Available online at www.sciencedirect.com
SCIENCE DIRECT
Journal of Molecular Catalysis A: Chemical 254 (2006) 78–84
JOURNAL OF MOLECULAR CATALYSIS A: CHEMICAL
www.elsevier.com/locate/molcata

Exploiting catalyst characteristics: A protocol for increasing diastereoselectivity in a double ring-closing metathesis reaction

Debra J. Wallace *

Department of Process Research, Merck Sharp and Dohme Research Laboratories, Hertford Road, Hoddesdon, Herts EN11 9BU, UK

Available online 9 May 2006

Abstract

A procedure for obtaining increased selectivity in a diastereoselective double ring-closing metathesis reaction is presented. The key to success was design of a substrate, which directed the reaction mechanism through a selective pathway and use of a suitable catalyst combination to achieve the desired balance between reactivity and selectivity.

Keywords: Diastereoselectivity; Ring-closing metathesis; Catalyst

1. Introduction

In the past two decades the ring-closing metathesis (RCM) reaction of alkenes has evolved to become a major tool for synthetic organic chemists and has successfully been applied to the synthesis of heterocyclic, carbocyclic and macrocyclic molecules [1]. Additionally, the use of multiple or cascade RCM reactions can be exploited to provide various bicyclic systems [2–5] from acyclic precursors in a single step. We recently used this strategy in an efficient synthesis of the NK1 receptor antagonist (**1**), in which the key step is the diastereoselective double RCM reaction of tetraene (**2**), to afford (**3a**) as the major product in 70% ds (Scheme 1) [6].

Although this synthesis offered significant advantages over other routes to the target [7] the modest selectivity in the key step lowered the overall yield and we sought a method to improve this transformation. Extensive mechanistic studies had indicated that the reaction proceeded via the intermediacy of four monocyclic intermediates (**4a**), (**4b**), (**5a**) and (**5b**) (Fig. 1). The relative ratio of these intermediates was shown to be catalyst dependant, as was their subsequent conversions to spirocycles [8]. As such, the use of different catalysts led to differing stereochemical outcomes, with first generation type catalysts such as the recently published (**6**) [9] giving 68% selectivity for the desired product (**3a**), whereas second generation type catalysts such as (**7**) [10] gave a near non-selective reaction, with a small preference for (**3b**).

With all catalysts tested to date [11], the major pathway for reaction of (**2**) is the initial formation of an equimolar mixture of the two five membered rings (**4a**) and (**4b**)—path A (Scheme 2), and subsequent reaction of these isolated compounds gave a mixture of spirocycles resulting from some inversion at the quaternary centre. The minor pathway leading to the formation of the six membered rings—path B, gave high selectivity for the formation of (**5a**) over (**5b**) when using (**6**), but a near 1:1 mixture when using (**7**). Clean conversion of (**5a**) and (**5b**) to (**3a**) and (**3b**), respectively was observed with all catalysts. Based on these observations it was proposed that if a method were available to direct the reaction through path B, a more selective outcome might be obtained. In this paper we describe the scope and limitations of such an approach to achieve an improved selectivity for the formation of (**3a**).

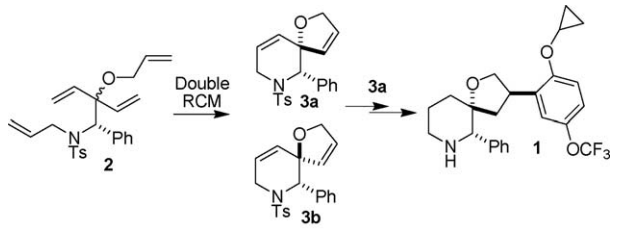
2. Experimental

2.1. General

Melting points were measured on a Bibby SMP3 melting point apparatus and are uncorrected. Optical rotations were measured on a Perkin-Elmer 341 polarimeter at the sodium D-line. ^{1}H and ^{13}C NMR spectra were recorded on Bruker DRX400 instrument using an internal deuterium lock at ambient probe temperature. Mass spectrometry was performed on a Hewlett Packard Series 1100 MSD. Accurate mass determinations were

* Tel.: +44 1992 452083; fax: +44 1992 470437.
E-mail address: debra_wallace@merck.com.

1381-1169/$ – see front matter © 2006 Elsevier B.V. All rights reserved.
doi:10.1016/j.molcata.2006.02.072



Scheme 1.

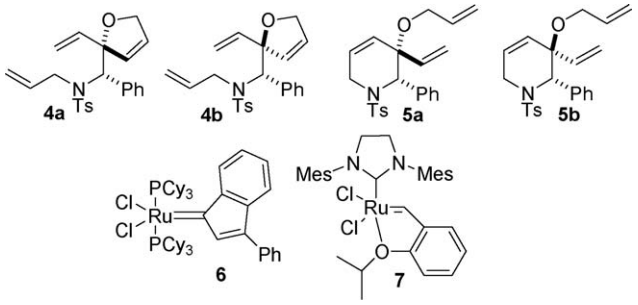


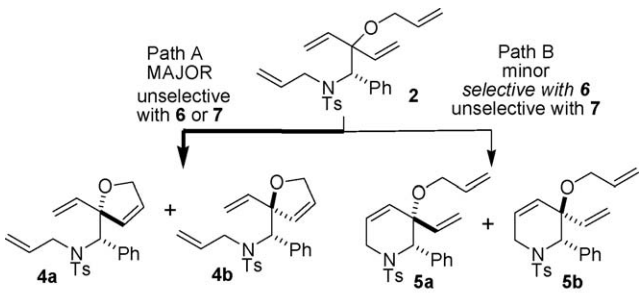
Fig. 1. Metathesis intermediates and catalysts.

run on a Waters/Micromass LCT Time of Flight mass spectrometer using positive ion electrospray ionisation. High performance liquid chromatography (HPLC) analysis were performed on an Agilent 1100 series machine with a Zorbax Eclipse XDB-C8 4.6 mm × 250 mm column with acetonitrile and 0.1% H_3PO_4 as eluant.

Reactions were carried out under a nitrogen atmosphere unless otherwise stated. Chemicals and solvents were obtained from commercial sources and were used as received. The term brine refers to a saturated aqueous solution of sodium chloride. Thin layer chromatography was performed on Merck KGaA silica gel $60F_{254}$ glass precoated plates (250 μm thickness) and visualized by shortwave light or anisaldehyde dip.

Catalyst (**6**) was purchased from Strem Chemical company and catalyst (**7**) from Aldrich Chemical company.

The synthesis and characterisation of compounds (**2**), (**3a**), (**3b**), (**4a**), (**4b**), (**5a**), (**5b**), (**12**) and (**16**) have been reported previously [6,8]. Crotyl bromide was purchased as a 85:15 *trans*:*cis* ratio, and these isomers were inseparable in compounds (**8**), (**10a**) and (**10b**) which are characterised by ^{1}H NMR and LCMS only.



Scheme 2.

2.2. Preparation of tertiary alcohol (*14*)

2.2.1. N-Allyl-[(1S)-2-hydroxy-1-phenyl-2-vinylbut-3-en-1-yl]-4-methylbenzenesulfonamide (*14*)

To a solution of methyl ester (**12**) (1.91 g, 5.99 mmol) in acetonitrile (40.0 mL) at room temperature was added K_2CO_3 (1.65 g, 12.0 mmol) followed by allyl bromide (1.0 mL, 12.0 mmol). The mixture was warmed to 40 °C and stirred for 16 h at which stage HPLC analysis indicated >95% conversion. The solids were removed by filtration and acetonitrile removed under vacuum. The resulting oil was partitioned between ethyl acetate (40 mL) and water (40 mL) and the organic layer concentrated to give (**13**), which was used without further purification in the next reaction.

Anhydrous cerium chloride (7.38 g, 29.9 mmol) was heated to 150 °C under high vacuum with stirring for 2 h and then cooled under a stream of nitrogen. THF (50 mL) was added at room temperature and the slurry stirred overnight. A solution of the crude methyl ester (**13**) in THF (10 mL) was added and the slurry cooled to 0 °C and vinylmagnesium bromide (20.0 mL, 1.0 M in THF, 20.0 mmol) added. After 1 h the reaction was quenched by addition of aqueous citric acid (50 mL, 1.0 M) and extracted with MeOtBu (50 mL). The organic layer was washed with brine (50 mL) and concentrated in vacuo. The crude oil was purified by flash column chromatography (10:90 EtOAc:hexanes increasing to 30:70 EtOAc:hexanes) to afford the tertiary alcohol (**14**) as a viscous oil, 982 mg, 43% over two steps.

Rotation $\alpha_D = +40.7$, $c = 0.3$, CH_2Cl_2: ^{1}H (400 MHz, $CDCl_3$) δ 7.57 (d, $J = 8.0$ Hz, 2H), 7.45 (d, $J = 6.8$ Hz, 2H), 7.21 (m, 3H), 7.17 (d, $J = 8.0$ Hz, 2H), 6.26 (dd, $J = 17.2$, 10.8 Hz, 1H), 5.85 (dd, $J = 17.2$, 10.8 Hz, 1H), 5.68 (m, 1H), 5.42 (d, $J = 16.8$ Hz, 1H), 5.30 (d, $J = 16.8$ Hz, 1H), 5.24 (d, $J = 17.2$ Hz, 1H), 5.15–5.03 (m, 4H), 4.05 (dd, $J = 16.8$, 6.8 Hz, 1H), 3.98 (dd, $J = 16.8$, 5.6 Hz, 1H), 2.39 (s, 3H): ^{13}C (100.6 MHz, $CDCl_3$) δ 143.2, 141.8, 140.3, 137.3, 136.4, 135.8, 130.9, 129.2, 128.0, 127.95, 127.93, 117.3, 114.9, 114.1, 79.9, 67.3, 49.0, 21.4: LCMS 406.2 (M + Na) 100%, 366 ($MH^+ - H_2O$) 50%, 212, 90%: HRMS ($C_{22}H_{26}NO_3S$) (MH^+) requires 384.1633, found 384.1629.

2.3. Ring closing metathesis of (*14*)

To a stirred solution of triene (**14**) (520 mg, 1.36 mmol) in CH_2Cl_2 (15 mL) under a nitrogen atmosphere was added catalyst (**6**) (45 mg, 0.050 mmol). The mixture was stirred at room temperature for 16 h and then concentrated in vacuo. The crude mixture was purified by flash column chromatography (30:70 EtOAc:hexanes) to afford (**15a**) 115 mg (24%) and (**15b**) (230 mg, 48%).

(2*S*,3*S*)-1-[(4-Methylphenyl)sulfonyl]-2-phenyl-3-vinyl-1,2,3,6-tetrahydropyridin-3-ol (**15a**): MP = 148–150 °C: Rotation $\alpha_D = -67.5$, $c = 0.16$, CH_2Cl_2: ^{1}H (400 MHz, $CDCl_3$) δ 7.38 (d, $J = 8.4$ Hz, 2H), 7.28–7.23 (m, 5H), 7.16 (d, $J = 8.4$ Hz, 2H), 6.11 (dd, $J = 16.8$, 10.4 Hz, 1H), 5.95 (ddd, $J = 10.4$, 3.6, 2.8 Hz, 1H), 5.75 (ddd, $J = 10.4$, 2.4, 1.2 Hz, 1H), 5.32 (dd, $J = 16.8$, 0.8 Hz, 1H), 5.20 (dd, $J = 10.4$, 0.8 Hz, 1H), 5.17 (s, 1H), 4.16 (ddd, $J = 17.6$, 3.6, 2.4 Hz, 1H), 3.61 (app dt, $J = 17.6$, 2.4 Hz,

1H), 2.33 (s, 3H): ^{13}C (100.6 MHz, $CDCl_3$) δ 143.0, 141.0, 136.1, 131.2, 129.6, 129.2, 129.1, 128.6, 128.3, 127.4, 123.0, 114.8, 72.4, 63.3, 41.9, 21.4: LCMS 378.3 (M + Na) 70%, 338 ($MH^+ - H_2O$) 100%: HRMS ($C_{20}H_{22}NO_3S$) (MH^+) requires 356.1320, found 356.1334.

(2*S*,3*R*)-1-[(4-Methylphenyl)sulfonyl]-2-phenyl-3-vinyl-1,2,3,6-tetrahydropyridin-3-ol (**15b**): MP = 126–127 °C: Rotation $\alpha_D = -49.6$, $c = 0.26$, CH_2Cl_2: ^{1}H (400 MHz, $CDCl_3$) δ 7.44 (d, J = 8.2 Hz, 2H), 7.19–7.14 (m, 5H), 7.06 (d, J = 8.2 Hz, 2H), 6.06 (s, 2H), 5.51 (dd, J = 17.2, 10.4 Hz, 1H), 5.42 (dd, J = 10.4, 1.6 Hz, 1H), 5.14 (s, 1H), 5.05 (dd, J = 10.4, 1.6 Hz, 1H), 4.23 (dd, J = 17.7, 2.4 Hz, 1H), 3.56 (d, J = 17.8 Hz, 1H), 2.59 (s, 1H), 2.33 (s, 3H): ^{13}C (100.6 MHz, $CDCl_3$) δ 143.2, 138.3, 135.7, 130.5, 129.6, 129.2, 129.1, 128.3, 128.0, 127.5, 126.4, 115.8, 70.9, 66.4, 41.7, 21.4: LCMS 378.3 (M + Na) 30%, 338 ($MH^+ - H_2O$) 100%: HRMS ($C_{20}H_{22}NO_3S$) (MH^+) requires 356.1230, found 356.1322.

2.4. Preparation of (*11a*), (*11b*), (*10a*), (*10b*)

(2*S*,3*S*)-3-[(3-Methylbut-2-en-1-yl)oxy]-1-[(4-methylphenyl)sulfonyl]-2-phenyl-3-vinyl-1,2,3,6-tetrahydropyridine (**11a**): To a stirred, cooled (5 °C) solution of (**15a**) (31.1 mg, 0.087 mmol) in THF (0.5 mL) and DMPU (0.5 mL) was added 4-bromo-2-methyl-2-butene (50 μL, 0.43 mol), followed by sodium hydride (17.3 mg, 60 wt.%, 0.43 mmol). The mixture was stirred at the same temperature for 4 h and then quenched by dropwise addition of water (10 mL), and extracted with ethyl acetate (10 mL). The organic layer was washed with water (10 mL) and brine (10 mL) and concentrated in vacuo to afford an oil which was purified by flash column chromatography (20:80 EtOAc:hexanes) to give (**11a**) (27.0 mg, 73%) as a colourless oil.

Rotation $\alpha_D = -36.3$, $c = 0.54$, CH_2Cl_2: ^{1}H (400 MHz, $CDCl_3$) δ 7.45 (d, J = 8.2 Hz, 2H), 7.42 (d, J = 7.6 Hz, 2H), 7.20 (m, 3H), 7.09 (d, J = 8.2 Hz, 2H), 7.06 (d, J = 8.2 Hz, 2H), 6.10 (dd, J = 17.6, 11.1 Hz, 1H), 5.94 (dd, J = 10.4, 0.4 Hz, 1H), 5.83 (ddd, J = 10.4, 4.0, 2.4 Hz, 1H), 5.45 (s, 1H), 5.37 (dd, J = 17.6, 0.8 Hz, 1H), 5.33 (dd, J = 11.1, 0.8 Hz, 1H), 4.89 (app t septet, J = 7.2, 1.2 Hz, 1H), 4.00 (ddd, J = 17.4, 4.0, 2.4 Hz, 1H), 3.90 (dd, J = 10.8, 7.2 Hz, 1H), 3.59 (dd, J = 10.8, 7.2 Hz, 1H), 3.40 (app dt, J = 17.4, 2.4 Hz, 1H), 2.34 (s, 3H), 1.59 (s, 3H), 1.32 (s, 3H): ^{13}C (100.6 MHz, $CDCl_3$) δ 143.0, 139.1, 136.4, 136.2, 135.7, 129.9, 129.8, 129.1, 127.9, 127.7, 127.4, 122.4, 120.9, 116.8, 76.9, 60.6, 59.4, 41.4, 25.7, 21.4, 17.6: LCMS 446.3 (M + Na) 100%, 338, 35%: HRMS ($C_{25}H_{30}NO_3S$) (MH^+) requires 424.1946, found 424.1940.

(2*S*,3*R*)-3-[(3-Methylbut-2-en-1-yl)oxy]-1-[(4-methylphenyl)sulfonyl]-2-phenyl-3-vinyl-1,2,3,6-tetrahydropyridine (**11b**): In a similar manner (**15b**) (30.0 mg, 0.084 mmol) was converted to (**11b**) as an off white solid (25 mg, 69%).

MP = 76–77 °C (hexanes): Rotation $\alpha_D = -29.4$, $c = 0.36$, CH_2Cl_2: ^{1}H (400 MHz, $CDCl_3$) δ 7.67 (d, J = 8.2 Hz, 2H), 7.22–7.21 (m, 5H), 7.12 (d, J = 8.2 Hz, 2H), 6.19 (dt, J = 10.2 Hz, 3.2 Hz, 1H), 6.14 (br d, J = 10.2 Hz, 1H), 5.50 (dd, J = 17.6, 10.8 Hz, 1H), 5.30 (s, 1H), 5.22 (dd, J = 17.6, 0.8 Hz, 1H), 5.19 (m, 1H), 5.11 (dd, J = 10.8, 0.8 Hz, 1H), 4.02 (ddd, J = 18.4, 3.6, 2.8 Hz, 1H), 3.89 (dd, J = 10.8, 7.2 Hz, 1H), 3.83 (dd, J = 10.8, 6.4 Hz, 1H), 3.73 (app dt, J = 18.4, 2.0 Hz, 1H), 2.37 (s, 3H), 1.76 (s, 3H), 1.61 (s, 3H): ^{13}C (100.6 MHz, $CDCl_3$) δ 142.5, 138.2, 137.6, 136.9, 135.1, 129.1, 129.0, 128.7, 128.1, 127.8, 127.6, 126.6, 122.1, 116.7, 75.1, 64.1, 60.0, 41.8, 25.8, 21.5, 18.1: LCMS 446.3 (M + Na) 100%, 338, 50%: HRMS ($C_{25}H_{30}NO_3S$) (MH^+) requires 424.1946, found 424.1931.

(2*S*,3*S*)-3-[(2*E*)-But-2-en-1-yloxy]-1-[(4-methylphenyl)sulfonyl]-2-phenyl-3-vinyl-1,2,3,6-tetrahydropyridine (**10a**): In a similar manner (**15a**) (12.0 mg) was converted to (**10a**) (9.5 mg, 67%) using crotyl bromide in place of 4-bromo-2-methyl-2-butene. The product was obtained as a ca 80:20 mixture of *E,Z*-double bond isomers.

^{1}H (400 MHz, $CDCl_3$) δ 7.42 (d, J = 8.0 Hz, 2H), 7.37 (dd, J = 7.6, 1.6 Hz, 2H), 7.19 (m, 3H), 7.07 (d, J = 8.0 Hz, 2H), 6.06 (dd, J = 17.2, 10.4 Hz, 1H), 5.93 (m, 1H), 5.85 (ddd, J = 10.4, 4.4, 2.4 Hz, 1H), 5.11 (m, 1H), 3.98 (ddd, J = 17.6, 3.6, 2.0 Hz, 1H), 3.90 (ddt, J = 11.2, 6.0, 1.2 Hz, 1H), 3.57 (ddt, J = 11.2, 5.6, 1.2 Hz, 1H), 3.42 (app dt, J = 17.2, 2.0 Hz, 1H), 2.34 (s, 3H), 1.53 (dd, J = 5.2, 1.6 Hz, 3H): LCMS 432.2 (M + Na) 100%, 338, 60%: HRMS ($C_{24}H_{28}NO_3S$) (MH^+) requires 410.1790, found 410.1783.

(2*S*,3*R*)-3-[(2*E*)-But-2-en-1-yloxy]-1-[(4-methylphenyl)sulfonyl]-2-phenyl-3-vinyl-1,2,3,6-tetrahydropyridine (**10b**): In a similar manner (**15b**) (30.4 mg) was converted to (**10b**) (28.2 mg, 81%), the product was obtained as a ca. 80:20 mixture of *E,Z*-double bond isomers.

^{1}H (400 MHz, $CDCl_3$) δ 7.68 (d, J = 8.0 Hz, 2H), 7.21 (m, 5H), 7.12 (d, J = 8.0 Hz, 2H), 6.18 (m, 1H), 6.10 (m, 1H), 5.69–5.61 (m, 1H), 5.49–5.41 (m, 2H), 5.30 (s, 1H), 5.19 (d, J = 17.6 Hz, 1H), 5.11 (d, J = 11.2 Hz, 1H), 4.00 (app dt, J = 15.6 Hz, 1H), 3.30 (m, 2H), 3.72 (app dt, J = 18.0, 2.4 Hz, 1H), 2.27 (s, 3H), 1.73 (dd, J = 6.4, 1.2 Hz, 3H): ^{13}C (100.6 MHz, $CDCl_3$) δ 142.6, 138.1, 137.4, 136.9, 129.1, 129.0, 128.7, 128.4, 128.1, 128.0, 127.7, 127.6, 126.4, 116.8, 75.2, 64.1, 63.9, 41.7, 21.5, 17.8. LCMS 432.2 (M + Na) 100%, 338, 40%: HRMS ($C_{24}H_{28}NO_3S$) (MH^+) requires 410.1790, found 410.1791.

2.5. Preparation of (*8*) and (*9*)

N-Allyl-*N*-{[(1*S*)-2-[(2*E*)-but-2-en-1-yloxy]-1-phenyl-2-vinylbut-3-en-1-yl]}-4-methylbenzenesulfonamide (**8**): To a stirred, cooled (0 °C) solution of alcohol (**14**) (297 mg, 0.775 mmol) in THF (4.5 mL) and DMPU (1.5 mL) was added crotyl bromide (0.62 mL, 6.20 mmol) followed by sodium hydride (124.0 mg, 60 wt.% in mineral oil, 3.10 mmol). The mixture was stirred at the same temperature for 4 h and then quenched by dropwise addition of water (20.0 mL) and extracted with IPAc (20.0 mL). The organic layer was washed with water (20.0 mL) and brine (20 mL) and concentrated in vacuo. Purification by flash column chromatography (hexanes increasing to 10:90 EtOAc:hexanes) afforded (**8**) as a colourless oil (115.0 mg, 34%) as a ca. 60:40 mixutre of *E,Z*-double bond isomers and identity was confirmed by ^{1}H and LCMS only.

^{1}H (400 MHz, $CDCl_3$) δ 7.58–7.45 (m, 4H), 7.23–7.21 (m, 3H), 7.13 (d, J = 8.4 Hz, 2H), 6.12 (dd, J = 17.2, 11.2 Hz, 1H), 5.78–5.53 (m, 4H), 5.43–5.33 (m, 2H), 5.21–5.14 (m, 2H), 5.09 (s, 1H), 4.98 (d, J = 17.2 Hz, 1H), 4.87 (d, J = 10.4 Hz, 1H),4.28 (ddd, J = 16.4, 6.0, 4.4 Hz, 1H), 4.07–4.04 (m, 1H), 3.82–3.78 (m, 2H) 2.36 (s, 3H), 1.73 (d, J = 6.4 Hz, 3H); LCMS 474.2.3 (M + Na) 100%, 366 50%: HRMS ($C_{26}H_{32}NO_3SNa$) (M + Na) requires 460.1922, found 460.1931.

4-Methyl-*N*-{[(1*S*)-2-[(3-methylbut-2-en-1-yl)oxy]-1-phenyl-2-vinylbut-3-en-1-yl]}-benzenesulfonamide (**17**): To a stirred, cooled (0 °C) solution of alcohol (**16**) (195 mg, 0.568 mmol) in THF (3.0 mL) and DMPU (1.0 mL) was added sodium hydride (136 mg, 60 wt.%, 3.41 mmol) followed by 4-bromo-2-methyl-2-butene (67 μL, 0.625 mmol) and the mixture stirred at the same temperature until HPLC analysis indicated 10% residual starting material. The reaction was quenched by dropwise addition of water (5.0 mL) and extracted with IPAc (10 mL). The organic layer was washed with water (10 mL), and brine and concentrated in vacuo. The crude oil was purified by flash column chromatography (10:90 EtOAc:hexanes) to afford (**17**) as an off white solid (93 mg, 40%).

Rotation α_D = +56.0, c = 0.18, CH_2Cl_2: ^{1}H (400 MHz, $CDCl_3$) δ 7.42 (d, J = 8.0 Hz, 2H), 7.14–7.08 (m, 5H), 7.01 (d, J = 8.0 Hz, 2H), 5.85 (dd, J = 17.6, 10.8, 1H), 5.70 (d, J = 6.8 Hz, 1H), 5.50 (dd, J = 17.6, 10.8 Hz, 1H), 5.36 (dd, J = 10.8, 1.2 Hz, 1H), 5.27 (dd, J = 8.8, 1.2 Hz, 1H), 5.24–5.22 (m, 2H), 5.19 (dd, J = 17.6, 1.6 Hz, 1H), 4.26 (d, J = 6.8 Hz, 1H), 3.78 (dd, J = 11.6, 4.8 Hz, 1H), 3.72 (dd, J = 11.6, 4.8 Hz, 1H), 2.31 (s, 3H), 1.74 (s, 3H), 1.58 (s, 3H): ^{13}C (100.6 MHz, $CDCl_3$) δ 142.5, 137.6, 136.9, 135.9, 135.5, 135.2, 129.3, 128.9, 127.3, 127.2, 127.1, 124.1, 119.1, 118.9, 82.3, 64.9, 61.0, 25.7, 21.4, 18.1: LCMS 434.2 (M + Na) 100%, 326 (90%). HRMS ($C_{24}H_{30}NO_3S$) (M + H) requires 412.1945, found 412.1946.

N-Allyl-4-methyl-*N*{[(1*S*)-2-[(3-methylbut-2-en-1-yl)oxy]-1-phenyl-2-vinylbut-3-en-1-yl]}-4-methylbenzenesulfonamide (**9**):

From alcohol (**14**): To a stirred, cooled (0 °C) solution of alcohol (**14**) (75.0 mg, 0.196 mmol) in THF (2.0 mL) and DMPU (1.0 mL) was added sodium hydride (23.0 mg, 60 wt.%, 0.587 mmol) and 4-bromo-2-methyl-2-butene (83 μL, 0.784 mmol). The mixture was allowed to warm to room temperature and stirred for 16 h. The mixture was quenched by dropwise addition of water (10.0 mL) and extracted with IPAc (10.0 mL). The organic layer was washed with water (10.0 mL) and brine (10 mL) and concentrated in vacuo. Purification by flash column chromatography (10:90 EtOAc:hexanes) afforded (**9**) as a colourless oil (15.0 mg, 17%).

From triene (**17**): To a stirred, cooled solution of triene (**17**) (80.0 mg, 0.195 mmol) in THF (1.0 mL) and DMPU (1.0 mL) was added allyl bromide (67.0 μL, 0.778 mmol), followed by NaH (31.0 mg, 60 wt.%, 0.778 mmol) and the mixture allowed to warm to room temperature and stirred for 16 h. The mixture was quenched by dropwise addition of water (10.0 mL) and extracted with IPAc (10.0 mL). The organic layer was washed with water (10.0 mL) and brine (10 mL) and concentrated in vacuo. Purification by flash column chromatography (10:90 EtOAc:hexanes) afforded (**9**) as a colourless oil (41.5 mg, 47%).

Rotation α_D = +23.9, c = 0.18, CH_2Cl_2: ^{1}H (400 MHz, $CDCl_3$) δ 7.60 (d, J = 8.0 Hz, 2H), 7.57–7.55 (m, 2H), 7.25–7.22 (m, 3H), 7.14 (d, J = 8.0 Hz, 2H), 6.14 (dd, J = 17.2, 11.2 Hz, 1H), 5.70 (dd J = 17.2, 11.6 Hz, 1H), 5.60 (m, 1H), 5.42–5.36 (m, 3H), 5.20 (s, 1H), 5.17 (dd, J = 7.6, 1.2 Hz, 1H), 5.08 (s, 1H), 4.97 (dd, J = 17.2, 1.2 Hz, 1H), 4.87 (dd, J = 10.4, 1.6 Hz, 1H), 4.17 (dd, J = 16.4, 5.2 Hz, 1H), 4.03 (dd, J = 16.4, 6.4 Hz, 1H), 3.90 (dd, J = 11.6, 6.8 Hz, 1H), 3.84 (dd, J = 11.6, 6.8 Hz, 1H), 2.38 (s, 3H), 1.77 (s, 3H), 1.62 (s, 3H): ^{13}C (100.6 MHz, $CDCl_3$) δ 142.7, 138.0, 137.1, 137.0, 136.5, 135.1, 131.2, 128.9, 128.8, 128.1, 127.8, 127.6, 121.7, 118.5, 118.0, 115.7, 85.7, 67.4, 61.3, 49.1, 25.7, 21.4, 18.1: LCMS 474.2.3 (M + Na) 100%, 366, 50%: HRMS ($C_{27}H_{33}NO_3SNa$) (M + Na) requires 474.2079, found 474.2086.

2.6. Double RCM reactions

2.6.1. RCM of (*8*)

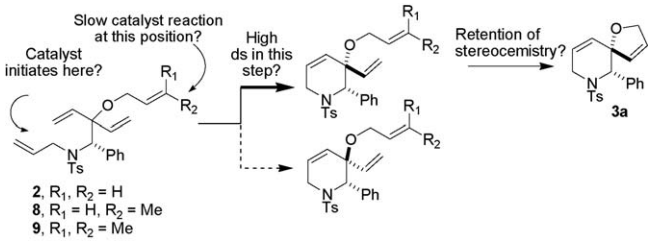
To a solution of (**8**) in CH_2Cl_2 under a nitrogen atmosphere was added catalyst (**6**) or (**7**) (5 mol%) and the progress of the reaction monitored by HPLC. In the case of catalyst (**6**) a further 5 mol% was added to allow the reaction to reach completion. The relative ratios of intermediates and product are given in Scheme 7, the products were not isolated.

2.6.2. RCM of (*9*)

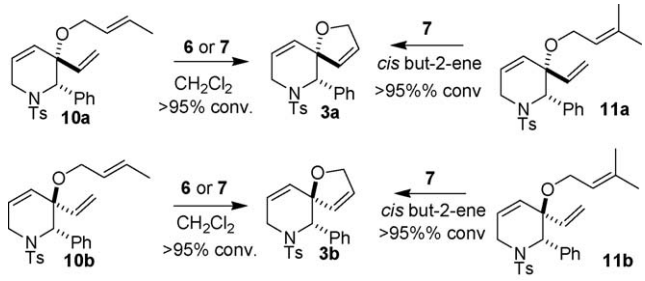
To a stirred, cooled (0 °C) solution of (**9**) (12.2 mg, 0.027 mmol) in CH_2Cl_2 (1.0 mL) under a nitrogen atmosphere was added catalyst (**6**) (0.9 mg, 0.0014 mmol, 5 mol%) and the progress of the reaction monitored by HPLC. When all starting material had been consumed most of the solvent was removed by nitrogen sweep and the reaction cooled to −78 °C. Butene was condensed into the flask (ca. 0.5 mL), catalyst (**7**) (1.2 mg, 5 mol%) added, and the reaction stirred at 3 °C for 24 h, a further 1.2 mg of catalyst (**7**) was added and stirring continued for an additional 24 h at the same temperature. At this time 95% conversion of intermediates to a 84:16 mixture of (**3a**):(**3b**) was observed by HPLC analysis. The known products were not isolated.

3. Results and discussion

We propose that the rate determining step for the formation of the mono-cyclic intermediates is the intermolecular reaction of the catalyst with one of the allyl groups, with the subsequent intramolecular cyclisation being fast [12]. As such the preponderance of path A is due to a non-obvious preference for the catalyst to react at the oxygen bound allyl group, rather than a kinetic preference for the formation of five membered rings per se, and hence it might be possible to overcome this preference by catalyst or substrate design. As a thorough catalyst screen had already been undertaken attention turned to substrate design. Derivatives of (**2**) in which initial catalyst interaction at the oxygen-allyl group was rendered unfavorable, for example, by incorporation of a blocking group in this position, should direct initiation to the next most accessible position, i.e. the



Scheme 3.

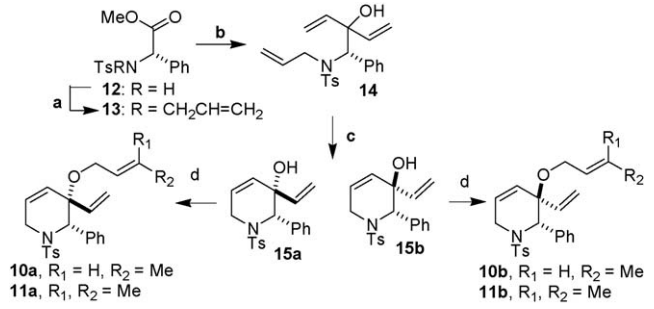


Scheme 5.

nitrogen-allyl group and the reaction would proceed through path B (Scheme 3). For this strategy to be effective three criteria must be met; firstly, the reaction could be directed through initial formation of the six membered rings; secondly, high selectivity for the desired six membered ring would still be obtained with these modified substrates; thirdly, these new six membered rings would cyclise with retention of stereochemistry.

The *O*-crotyl (**8**) and *O*-isopentyl (**9**) derivatives of (**2**) were considered as suitable substrates to test this hypothesis. Prior to undertaking the synthesis and double ring closing metathesis reaction of these substrates genuine samples of the putative new intermediates (**10a**), (**10b**), (**11a**), (**11b**) were prepared. In addition to aiding reaction analysis [13] this would allow for development of conditions to effect conversion of the proposed intermediates to (**3a**) or (**3b**) with retention of stereochemistry. These compounds were prepared in a straightforward manner as outlined in Scheme 4. Hence, allylation of the *N*-tosyl methyl ester (**12**) with allyl bromide and potassium carbonate in acetonitrile afforded the crude *N*-allyl amino ester (**13**). This was converted without further purification to the tertiary alcohol (**14**) in modest yield. The previously described non-selective RCM reaction [8] of this triene was used to advantage to afford samples of both (**15a**) and (**15b**) which were separable by chromatography and subsequent reaction of the alcohols with crotyl bromide or 4-bromo-2-metyl-2-butene in the presence of sodium hydride afforded the expected intermediates (**10**) and (**11**) for the proposed double RCM reaction.

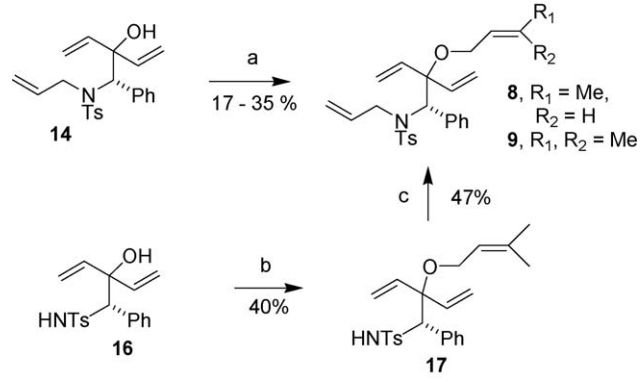
With compounds (**10**) and (**11**) in hand their conversion to (**3**) was addressed (Scheme 5). Gratifyingly, treatment of (**10a**) with either catalyst (**6**) or (**7**) gave exclusively (**3a**), and likewise (**3b**) was formed as the only product from (**10b**), indicating direct cyclisation with retention of stereochemistry is the only



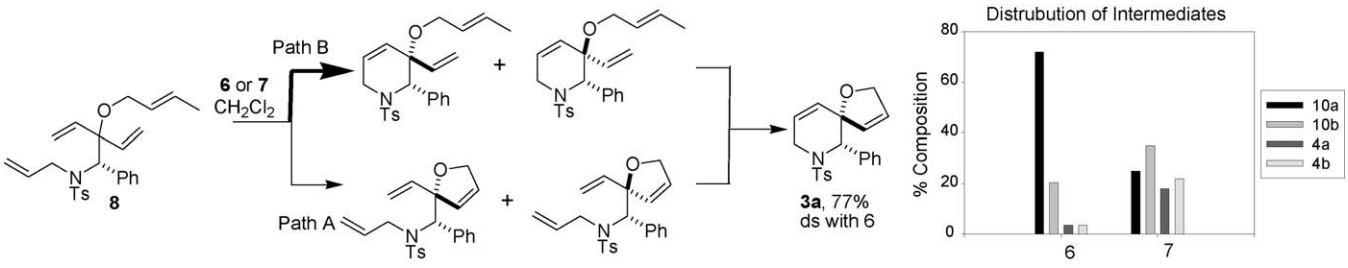
Scheme 4. Reagents and conditions: (a) K_2CO_3, MeCN, allyl bromide, RT, 16 h: (b) $CeCl_3$, THF, vinylmagnesium bromide, 0 °C, 1 h: (c) catalyst (**6**), CH_2Cl_2, RT, 2 h: (d) NaH, THF, DMPU, crotyl bromide or 4-bromo-2-methyl-2-butene.

mechanistic pathway operating in this reaction, and mirroring the reactions seen in the allyl series [8]. The more sterically hindered (**11a**) and (**11b**) did not react with either catalyst under a nitrogen atmosphere, however after activation with ethylene, catalyst (**7**) allowed for 50% conversion of (**11a**) to (**3a**) and (**11b**) to (**3b**) [14]. More encouragingly, carrying out this transformation in butene as solvent gave full conversion of either (**11a**) or (**11b**) to a single spirocycle. This reaction proceeded via the intermediacy of the crotyl species (**10a** or **10b**) resulting from an initial cross metathesis reaction with the solvent [15] and offers an efficient "in situ" method for activation of the hindered isopentenyl group. Neither the ethylene or butene activation proceedure was sufficient to allow catalyst (**6**) to be used with (**11**). Based on these results, formation of spirocyclic compounds from (**10**) or (**11**) is expected to proceed with retention of stereochemistry, but in the case of (**11**) a second generation catalyst and additional activation will be required.

With confirmation that any six membered ring intermediates would cyclise with retention of stereochemistry, attention turned to preparation of the desired tetraenes (Scheme 6). Alcohol (**14**) could be converted to (**8**) or (**9**), however yields in these reactions were low, possibly due to competing reactions of the oxygen anion. A more efficient route to generate useful amounts of material was found to be sequential alkylations of alcohol (**16**) – an intermediate in the original route to (**1**). Hence, alcohol (**16**) was treated with sodium hydride, followed by 1 equiv. of 4-bromo-2-methyl-2-butene, which gave preferential reaction at the oxygen anion to afford (**17**) in modest yield. Triene (**17**) was then converted to (**9**) in a straightforward manner. Although



Scheme 6. Reagents and conditions: (a) NaH, DMPU, 0 °C, crotyl bromide or 4-bromo-2-methyl-2-butene; (b) NaH, DMPU, 0 °C, 4-bromo-2-methyl-2-butene; (c) NaH, DMPU, RT, allyl bromide.



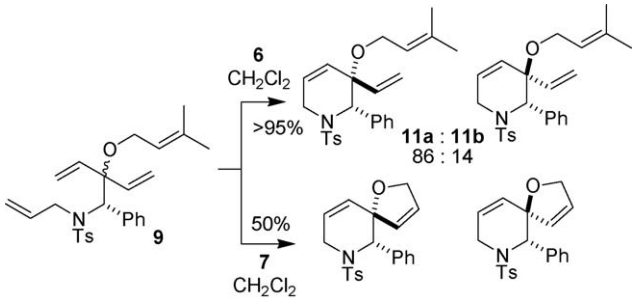
Scheme 7.

yields for the formation of (**8**) and (**9**) were less than optimum sufficient material was obtained to study the double RCM reaction.

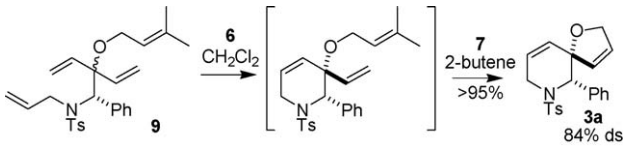
Treatment of a dichloromethane solution of (**8**) with catalyst (**6**) gave >95% conversion to a 77:23 ratio of (**3a**):(**3b**) after 16 h (Scheme 7). While this represents an improved selectivity compared to the original substrate (**2**) (68:32 with catalyst (**6**)) the increase was less significant than hoped for and the distribution of intermediates was examined. The use of the crotyl as a "blocking group" was found to be moderately effective with 93% of the reaction proceeding through path B, however the diastereoselection achieved within path B was *less than that obtained* in the allyl case with a 78:22 mixture of (**10a**) and (**10b**) being formed (cf. (**2**) affords (**5a**):(**5b**) = 90:10 with (**6**)). Coupled with the leakage to path A this distribution of intermediates accounts for the final stereochemical outcome of the reaction. As expected, treatment of (**8**) with catalyst (**7**) also gave good conversion to products, in a near identical ratio to that obtained from treatment of (**2**) with second-generation catalysts i.e. a slight preference for (**3b**). With the more reactive catalyst the blocking effect of the crotyl group was less effective (60% reaction through path B) and more significantly, as already shown when using second generation catalysts both path A and B are non-selective, leading to a near 1:1 mixture of (**3a**):(**3b**).

While the increase in diastereoselectivity for reaction of (**8**) was not as significant as hoped, the ability to direct the course of the reaction through path B had been demonstrated and reactions of (**9**) were explored. The isopentenyl group would be expected to completely block path A, and as subtle differences on the oxygen substituent (allyl versus crotyl) can have a significant effect on diastereoselectivity within path B an improved selectivity might still be obtained. Indeed reaction of (**9**) with catalyst (**6**) gave an 86:14 mixture of (**11a**) and (**11b**) with *no five membered rings detectable*, however as already demonstrated this catalyst was not reactive enough to convert these compound to the desired spirocycles. Reaction of (**9**) promoted by catalyst (**7**) gave about 50% conversion to spirocyclic products [16], with the reaction proceeding almost entirely through path B, but in line with results from (**2**) and (**8**), there is little diastereoselectivity (Scheme 8).

A solution to the problem was finally obtained by sequentially exploiting the selectivity that could be obtained with catalyst (**6**) and the reactivity of catalyst (**7**). Tetraene (**9**) was allowed to react with 5 mol% of catalyst (**6**) at 0 °C, which gave complete conversion to the two six membered rings (**11a**) and (**11b**) in an 84:16 ratio within 2 h, at which time solvent was



Scheme 8.



Scheme 9.

removed by nitrogen purge and replaced with butene. Catalyst (**7**) (10 mol%) was then added to the reaction mixture, allowing for the second cyclisation to take place via initial cross metathesis of the isopropenyl group with the solvent. The reaction proceeded to >95% conversion, and a final ratio of 84:16 (**3a**):(**3b**) was obtained, representing the best selectivity obtained to date for this transformation (Scheme 9). In line with results from cyclisations of isolated (**11a**) and (**11b**), no conversion of the intermediate mixture was seen in the absence of catalyst activation, and ethylene activation of (**7**) was only moderately effective, giving 50% conversion to spirocycles.

4. Conclusions

In conclusion, we have shown the course of a double RCM reaction can be diverted through a previously minor, but more selective pathway, to allow for higher selectivity to be obtained. Incorporation of blocking groups on the oxygen allyl group led to the reaction proceeding through initial formation of the six membered ring, with the selectivity depending on both the nature of the blocking group and the catalyst used. Judicious use of two catalysts allowed for the highest selectivity to be realized in the initial step, with a more reactive catalyst giving conversion to the desired spirocyclic product. While for practical purposes the extra synthetic steps required to differentiate the two allyl groups would make this a less attractive option that the original

cyclisation of (**2**) this study provides valuable insight into how controlling the order of ring closing events [17] can have a profound effect on the stereochemical outcome of the reaction.

Acknowledgments

We thank Dr. Simon Hamilton for the high-resolution mass spectral data, Dr. J.K.M. Brands for helpful discussions and Dr. Andrea Robinson (Monash University) for suggesting butenolysis as an alternative to ethenolysis for activation of the isopropenyl groups.

References

[1] (a) For recent reviews on ring closing alkene metathesis, see:. S.K. Armstrong, J. Chem. Soc., Perkin Trans. 1 (1998) 371;
(b) R.H. Grubbs, S. Chang, Tetrahedron 54 (1998) 4413;
(c) M.L. Snapper, A.H. Hoveyda (Eds.), Tetrahedron Symposium 55, 1999, p. 8141.;
(d) A. Furstner (Ed.), Top. Organomet. Chem. 1 (1998);
(e) S. Blechert, Pure Appl. Chem. 8 (1999) 1393;
(f) A. Furstner, Angew. Chem., Int. Ed. Engl. 39 (2000) 3012;
(g) T.M. Trnka, R.H. Grubbs, Acc. Chem. Res. 34 (2001) 18;
(h) R.R. Schrock, A.H. Hoveyda, Angew. Chem., Int. Ed. Engl. 42 (2003) 4592;
(i) M.A. Walters, Prog. Heterocycl. Chem. 15 (2003) 1;
(j) A. Deiters, S.F. Martin, Chem. Rev. 104 (2004) 2199;
(k) K.C. Nicolaou, P.G. Bulger, D. Sarlah, Angew. Chem., Int. Ed. Engl. 44 (2005) 4490.

[2] (a) For double RCM approaches to fused bicyclic compounds:. M. Lautens, G. Hughes, Angew. Chem., Int. Ed. Engl. 38 (1999) 129;
(b) M.J. Bassingdale, A.S. Edwards, P. Hamley, H. Adams, J.P.A. Harrity, Chem. Commun. (2000) 1035;
(c) M. Lautens, G. Hughes, V. Vunic, Can. J. Chem. 78 (2000) 868;
(d) S. Ma, B. Ni, Org. Lett. 4 (2002) 639;
(e) S. Ma, B. Ni, Z. Liang, J. Org. Chem. 69 (2004) 6305;
(f) M. Lautens, V. Zunic, Can. J. Chem. 82 (2004) 399.

[3] (a) For approaches to spirocyclic compounds:. M.J. Bassindale, P. Hamley, A. Leitner, J.P.A. Harrity, Tetrahedron Lett. 40 (1999) 3247;
(b) D.J. Wallace, C.J. Cowden, D.J. Kennedy, M.S. Ashwood, I.F. Cottrell, U.-H. Dolling, Tetrahedron Lett. 41 (2000) 2027;
(c) B. Schmidt, M. Westhus, Tetrahedron 56 (2000) 2421;
(d) B. Schmidt, H. Wildemann, J. Org. Chem. 65 (2000) 5817;
(e) B. Schmidt, H. Wildemann, J. Chem. Soc., Perkin Trans. 1 (2000) 2916;
(f) D.J. Wallace, P.G. Bulger, D.J. Kennedy, M.S. Ashwood, I.F. Cottrell, U.-H. Dolling, Synlett (2001) 357;
(g) M.-P. Heck, C. Baylon, S.P. Nolan, C. Mioskowski, Org. Lett. 3 (1989);
(h) R.A.J. Wybrow, L.A. Johnson, B. Auffray, W.J. Moran, H. Adams, J.P.A. Harrity, Tetrahedron Lett. 43 (2002) 7851;
(i) A.S. Edwards, R.A. Wybrow, C. Johnson, H. Adams, Harrity, Chem. Comm. (2002) 1542;
(j) D.J. Wallace, Tetrahedron Lett. 44 (2003) 2145;
(k) S.J. Dolman, R.R. Schrock, A.H. Hoveyda, Org. Lett. 5 (2003) 4899;
(l) R.A.J. Wybrow, N.G. Stevenson, J.P.A. Harrity, Synlett (2004) 140;
(m) R.A.J. Wybrow, A.S. Edwards, N.G. Stevenson, H. Adams, C. Johnstone, J.P.A. Harrity, Tetrahedron 60 (2004) 8869;
(n) T. Kato, K. Marubayahi, S. Takizawa, H. Sasai, Tetrahedron: Asymm. 15 (2004) 3693.

[4] (a) Other bicyclic systems:. G.C. Fu, R.H. Grubbs, J. Am. Chem. Soc. 114 (1992) 7324;
(b) G.C. Fu, S.Y. Nguyen, R.H. Grubbs, J. Am. Chem. Soc. 115 (1993) 9856;
C. Baylon, M.-P. Heck, C. Mioskowski, J. Org. Chem. 64 (1999) 3354;
(c) M. Trevitt, V. Gouverneur, Tetrahedron Lett. 40 (1999) 7333;
(d) J.S. Clark, O. Hamelin, Angew. Chem. Int. Ed. Eng. 39 (2000) 372;
(e) A. Ahmed, E. Ohler, J. Mulzer, Synthesis (2001) 2007;
(e) J.S. Clark, M.C. Kimber, J. Robertson, C.S.P. McErlean, C. Wilson, Angew. Chem. Int. Ed. Eng. 44 (2005) 6157.

[5] (a) For some examples of ring opening, double ring closing strategies see:. W.J. Zuercher, M. Hashimoto, R.H. Grubbs, J. Am. Chem. Soc. 118 (1996) 6634;
(b) W.J. Zuercher, M. Scholl, R.H. Grubbs, J. Org. Chem. 63 (1998) 4291;
(c) S.D. Burke, K.J. Quinn, V.J. Chen, J. Org. Chem. 63 (1998) 8628;
(d) K.C. Nicolaou, J.A. Vega, G. Vassilikogiannakis, Angew. Chem. Int. Ed. Eng. 40 (2001) 4441;
(e) M. Schaudt, S. Blechert, J. Org. Chem. 68 (2003) 2913;
(f) S. Ma, B. Ni, Chem. Eur. J. 10 (2004) 3286;
(g) M.W.B. Pfeiffer, A.J. Phillips, J. Am. Chem. Soc. 127 (2005) 5334.

[6] D.J. Wallace, J.M. Goodman, D.J. Kennedy, A.J. Davies, C.J. Cowden, M.S. Ashwood, I.F. Cottrell, U.-H. Dolling, P.J. Reider, Org. Lett. 3 (2001) 671.

[7] (a) J.J. Kulagowski, N.R. Curtis, C.J. Swain, B.J. Williams, Org. Lett. 3 (2001) 667;
(b) P.E. Maligres, M.M. Waters, J. Lee, R.A. Reamer, D. Askin, M.S. Ashwood, M. Cameron, J. Org. Chem. 67 (2002) 1093;
(c) C.E. Raab, D.C. Dean, D.G. Menlillo, J. Label. Compd. Radiopharm. 44 (2001) 815.

[8] D.J. Wallace, Tetrahedron Lett. 46 (2005) 591.

[9] A. Fürstner, Chem. Eur. J. 7 (2001) 4811–4820.

[10] (a) S.B. Garber, J.S. Kingsbury, B.L. Gray, A.H. Hoveyda, J. Am. Chem. Soc. 122 (2000) 8168;
(b) S. Gessler, S. Randl, S. Blechert, Tetrahedron Lett. 41 (2000) 9973.

[11] In this paper we use the term "first generation catalyst" to cover those lacking the dihydroimidazole ligand, e.g. (**6**) and "second generation catalyst" to cover those with the dihydroimidazole ligand, e.g. (**7**).

[12] (a) M. Ulman, R.H. Grubbs, Organometallics 17 (1998) 2484;
(b) T.R. Hoye, H. Zhao, Org. Lett. 1 (1999) 1123.

[13] Any reaction through path A would generate the same five membered rings as previously isolated, i.e. (**4a**) and (**4b**).

[14] (a) These reactions typically stalled at 50% conversion, which may be due to decomposition of the catalyst via the ruthenium methylidene which could be accelerated by the ethylene atmosphere, see:. S.H. Hong, M.W. Day, R.H. Grubbs, J. Am. Chem. Soc. 126 (2004) 7414;
(b) W.J. van Rensburg, P.J. Steynberg, W.H. Meyer, M. Kirt, G.S. Forman, J. Am. Chem. Soc. 126 (2004) 14332.

[15] A.J. Robinson, Contributed lecture at International Symposium on Olefin Metathesis and Related Chemistry, Poznan, Poland, August 2005.

[16] In the absence of further catalyst activation this reaction typically stalled at 50% conversion.

[17] (a) Relay RCM is an alternative method to control the order of ring closing events, see:. T.R. Hoye, C.S. Jeffrey, M.A. Tennakoon, J. Wang, H. Zhau, J. Am. Chem. Soc. 126 (2004) 10210;
(b) D.J. Wallace, Angew. Chem. Int. Ed. Eng. 44 (2005) 1912.