.11 ($NCH(CH_3)Ar$), 16.42 (OCH_2CH_3), 30.32, 30.17 ($NCH_2CHCH_2CO_2Et$), 38.59, 38.81 ($NCH_2CHCH_2CO_2Et$), 46.80 (NCH_2), 47.06, 47.39 (d, J_{C-P} 141 and J_{C-P} 119, $POCHCO$), 49.32, 49.54 ($NCH(CH_3)Ar$), 60.67, 60.78 ($CO_2CH_2CH_3$), 62.96, 63.18 (OCH_2CH_3), 127.00, 127.10, 127.56, 127.66, 128.54, 128.61, 139.46 (q), 139.65 (q), 167.93 (*C*=O), 171.04, 171.13 (CO_2Et); ^{31}P-NMR (160 MHz, $CDCl_3$, 25 °C): 23.19, 23.30; MS (EI) *m*/*e* 411, 306, 260, 220, 105; HMRS (EI) *m*/*e* calculated $[M]^+$ 411.181076, found $[M]^+$ 411.181733.

2.3.5. General procedure for the cyclisation of α-diazo-α-(diethylphosphono)acetamides with chiral dirhodium(II) catalysts

To a suspension of the chiral dirhodium(II) catalyst (1.0 mol%) in 1.75 ml of anhydrous $C_2H_4Cl_2$, was added the appropriated α-diazo-α-(diethoxyphosphoryl)acetamide (0.15 mmol). The resulting mixture was refluxed until all α-diazo-α-(diethoxyphosphoryl)acetamide was consumed. Then the mixture was concentrated and the residue purified by flash chromatography (basic alumina AcOEt/Hex).



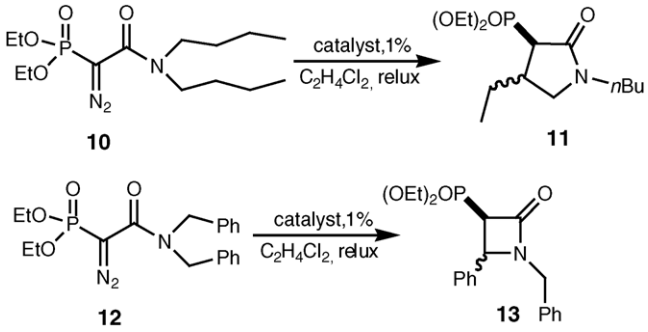
Scheme 3.

2.4. Preparation of γ-lactam 29

A solution of γ-lactam **28** (0.08 g, 0.21 mmol) in THF (3 ml) was slowly added to a magnetically stirred mixture of NaH in 6 ml of THF at 0 °C. The mixture was stirred 15 mim and acetaldehyde (0.028 g, 0.65 mmol) was added. The mixture was stirred at this temperature for 3 h. The reaction mixture was concentrated and the residue was chromatographed on SiO_2 (preparative TLC, AcOEt/Hex 3:7) yielding 31% of γ-lactam *Z*-**29** and 38% of *E*-**29**. The γ-lactam Z-**29** diastereomer is a mixture of (*R*,*S*)-*Z*-**29** (major, de = 27%, by HPLC) and (*R*,*R*)-*Z*-**29** (minor) by comparison with reported ^{1}H- and ^{13}C-NMR data for (*R*,*R*)-*Z*-**29** [11].

3. Results and discussion

Taking advantaged of the structural diversity of chiral dirhodium(II) catalysts described in the literature



Scheme 4.

(Scheme 3), we performed the cyclisation of the symmetrical α-diazo-α-(dialkoxyphosphoryl)acetamides **10** and **12**, with some of the most successful catalysts reported for dirhodium(II) mediated diazo transformations (Scheme 4 and Table 1).

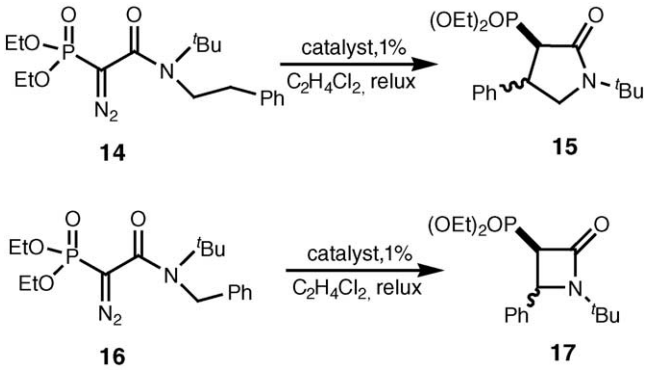
The cyclisation with Rh_2(*S*-DOSP)$_4$**5** and Rh_2(*S*-TBSP)$_4$**6** afforded moderate to high yields of the desired lactams **11** and **13**, nevertheless, low asymmetric-induction was achieved with these catalysts (entries 2 and 3).

As in the previous cases, low levels of enantioselectivities, were observed when using the less electronwithdrawing and presumably more selective catalyst, Rh_2(4*S*-MEOX)$_4$**4** (entry 1).The efficiency observed by Hashimoto and co-workers [8] on the cyclisation of α-diazo-α-(methoxycarbonyl)acetamides with Rh_2(*S*-PTPA)$_4$**7** was then again not repeated in this case, though a moderate enantiomeric excess was observed on the cyclisation of substrate **12**, yielding β-lactam **13** in 72% yield and 28%*ee*. (entry 4). More interesting results were obtained when the cyclisation was performed with Rh_2(*S*-mandelate)$_4$ [10] **8** and Rh_2(*R*-methoxy-mandelate)$_4$ [10] **9**, both catalysts induced a similar level of stereoselectivity and enantioselectivity on the γ-lactam formation (entries 5 and 6) but when the cyclisation of α-diazoacetamide **12** was performed with Rh_2(*R*-methoxy-

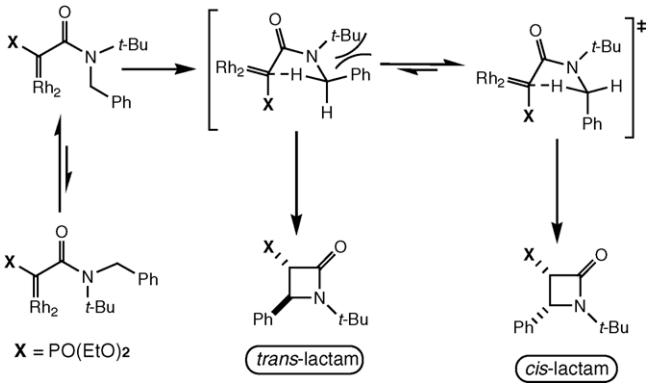
Table 1
Cyclisation of α-diazo-α-(dialkoxyphosphoryl)acetamides **10** and **12** with chiral dirhodium(II) catalysts

Entry	Catalyst	Substrate **10**				Substrate **12**			
		Conditions	*cis*/*trans* (crude, %)[a]	Yield (isolated) (%)[b]	*ee* (%)	Conditions	*cis*/*trans* (crude, %)[a]	Yield (isolated) (%)[b]	*ee* (%)
1	**4**	24 h, reflux	0/100	72	14[c]	48 h, reflux	29/71	52	1
2	**5**	4 h, reflux	14/86	91	7[c]	4 h, reflux	20/80	80	10[e]
3	**6**	4 h, reflux	14/86	90	1	4 h, reflux	20/80	65	8[e]
4	**7**	4 h, reflux	17/83	73	12[d]	4 h, reflux	17/83	72	28[f]
5	**8**	4 h, reflux	10/90	87	14[c]	4 h, reflux	19/81	60	26[f]
6	**9**	4 h, reflux	15/85	89	10[d]	4 h, reflux	25/75	70	40[e]

[a] *cis*/*trans* ratio obtained by ^{31}P-NMR.
[b] All isolated compounds are *trans* diastereomers as a result of epimerization during purification on basic alumina.
[c] Major enantiomer t_R (min)-12.18.
[d] Major enantiomer t_R (min)-21.18.
[e] Major enantiomer t_R (min)-11.63.
[f] Major enantiomer t_R (min)-13.11.



Scheme 5.



Scheme 6.

mandelate)$_4$**9** the β-lactam **13** was obtained in 70% yield and with 40% *ee*.

Further evaluation of the more active catalysts, was undertaken on the cyclisation of the asymmetrical α-diazo-α-(dialkoxyphosphoryl)acetamides **14** and **16**, as shown in Scheme 5 and Table 2.

Once again, the Rh$_2$(*R*-methoxy-mandelate)$_4$**9** furnished the highest degree of enantioselectivity. In this case, cyclisation of α-diazoacetamide **14** with an aryl group nearby the insertion center yielded the γ-lactam in 86% and with 40% *ee*. The introduction of the *tert*-butyl in the α-diazoacetamide **16** resulted in a decrease of the enantioselectivity when compared with the formation of β-lactam **13** with the same catalyst. This fact is probably related with the steric effect exerted by the *tert*-butyl on the transition state conformation, altering in this way, the C–H insertion stereo and enantioselectivity as shown in Scheme 6 [4].

The observed ligand influence on the cyclisation, specially when Rh$_2$(*S*-mandelate)$_4$**8** and the Rh$_2$(*R*-methoxy-mandelate)$_4$**9** catalysts were used, drew our attention to the catalyst design in order to enhance the enantioselectivity rate. Taking these two catalysts as structural models we envisioned that substitution of the methoxy on the α-methoxy-mandelate by a bulkier group, could improve the enantioselectivity. Unfortunately catalyst **18** (Scheme 7) prepared with mandelate protected with TBDMS [10], catalyzed the cyclisation of α-diazoacetamide **14** and **16** only with moderate enanteomeric excesses (15–21%). Catalysts **19** and **20** prepared with commercially available chiral carboxylic acids [10], also did not improve the cyclisation enantioselectivity on both substrates tested, as shown in Table 3.

The influence of a more constrained α-diazoacetamide framework was also considered. Cyclisation of α-diazoacetamide **23**, resulted in the formation of the β-lactam **24** in good overall yields with high regio and stereoselectivity, surprisingly, no addition to the aromatic moiety was observed (Scheme 8). The catalyzed cyclisation with chiral catalysts **7**, **8**, **9**, **18**, **19**, **20** yielded the desired β-lactam **24** with low enantioselectivity (Table 4, ≤16%).

Catalyzed cyclisation of α-diazoacetamide **27** with Rh$_2$(*S*-mandelate)$_4$ resulted in the formation of product **28** in 54% yield as a mixture with a 1:1.7 diastereomeric ratio (based on ^{31}P-NMR). Condensation of γ-lactam **28** with acetaldehyde, yielded product **29** as a mixture of *E* and *Z* diastereomers

Table 2
Cyclisation of α-diazo-α-(dialkoxyphosphoryl)acetamides **14** and **16** with Rh$_2$(*S*-PTPA)$_4$**7**, Rh$_2$(*S*-mandelate)$_4$**8** and Rh$_2$(*R*-methoxy-mandelate)$_4$**9**

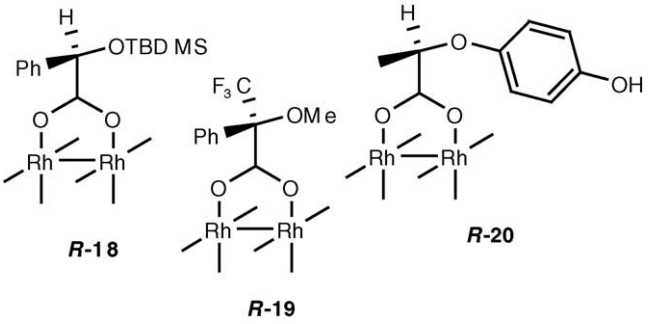
Entry	Catalyst	Conditions $C_2H_4Cl_2$	*cis*/*trans* (crude, %)[a]	Yield (isolated) (%)[b]	*ee* (%)
Substrate **14**					
1	**7**	4 h, reflux	7/93	70	15[c]
2	**8**	4 h, reflux	12/88	76	18[c]
3	**8**	24 h, 60 °C	11/89	97	22[c]
4	**9**	4 h, reflux	17/83	86	40[d]
Substrate **16**					
5	**7**	4 h, reflux	83/17	83	20[e]
6	**8**	4 h, reflux	70/30	81	11[f]
7	**8**	48 h, 60 °C	80/20	91	16[f]
8	**9**	4 h, reflux	80/20	90	15[e]

[a] *cis*/*trans* ratio obtained by ^{31}P-NMR.
[b] All isolated compounds are *trans* diastereomers as a result of epimerization during purification on basic alumina.
[c] Major enantiomer t_R (min)-15.78.
[d] Major enantiomer t_R (min)-28.67.
[e] Major enantiomer t_R (min)-12.91.
[f] Major enantiomer t_R (min)-16.76.

Table 3
Cyclisation of α-diazo-α-(dialkoxyphosphoryl)acetamides **14** and **16** with catalysts **18–20**

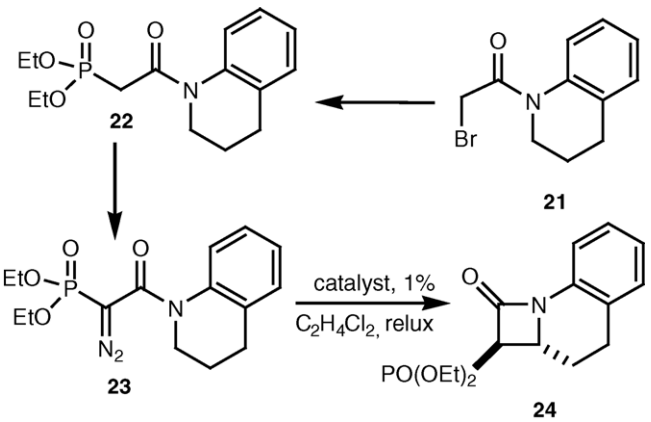
Entry	Catalyst	Conditions $C_2H_4Cl_2$	*cis*/*trans* (crude, %)[a]	Yield (isolated) (%)[b]	*ee* (%)
Substrate **14**					
1	**18**	4 h, reflux	7/93	70	21[c]
2	**19**	4 h, reflux	7/93	81	16[d]
3	**20**	4 h, reflux	6/94	76	24[c]
Substrate **16**					
4	**18**	4 h, reflux	91/9	76	15[e]
5	**19**	4 h, reflux	82/18	94	6[e]
6	**20**	4 h, reflux	94/6	88	15[e]

[a] *cis*/*trans* ratio obtained by ^{31}P-NMR.
[b] All isolated compounds are *trans* diastereomers as a result of epimerization during purification on basic alumina.
[c] Major enantiomer t_R (min)-15.78.
[d] Major enantiomer t_R (min)-28.67.
[e] Major enantiomer t_R (min)-12.91.

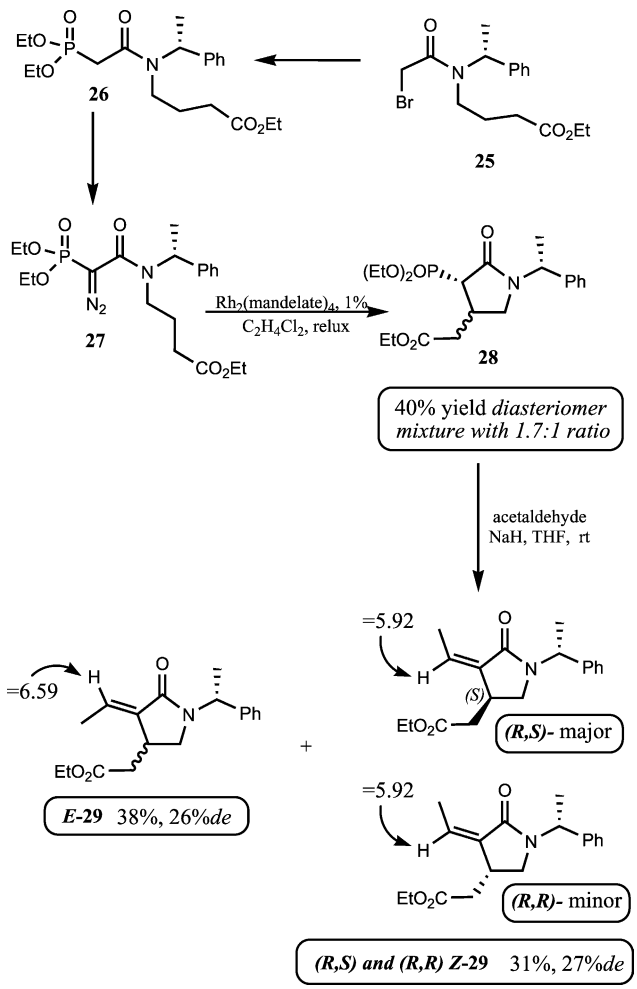


Scheme 7.

which were separated by preparative TLC and assigned based on the δ_H of the olefinic protons (Scheme 9). The preparation of this molecule allowed the determination of the absolute configuration at C-4 for the major diastereomer of γ-lactam **28**, as the *S* configuration, by comparison of the spectral data (^{1}H- and ^{13}C-NMR) with the reported one for the diastereomer (*R*,*R*)-*Z*-**29** [11], as shown in Scheme 9. In case of the $Rh_2(OAc)_4$ catalyzed C–H insertion for other diazo substrates containing the (*R*)-*N*-(phenylethylamino) group, low diastereocontrol was observed [4], probably due to the conformation adopted by the intermediate, in which the larger *N*-substituent was placed *syn* to the sterically less demanding amide carbonyl group (Scheme 1), distanced from the reactive metal-carbene centre. Assuming that similar behavior is expected for the chiral catalysts used, we can assume that the chiral catalyst stereocontrol for the other substrates is similar to the one determined for the substrate **28**.



Scheme 8.



Scheme 9.

Table 4
Cyclisation of α-diazo-α-(dialkoxyphosphoryl)acetamide **23** with $Rh_2(OAc)_4$, catalysts **7**–**9** and **18**–**20**

Entry	Catalyst	Conditions $C_2H_4Cl_2$	*cis*/*trans* (crude, %)[a]	Yield (isolated) (%)[b]	*ee* (%)
Substrate **23**					
1	**$Rh_2(OAc)_4$**	4 h, reflux	21/79	73	–
2	**7**	4 h, reflux	25/75	80	10[c]
3	**8**	4 h, reflux	25/75	65	2[d]
4	**9**	4 h, reflux	17/83	75	5[d]
5	**18**	4 h, reflux	28/72	65	16[d]
6	**19**	4 h, reflux	7/93	73	15[d]
7	**20**	4 h, reflux	22/72	67	6[d]

[a] *cis*/*trans* ratio obtained by ^{31}P-NMR.
[b] All isolated compounds are *trans* diastereomers as a result of epimerization during purification on basic alumina.
[c] Major enantiomer t_R (min)-10.34.
[d] Major enantiomer t_R (min)-14.30.

4. Conclusion

In summary this paper describes a strategy for the preparation of enantioselective enriched α-(dialkoxyphosphoryl)lactams via dirhodium(II) catalyzed C–H insertion on α-diazo-α-(dialkoxyphosphoryl)acetamides with enantiomeric excesses up to 40%. Although only modest to moderate enantioselectivities were obtained, they are the highest reported until now for this transformation. The systematic study presented offers a clear overview of the unique effect of the α-phosphoryl group, and the consequent difficulties to achieve a enantioselective procedure to prepare this molecules, namely in terms of choosing the right ligands for the chiral dirhodium(II) catalyst and structure of the α-diazo-α-(dialkoxyphosphoryl)acetamides. Taking in consideration the catalysts tested, the chiral dirhodium(II) with carboxylate ligands derived from the mandelic acid and the dirhodium(II) incorporating *N*-phthaloyl-(*S*)amino acids appeared to be the most promising catalysts for this transformation.

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References

[1] T. Ye, A. McKervey, Chem. Rev. (1994) 1091;
A. Padwa, S.F. Hornbukle, Chem. Rev. (1991) 263;
M.P. Doyle, M.A. McKervey, T. Ye, Modern Catalytic Methods for Organic Synthesis with Diazo Compounds, Wiley–Interscience, New York, 1998;
A.F. Khlebnikov, M.S. Novikov, R.R. Kostikov, Adv. Heterocycl. Chem. (1996) 93.
[2] C.A. Merlic, A.L. Zechman, Synthesis (2003) 1137;
P.M.P. Gois, C.A.M. Afonso, Eur. J. Org. Chem. (2004) 3773.
[3] E. Nakamura, N. Yoshikai, M. Yamanaka, J. Am. Chem. Soc. (2002) 7181;
N. Yoshikai, E. Nakamura, Adv. Synth. Catal. (2003) 1159.
[4] P.M.P. Gois, C.A.M. Afonso, Eur. J. Org. (2003) 3798;
P.M.P. Gois, C.A.M. Afonso, Tetrahedron Lett. (2003) 6571.
[5] Y. Du, D.F. Wiemer, J. Org. Chem. (2002) 5709;
Y. Du, D.F. Wiemer, J. Org. Chem. (2002) 5701;
K. Lee, J.A. Jackson, D.F. Wiemer, J. Org. Chem. (1993) 5967;
M. Macchia, N. Jannitta, G. Gervasi, R. Danesi, J. Med. Chem. (1996) 1352;
Y. Okada, T. Minami, M. Miyamoto, T. Otaguro, S. Sawasaki, J. Ichikawa, J. Heteroat. Chem. (1995) 195.
[6] B.E. Maryanoff, A.B. Reitz, Chem. Rev. (1989) 863.
[7] M.P. Doyle, D.C. Forbes, Chem. Rev. (1998) 911;
H.M.L. Davies, R.E.J. Beckwith, Chem. Rev. (2003) 2861;
H.M.L. Davies, E.G. Antoulinakis, J. Organomet. Chem. (2001) 47.
[8] N. Watanabe, M. Anada, S. Hashimoto, S. Ikegami, Synlett (1994) 1031;
M. Anada, S. Hashimoto, Tetrahedron Lett. (1998) 79;
M. Anada, O.M. Watanabe, S. Kitagaki, S. Hashimoto, Synlett (1999) 1775;
M. Anada, S. Kitagaki, S. Hashimoto, Heterocycles (2000) 875;
M. Anada, N. Watanabe, S. Hashimoto, J. Chem. Soc., Chem. Commun. (1998) 1517.
[9] M.P. Doyle, M.N. Protopopova, W.R. Winchester, K.L. Daniel, Tetrahedron Lett. (1992) 7819;
M.P. Doyle, S. Oon, F.R. van der Heide, C.B. Brown, Biorg. Med. Chem. Lett. (1993) 2409;
M.P. Doyle, A.V. Kalinin, Synlett (1995) 1075;
M.P. Doyle, M. Yan, I.M. Phillips, D.J. Timmons, Adv. Synth. Catal. (2002) 91.
[10] Chiral dirhodium(II) catalysts were prepared following Cotton procedure P.A. Agaskar, F.A. Cotton, L.R. Falvello, S. Han, J. Am. Chem. Soc. (1986) 121.
[11] R. Galeazzi, S. Geremia, G. Mobbili, M. Orena, Tetrahedron: Asymmetry (1999) 587.