Diastereoselective Osmium-catalyzed Vicinal Oxyamination of Acyclic Allylic Alcohol Derivatives

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Abstract

The osmium-catalyzed oxyamination of chiral acyclic allylic alcohol derivatives bearing mono- and 1,1-di-substituted double bonds with benzyl *N*-(4-tosyloxy)carbamate proceeds with high regioselectivity and moderate levels of diastereoselectivity favoring the *anti* product. The observed stereoselectivity shows a clear and systematic trend with *anti:syn* ratios increasing in line with the size of substituent at both the allylic stereocenter and double bond α -carbon. The stereoinduction is in accord with the sense of diastereoselectivity predicted by Kishi's empirical rule and a previously reported transition state model for the osmium-catalyzed dihydroxylation of allylic alcohol derivatives. In contrast, allylic alcohol derivatives bearing trisubstituted double bonds show low or no reactivity in the oxyamination reaction affording the *syn* product in low yield in the cases examined.

Introduction

The osmium-catalyzed oxyamination of alkenes is among the most powerful and general of methods for the synthesis of the vicinal amino alcohol functional array^{1,2} and is typified by the catalytic Asymmetric Aminohydroxylation (AA) reaction developed by Sharpless and co-workers.^{3,4} The recent development of pre-formed nitrogen sources has improved the efficiency, chemoselectivity and control of the osmium-catalyzed oxyamination reaction. Advances include the development of the intramolecular Tethered Aminohydroxylation (TA) reaction⁵ of carbamates^{6,7} and amides⁸ that provides secure control over regioselectivity. The development of non-tethered pre-formed nitrogen sources has further expanded the scope of this process,⁹⁻¹² and includes the introduction of *N*-(4-chlorobenzoyloxy)carbamates which allow for the enantioselective intermolecular oxyamination of mono- and di-substituted alkenes in the presence of cinchona alkaloid-derived chiral ligands.^{9,10} We recently reported the development of *N*-(4-tosyloxy)carbamates as pre-formed nitrogen sources in the osmium-catalyzed vicinal oxyamination reaction of a range of mono-, di- and tri-substituted alkenes.¹² The reactions occur with low catalyst loadings and afford good regioselectivity for unsymmetrically substituted alkenes. However, preliminary investigations showed that these nitrogen sources could not be directly substituted for the *N*-chlorocarbamates in the Sharpless AA reaction.

The diastereoselectivity of the osmium-catalyzed oxyamination reaction of chiral alkenes is also of importance for the stereoselective synthesis of amino-alcohol containing products, either in its own right, or as a complicating factor in reactions promoted by chiral ligands. Several reports of diastereoselectivity the intermolecular oxyamination reaction serve to highlight the potential of this element of stereocontrol for the synthesis of amino alcohol containing compounds,^{4,13,14} including natural products.¹⁵⁻¹⁷ Despite these disclosures there have been few systematic investigations of the influence of diastereoselectivity in the oxyamination reaction. Recently, a study reported the influence of exocyclic stereochemistry on the on the intramolecular osmium-catalyzed TA reaction.¹⁴ Herein we disclose a study on the diastereoselectivity of the osmium-catalyzed intermolecular vicinal oxyamination of acyclic allylic alcohol derivatives with benzyl *N*-(4-tosyloxy)carbamate (**1**, Scheme 1). These reactions proceed with high regioselectivity and moderate levels of diastereoselectivity favoring the *anti* product for substrates bearing mono- and 1,1-di-substituted double bonds. The observed stereoselectivity shows a clear and systematic trend that varies with substrate substitution patterns. The stereoinduction is in accord with the sense of diastereoselectivity predicted by Kishi's empirical rule^{18,19} and conforms to a previously reported transition state model for the osmium-catalyzed dihydroxylation of allylic alcohol derivatives.²⁰ In

contrast, allylic alcohol derivatives bearing trisubstituted double bonds show low or no reactivity in the oxyamination reaction, affording the *syn* product in the two successful examples studied.

<Scheme 1 here>

Scheme 1. The oxyamination of acyclic allylic alcohol derivatives.

Materials and Methods

The general materials and methods are as previously reported.¹²

General procedure 1 for the osmium-catalyzed oxyamination reaction

To a stirred solution of allylic alcohol or derivative (1.0 equiv) and potassium osmate dihydrate (0.04 equiv) in acetonitrile/water (1:1, 5 mL mmol⁻¹ allylic alcohol or derivative) was added a solution of benzyl *N*-(4-tosyloxy)carbamate (**1**)¹² (1.2 equiv) in acetonitrile (5 mL mmol⁻¹ allylic alcohol or derivative) at 0 °C. The reaction mixture was stirred at room temperature until the reaction was complete. The reaction was quenched with aqueous sodium hydrogen sulfite (5.00 ml, 0.05 M) and then stirred for 30 min. The mixture was filtered through celite and extracted with ethyl acetate (3 × 10 ml). The combined organic extract was washed with brine (10 ml), dried over sodium sulfate and concentrated under reduced pressure to afford the crude product. Purification by flash chromatography provided the target compounds.

General procedure 2 for acetonide formation

To a stirred solution of diol (1.0 equiv) in dichloromethane (3 ml) and 2,2-dimethoxypropane (4.0 equiv) at room temperature was added camphorsulfonic acid (0.04 equiv) and *p*-toluenesulfonic acid (0.04 equiv). The reaction mixture was stirred until the reaction was complete. The reaction was quenched with aqueous sodium hydrogen carbonate (3.0 ml, 1.0 M), and extracted with dichloromethane (3 × 5 ml). The combined organic extract was washed with brine (5 ml), dried over sodium sulfate and concentrated under reduced pressure. Purification by flash chromatography afforded the target compounds.

***rac*-(2*R*,3*S*)-4-(Benzyloxycarbonylamino)-3-hydroxybutan-2-yl acetate (4a) and *rac*-(2*R*,3*R*)-4-(benzyloxycarbonylamino)-3-hydroxybutan-2-yl acetate (6a)**

The reaction was conducted according to general procedure 1 with *rac*-but-3-en-2-yl acetate (**2a**)²¹ (60.0 mg, 0.53 mmol), potassium osmate dihydrate (7.00 mg, 0.02 mmol) and benzyl *N*-(4-

tosyloxy)carbamate (**1**) (221 mg, 0.69 mmol). Purification by flash chromatography (30% ethyl acetate/*n*-hexane) afforded *rac*-(2*R*,3*S*)-4-(benzyloxycarbonylamino)-3-hydroxybutan-2-yl acetate (**4a**) as a colorless oil (42.4 mg, 29%), *R_f* 0.44 (70% ethyl acetate/*n*-hexane). IR (thin film, cm⁻¹) 3369 (O–H, N–H), 3066, 3034, 2981, 2925, 2825 (C–H), 1717 (C=O), 1533. ¹H-NMR (400 MHz, CDCl₃) 7.29–7.38 (5H, m, ArH), 5.29 (1H, s, NH), 5.07–5.13 (2H, m, CH₂Ar), 4.90 (1H, dq, *J* 6.1, 6.1 Hz, H2), 3.70 (1H, m, H3), 3.50 (1H, ddd, *J* 14.0, 6.8, 2.8 Hz, H4A), 3.11 (1H, m, H4B), 3.01 (1H, s, OH), 2.05 (3H, s, CH₃), 1.27 (3H, d, *J* 6.8 Hz, H1). ¹³C-NMR (100 MHz, CDCl₃) 170.83, 156.93, 136.26, 128.54, 128.19, 128.11, 73.08, 71.56, 66.96, 43.48, 21.19, 16.23. LRMS (ESI⁺) 304 ([M+Na]⁺, 100%), 238 (5), 178 (5), 120 (6), 91 (64). HRMS (ESI⁺) calcd for C₁₄H₂₀NO₅ ([M+H]⁺) 282.1341, found 282.1339; calcd for C₁₄H₁₉NO₅Na ([M+Na]⁺) 304.1161, found 304.1159.

A second fraction afforded *rac*-(2*R*,3*R*)-4-(benzyloxycarbonylamino)-3-hydroxybutan-2-yl acetate (**6a**) as a colorless oil (36.6 mg, 25%), *R_f* 0.40 (70% ethyl acetate/*n*-hexane). IR (thin film, cm⁻¹) 3400 (O–H, N–H), 3066, 3034, 2982, 2940 (C–H), 1721 (C=O), 1533. ¹H-NMR (400 MHz, CDCl₃) 7.30–7.38 (5H, m, ArH), 5.24 (1H, s, NH), 5.10 (2H, s, CH₂Ar), 4.91 (1H, dq, *J* 6.1, 6.1 Hz, H2), 3.74 (1H, m, H3), 3.66 (1H, m, H4A), 3.28 (1H, m, H4B), 2.60 (1H, s, OH), 2.08 (3H, s, CH₃), 1.28 (3H, d, *J* 6.8 Hz, H1). ¹³C-NMR (100 MHz, CDCl₃) 170.84, 157.48, 136.22, 128.54, 128.20, 128.12, 73.28, 71.62, 67.05, 42.95, 21.21, 15.63. LRMS (ESI⁺) 304 ([M+Na]⁺, 100%), 218 (4), 120 (6), 91 (56). HRMS (ESI⁺) calcd for C₁₄H₁₉NO₅Na ([M+Na]⁺) 304.1161, found 304.1161.

***rac*-Benzyl (2*S*,3*R*)-2,3-dihydroxybutylcarbamate (**5a**) and *rac*-benzyl (2*R*,3*R*)-2,3-dihydroxybutylcarbamate (**7a**)**

Procedure 1: The reaction was conducted according to general procedure 1 with *rac*-3-buten-2-ol (**3a**) (45.9 mg, 0.64 mmol), potassium osmate dihydrate (9.40 mg, 0.03 mmol) and benzyl *N*-(4-tosyloxy)carbamate (**1**) (246 mg, 0.76 mmol). Integration of the NH signal in the 400 MHz ¹H-NMR spectrum of the crude reaction mixture provided a 1.8:1 ratio of *rac*-benzyl (2*S*,3*R*)-2,3-dihydroxybutylcarbamate (**5a**) [δ 5.46 (1H, s, NH)] and *rac*-benzyl (2*R*,3*R*)-2,3-dihydroxybutylcarbamate (**7a**) [δ 5.37 (1H, s, NH)]. Purification by flash chromatography (gradient from 50% to 100% ethyl acetate/*n*-hexane) afforded an inseparable mixture of two diastereomers as a colorless oil (121 mg, 79%), *R_f* 0.11 (60% ethyl acetate/*n*-hexane). HRMS (ESI⁺) calcd for C₁₂H₁₇NO₄Na ([M+Na]⁺) 262.1055, found 262.1049.

Procedure 2: To a solution of *rac*-(2*R*,3*S*)-4-(benzyloxycarbonylamino)-3-hydroxybutan-2-yl acetate (**4a**) (20.0 mg, 0.07 mmol) was added a solution of potassium carbonate (23.1 mg, 0.17

mmol) in methanol (3 ml) and water (1 ml) at 20 °C. This mixture was stirred at room temperature until the reaction was complete (2 h). The reaction was quenched with aqueous hydrochloric acid (1.0 ml, 1.0 M) and extracted with dichloromethane (3 × 10 ml). The combined organic extract was washed with brine (5 ml) dried over sodium sulfate and concentrated under reduced pressure to afford *rac*-benzyl (2*S*,3*R*)-2,3-dihydroxybutylcarbamate (**5a**) as a colorless oil (17.0 mg, 100%), *R_f* 0.18 (70% ethyl acetate/*n*-hexane). IR (thin film, cm⁻¹) 3341 (O–H), 3065, 3034, 2970, 2926 (C–H), 1695 (C=O), 1534. ¹H-NMR (400 MHz, CDCl₃) 7.30–7.38 (5H, m, ArH), 5.30 (1H, s, NH), 5.11 (2H, s, CH₂Ar), 3.75 (1H, m, H₃), 3.55 (1H, m, H₂), 3.35–3.43 (2H, m, H₁), 2.79 (1H, s, OH), 1.70 (1H, s, OH), 1.22 (3H, d, *J* 6.4 Hz, H₄). ¹³C-NMR (100 MHz, CDCl₃) 157.90, 136.16, 128.55, 128.25, 128.13, 75.05, 68.40, 67.15, 42.83, 18.41. LRMS (ESI+) 262 ([M+Na]⁺, 62%), 259 (6), 196 (10), 181 (5), 120 (4), 91 (100), 60 (6). HRMS (ESI+) calcd for C₁₂H₁₇NO₄Na ([M+Na]⁺) 262.1055, found 262.1053.

***rac*-Benzyl [(4*S*,5*R*)-2,2,5-trimethyl-1,3-dioxolan-4-yl]methylcarbamate (**17**)**

The reaction was conducted according to general procedure 2 with *rac*-benzyl (2*S*,3*R*)-2,3-dihydroxybutylcarbamate (**5a**) (16.4 mg, 0.07 mmol), 2,2-dimethoxypropane (35.7 mg, 0.34 mmol), camphorsulfonic acid (0.600 mg, 0.003 mmol) and *p*-toluenesulfonic acid (0.500 mg, 0.003 mmol). Purification by flash chromatography (20% ethyl acetate/*n*-hexane) afforded *rac*-benzyl [(4*S*,5*R*)-2,2,5-trimethyl-1,3-dioxolan-4-yl]methylcarbamate (**17**) as a colorless oil (10.1 mg, 53%). IR (thin film, cm⁻¹) 3340 (N–H), 3065, 3034, 2985, 2936 (C–H), 1722 (C=O), 1532. ¹H-NMR (400 MHz, CDCl₃) 7.30–7.37 (5H, m, ArH), 5.11 (2H, s, CH₂Ar), 5.07 (1H, s, NH), 4.33 (1H, dq, *J* 6.3, 6.3 Hz, H₅), 4.11 (1H, m, H₄), 3.48 (1H, m, CH_AH_BNH), 3.05 (1H, m, CH_AH_BNH), 1.44 (3H, s, CH₃), 1.33 (3H, s, CH₃), 1.23 (3H, d, *J* 6.4 Hz, CH₃). ¹³C-NMR (100 MHz, CDCl₃) 156.39, 136.45, 128.49, 128.11, 128.10, 108.09, 76.63, 72.61, 66.80, 41.59, 28.26, 25.51, 14.45. LRMS (ESI+) 302 ([M+Na]⁺, 88%), 222 (5), 181 (6), 149 (4), 91 (100). HRMS (ESI+) calcd for C₁₅H₂₁NO₄Na ([M+Na]⁺) 302.1368, found 302.1368.

***rac*-(2*S*,3*R*)-1-(Benzyloxycarbonylamino)-2-hydroxypentan-3-yl acetate (**4b**) and *rac*-(2*R*,3*R*)-1-(benzyloxycarbonylamino)-2-hydroxypentan-3-yl acetate (**6b**)**

The reaction was conducted according to general procedure 1 with *rac*-pent-1-en-3-yl acetate (**2b**)²² (53.9 mg, 0.42 mmol), potassium osmate dihydrate (6.00 mg, 0.02 mmol) and benzyl *N*-(4-tosyloxy)carbamate (**1**) (165 mg, 0.51 mmol). Purification by flash chromatography (40% ethyl acetate/*n*-hexane) afforded *rac*-(2*S*,3*R*)-1-(benzyloxycarbonylamino)-2-hydroxypentan-3-yl acetate (**4b**) as a colorless oil (53.1 mg, 43%), *R_f* 0.46 (65% ethyl acetate/*n*-hexane). IR (thin film, cm⁻¹)

3400 (O–H, N–H), 3066, 3034, 2935, 2882, 2853 (C–H), 1713, 1701 (C=O), 1537. ¹H-NMR (400 MHz, CDCl₃) 7.30–7.36 (5H, m, ArH), 5.29 (1H, s, NH), 5.07–5.14 (2H, m, CH₂Ar), 4.82 (1H, m, H3), 3.73 (1H, m, H2), 3.54 (1H, m, H1A), 3.06 (1H, ddd, *J* 14.0, 6.8, 4.8 Hz, H1B), 2.99 (1H, s, OH), 2.08 (3H, s, CH₃), 1.62–1.76 (2H, m, H4), 0.93 (3H, t, *J* 7.2 Hz, H5). ¹³C-NMR (400 MHz, CDCl₃) 171.55, 157.63, 136.23, 128.53, 128.19, 128.11, 76.32, 72.26, 67.05, 42.90, 23.31, 21.01, 9.69. LRMS (ESI+) 318 ([M+Na]⁺, 100%), 270 (5), 184 (6), 120 (8), 91 (68), 84 (8), 69 (4). HRMS (ESI+) calcd for C₁₅H₂₁NO₅Na ([M+Na]⁺) 318.1317, found 318.1318.

A second fraction afforded *rac*-(2*R*,3*R*)-1-(benzyloxycarbonylamino)-2-hydroxypentan-3-yl acetate (**6b**) as a colorless oil (34.8 mg, 28%), *R_f* 0.36 (65% ethyl acetate/*n*-hexane). IR (thin film, cm⁻¹) 3369 (O–H, N–H), 3034, 2924, 2853 (C–H), 1713 (C=O), 1537. ¹H-NMR (400 MHz, CDCl₃) 7.29–7.38 (5H, m, ArH), 5.33 (1H, s, NH), 5.09–5.10 (2H, m, CH₂Ar), 4.81 (1H, m, H3), 3.74 (1H, m, H2), 3.60 (1H, m, H1A), 3.26 (1H, m, H1B), 2.68 (1H, m, OH), 2.05–2.11 (3H, m, CH₃), 1.62–1.72 (2H, m, H4), 0.90 (3H, t, *J* 6.8 Hz, H5). ¹³C-NMR (100 MHz, CDCl₃) 171.35, 157.22, 136.29, 128.53, 128.27, 128.17, 75.86, 71.52, 67.14, 43.71, 25.91, 20.99, 10.21. LRMS (ESI+) 318 ([M+Na]⁺, 90%), 91 (100). HRMS (ESI+) calcd for C₁₅H₂₁NO₅Na ([M+Na]⁺) 318.1317, found 318.1318.

***rac*-Benzyl (2*S*,3*R*)-2,3-dihydroxypentylcarbamate (**5b**) and *rac*-benzyl (2*R*,3*R*)-2,3-dihydroxypentylcarbamate (**7b**)**

Procedure 1: The reaction was conducted according to general procedure 1 with *rac*-1-penten-3-ol (**3b**)²² (36.0 mg, 0.42 mmol), potassium osmate dihydrate (6.20 mg, 16.8 μmol) and benzyl *N*-(4-tosyloxy)carbamate (**1**) (148 mg, 0.46 mmol). Integration of the NH signals in the 400 MHz ¹H-NMR spectrum of the crude reaction mixture provided a 2.1:1 ratio of *rac*-benzyl (2*S*,3*R*)-2,3-dihydroxypentylcarbamate (**5b**) [δ 5.32 (1H, s, NH)] and *rac*-benzyl (2*R*,3*R*)-2,3-dihydroxypentylcarbamate (**7b**) [δ 5.25 (1H, s, NH)]. Purification by flash chromatography (60% ethyl acetate/*n*-hexane) afforded an inseparable mixture of two diastereomers as a white solid (58.9 mg, 55%), *R_f* 0.19 (60% ethyl acetate/*n*-hexane). HRMS (ESI+) calcd for C₁₃H₁₉NO₄Na ([M+Na]⁺) 276.1212, found 276.1213.

Procedure 2: To a solution of *rac*-(2*S*,3*R*)-1-(benzyloxycarbonylamino)-2-hydroxypentan-3-yl acetate (**4b**) (20.0 mg, 0.07 mmol) was added a solution of potassium carbonate (23.1 mg, 0.17 mmol) in methanol (3.0 ml) and water (1.0 ml) at 20 °C. This reaction mixture was stirred until the reaction was complete (2 h). The reaction was quenched with aqueous hydrochloric acid (1.0 ml, 1.0 M) and extracted with dichloromethane (3 × 10 ml). The combined organic extract was washed

with brine (5 ml), dried over sodium sulfate and concentrated under reduced pressure to afford *rac*-benzyl (2*S*,3*R*)-2,3-dihydroxypentylcarbamate (**5b**) as a colorless oil (15.1 mg, 88%), *R_f* 0.37 (70% ethyl acetate/*n*-hexane). IR (thin film, cm⁻¹) 3330 (broad, O–H, N–H), 2961, 2926 (C–H), 1689 (C=O), 1547. ¹H-NMR (400 MHz, CDCl₃) 7.30–7.37 (5H, m, ArH), 5.19 (1H, s, NH), 5.12 (2H, s, CH₂Ar), 3.59 (1H, m, H3), 3.39–3.49 (3H, m, H1 and H2), 2.58 (1H, s, OH), 2.51 (1H, s, OH), 1.62–1.43 (2H, m, H4), 1.01 (3H, t, *J* 7.2 Hz, H5). ¹³C-NMR (100 MHz, CDCl₃) 157.94, 136.17, 128.54, 128.24, 128.13, 73.86, 73.78, 67.14, 42.83, 25.49, 10.14. LRMS (ESI⁺) 276 ([M+Na]⁺, 100%), 181 (7), 149 (12), 120 (4), 107 (5), 91 (68). HRMS (ESI⁺) calcd for C₁₃H₁₉NO₄Na ([M+Na]⁺) 276.1212, found 276.1212.

***rac*-(2*S*,3*R*)-1-(Benzyloxycarbonylamino)-2-hydroxy-4-methylpentan-3-yl acetate (**4c**) and *rac*-(2*R*,3*R*)-1-(benzyloxycarbonylamino)-2-hydroxy-4-methylpentan-3-yl acetate (**6c**)**

The reaction was conducted according to general procedure 1 with *rac*-4-methylpent-1-en-3-yl acetate (**2c**)²² (60.0 mg, 0.42 mmol), potassium osmate dihydrate (6.2 mg, 0.02 mmol) and benzyl *N*-(4-tosyloxy)carbamate (**1**) (163 mg, 0.51 mmol). Purification by flash chromatography (30% ethyl acetate/*n*-hexane) afforded *rac*-(2*S*,3*R*)-1-(benzyloxycarbonylamino)-2-hydroxy-4-methylpentan-3-yl acetate (**4c**) as a colorless oil (62.2 mg, 48%), *R_f* 0.55 (65% ethyl acetate/*n*-hexane). Further purification was conducted by HPLC (SunFire Prep Silica 5 μm, 3% isopropanol 97% *n*-hexane, flow rate 10 ml/min) to give compound **4c** (*t_R* 8.9 min). IR (thin film, cm⁻¹) 3407 (O–H, N–H), 3090, 3066, 3034, 2965, 2938, 2878 (C–H), 1721 (C=O), 1530. ¹H-NMR (400 MHz, CDCl₃) 7.29–7.36 (5H, m, ArH), 5.35 (1H, s, NH), 5.06–5.15 (2H, m, CH₂Ar), 4.75 (1H, dd, *J* 6.8, 4.8 Hz, H3), 3.79 (1H, m, H2), 3.59 (1H, m, H1A), 2.99 (1H, ddd, *J* 14.4, 6.4, 4.8 Hz, H1B), 2.03–2.11 (4H, m, H4 and CH₃), 1.66 (1H, s, OH), 0.93–0.94 (6H, m, 2 × CH₃). ¹³C-NMR (100 MHz, CDCl₃) 171.80, 157.89, 136.22, 128.52, 128.18, 128.10, 78.46, 70.53, 67.07, 42.99, 28.20, 20.88, 19.54, 16.65. LRMS (ESI⁺) 332 ([M+Na]⁺, 98%), 293 (10), 266 (5), 250 (6), 232 (7), 188 (8), 120 (11), 91 (100), 81 (8). HRMS (ESI⁺) calcd for C₁₆H₂₄NO₅ ([M+H]⁺) 310.1654, found 310.1654; HRMS (ESI⁺) calcd for C₁₆H₂₃NO₅Na ([M+Na]⁺) 332.1474, found 332.1474.

A second fraction afforded *rac*-(2*R*,3*R*)-1-(benzyloxycarbonylamino)-2-hydroxy-4-methylpentan-3-yl acetate (**6c**) as a colorless oil (26.1 mg, 20%), *R_f* 0.29 (65% ethyl acetate/*n*-hexane). Further purification was conducted by HPLC (SunFire Prep Silica 5 μm, 5% isopropanol 95% *n*-hexane, flow rate 10 ml/min) to give compound **6c** (*t_R* 14.8 min). IR (thin film, cm⁻¹) 3406 (O–H, N–H), 3065, 3033, 2966, 2877 (C–H), 1718 (C=O), 1528. ¹H-NMR (400 MHz, CDCl₃) 7.30–7.36 (5H, m, ArH), 5.26 (1H, s, NH), 5.10 (2H, s, CH₂Ar), 4.64 (1H, dd, *J* 7.6, 3.2 Hz, H3), 3.87 (1H, m, H2),

3.27 (1H, m, H1A), 3.14 (1H, m, H1B), 2.35 (1H, d, J 7.2 Hz, OH), 2.06–2.14 (4H, m, H4 and CH₃), 0.95 (3H, d, J 6.8 Hz, CH₃), 0.91 (3H, d, J 7.2 Hz, H5). ¹³C-NMR (100 MHz, CDCl₃) 171.49, 156.91, 136.29, 128.52, 128.16, 128.09, 78.99, 70.10, 66.92, 44.13, 28.61, 20.84, 19.08, 18.15. LRMS (ESI⁺) 332 ([M+Na]⁺, 100%), 246 (5), 91 (21). HRMS (ESI⁺) calcd for C₁₆H₂₃NO₅Na ([M+Na]⁺) 332.1474, found 332.1473.

***rac*-Benzyl (2*S*,3*R*)-2,3-dihydroxy-4-methylpentylcarbamate (5c) and *rac*-benzyl (2*R*,3*R*)-2,3-dihydroxy-4-methylpentylcarbamate (7c)**

The reaction was conducted according to general procedure 1 with *rac*-4-methyl-1-penten-3-ol (**3c**)²² (41.7 mg, 0.42 mmol), potassium osmate dihydrate (6.1 mg, 16.6 μmol) and benzyl *N*-(4-tosyloxy)carbamate (**1**) (161 mg, 0.50 mmol). Integration of NH signal of 400 MHz ¹H-NMR spectrum of the crude reaction mixture showed a 3.1:1 ratio of *rac*-benzyl (2*S*,3*R*)-2,3-dihydroxy-4-methylpentylcarbamate (**5c**) and *rac*-benzyl (2*R*,3*R*)-2,3-dihydroxy-4-methylpentyl-carbamate (**7c**). Purification by flash chromatography (50% ethyl acetate/*n*-hexane) afforded an inseparable mixture of two diastereomers as a colorless oil (81.3 mg, 73%), R_f 0.22 (5:2:3 ethyl acetate/dichloromethane/*n*-hexane). IR (thin film, cm⁻¹) 3405 (O–H, N–H), 3067, 3034, 2960, 2930, 2875 (C–H), 1695 (C=O), 1532. ¹H-NMR (400 MHz, CDCl₃) 7.29–7.37 (5H, m, ArH), 5.40 (1H, m, NH) and 5.30* (1H, s, NH*), 5.07–5.14 (2H, m, CH₂Ar), 3.70 (1H, m, H3), 3.36–3.42 (2H, m, H2 and H1A), 3.31 (1H, m, H1B), 2.88 (1H, s, OH), 2.76 (1H, s, OH), 1.82 (1H, m, H4), 0.96–0.95 (6H, m, 2 × CH₃) and 0.92* (3H, d, J 6.8 Hz, CH₃*). ¹³C-NMR (100 MHz, CDCl₃) 157.93 (157.48*), 136.22, 128.54, 128.22, 128.11, 77.16, 71.61 (70.64*), 67.09, 42.90 (44.41*), 29.31 (29.66*), 19.33, 17.10 (18.03*). LRMS (ESI⁺) 290 ([M+Na]⁺, 100%), 91 (38). HRMS (ESI⁺) calcd for C₁₄H₂₁NO₄Na ([M+Na]⁺) 290.1368, found 290.1360. (* indicates peaks of the minor diastereomer).

***rac*-Benzyl (2*S*,3*R*)-2-hydroxy-3-(4-methoxybenzyloxy)-2-methylbutylcarbamate (11a) and *rac*-benzyl (2*R*,3*R*)-2-hydroxy-3-(4-methoxybenzyloxy)-2-methylbutylcarbamate (14a)**

The reaction was conducted according to general procedure 1 with *rac*-1-methoxy-4-[(3-methylbut-3-en-2-yloxy)methyl]benzene (**8a**)²³ (35.0 mg, 0.17 mmol), potassium osmate dihydrate (2.50 mg, 0.01 mmol) and benzyl *N*-(4-tosyloxy)carbamate (**1**) (65.4 mg, 0.20 mmol). Integration of the C2–CH₃ signals in the 400 MHz ¹H-NMR spectrum of the crude reaction mixture showed a 2.6:1 ratio of *rac*-benzyl (2*S*,3*R*)-2-hydroxy-3-(4-methoxybenzyloxy)-2-methylbutylcarbamate (**11a**) [δ 1.09 (3H, s, CH₃)] and *rac*-benzyl (2*R*,3*R*)-2-hydroxy-3-(4-methoxybenzyloxy)-2-methylbutylcarbamate (**14a**) [δ 1.11 (3H, s, CH₃)]. Purification by flash chromatography (30% ethyl acetate/*n*-hexane) afforded an inseparable mixture of two diastereomers as a yellow oil (43.6 mg, 69%), R_f 0.23 (40%

ethyl acetate/*n*-hexane). Further purification by preparative HPLC (μ Porasil silica 10 μ m, 3.9×300 mm, solvent 1% isopropanol/*n*-hexane, flow rate 0.7 ml/min) afforded *rac*-benzyl (2*R*,3*R*)-2-hydroxy-3-(4-methoxybenzyloxy)-2-methylbutylcarbamate (**14a**) (t_R 31.8 min) as a colorless oil. IR (thin film, cm^{-1}) 3419 (N–H, O–H), 3066, 3033, 2976, 2936, 2837 (C–H), 1717 (C=O), 1612, 1586 (C=C), 1514. ^1H -NMR (400 MHz, CDCl_3) 7.29–7.36 (5H, m, ArH), 7.24 (2H, d, J 8.4 Hz, ArH), 6.87 (2H, d, J 8.4 Hz, ArH), 5.10 (3H, s, broad, NH and CH_2), 4.60 (1H, d, J 10.8 Hz, $\text{CH}_\text{A}\text{H}_\text{B}\text{Ar}$), 4.31 (1H, d, J 11.2 Hz, $\text{CH}_\text{A}\text{H}_\text{B}\text{Ar}$), 3.79 (3H, s, OCH_3), 3.42 (1H, q, J 6.4 Hz, H3), 3.31 (1H, dd, J 13.6, 5.6 Hz, H1A), 3.20 (1H, dd, J 13.6, 6.6 Hz, H1B), 2.65 (1H, s, OH), 1.19 (3H, d, J 6.4 Hz, H4), 1.09 (3H, s, CH_3). ^{13}C -NMR (100 MHz, CDCl_3) 159.31, 156.82, 136.58, 130.14, 129.42, 128.48, 128.06, 128.01, 113.89, 77.95, 74.24, 70.79, 66.70, 55.24, 47.75, 20.22, 13.57. LRMS (ESI+) 396 ($[\text{M}+\text{Na}]^+$, 75%), 121 (100). HRMS (ESI+) calcd for $\text{C}_{21}\text{H}_{27}\text{NO}_5\text{Na}$ ($[\text{M}+\text{Na}]^+$) 396.1787, found 396.1790.

A second fraction afforded *rac*-benzyl (2*S*,3*R*)-2-hydroxy-3-(4-methoxybenzyloxy)-2-methylbutylcarbamate (**11a**) (t_R 36.4 min) as a colorless oil. IR (thin film, cm^{-1}) 3418 (N–H, O–H), 3065, 3033, 2975, 2936, 2874, 2837 (C–H), 1705 (C=O), 1612, 1586 (C=C), 1513. ^1H -NMR (400 MHz, CDCl_3) 7.29–7.38 (5H, m, ArH), 7.23 (2H, d, J 8.4 Hz, ArH), 6.86 (2H, d, J 8.8 Hz, ArH), 5.08 (3H, s, broad, NH and CH_2Ar), 4.60 (1H, d, J 10.8 Hz, $\text{CH}_\text{A}\text{H}_\text{B}\text{Ar}$), 4.30 (1H, d, J 11.6 Hz, $\text{CH}_\text{A}\text{H}_\text{B}\text{Ar}$), 3.77 (3H, s, OCH_3), 3.46 (1H, q, J 6.0 Hz, H3), 3.36 (1H, dd, J 14.0, 8.0 Hz, H1A), 3.20 (1H, dd, J 13.6, 3.6 Hz, H1B), 2.89 (1H, s, OH), 1.21 (3H, d, J 6.0 Hz, H4), 1.11 (3H, s, CH_3). ^{13}C -NMR (100 MHz, CDCl_3) 159.32, 157.34, 136.55, 130.13, 129.39, 128.47, 128.03, 127.98, 113.92, 79.37, 73.98, 70.76, 66.73, 55.23, 46.88, 21.05, 13.50. LRMS (ESI+) 396 ($[\text{M}+\text{Na}]^+$, 75%), 121 (100). HRMS (ESI+) calcd for $\text{C}_{21}\text{H}_{27}\text{NO}_5\text{Na}$ ($[\text{M}+\text{Na}]^+$) 396.1787, found 396.1788).

***rac*-Benzyl (2*S*,3*R*)-2,3-dihydroxy-2-methylbutylcarbamate (13a)**

To a stirred solution of *rac*-benzyl (2*S*,3*R*)-2-hydroxy-3-(4-methoxybenzyloxy)-2-methylbutylcarbamate (**11a**) (19 mg, 51 μ mol) in a mixture of dichloromethane (459 μ l) and water (51 μ l) at 0 $^\circ\text{C}$ was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (14 mg, 61 μ mol). Following overnight stirring, the reaction mixture was diluted with dichloromethane (1 ml). The reaction was quenched with saturated aqueous sodium hydrogen carbonate (1.5 ml) and the crude product was extracted into ethyl acetate (5×1 ml). The combined organic extract was washed with saturated aqueous sodium hydrogen carbonate and brine, dried over magnesium sulfate and concentrated under reduced pressure to afford the crude product. Purification by flash chromatography (30 to 100% ethyl acetate/40–60 petroleum spirit) afforded the title compound **13a** as a colorless oil (4

mg, 30%). The identity was confirmed by ^1H and ^{13}C NMR comparison with authentic *rac*-benzyl (2*S*,3*R*)-2,3-dihydroxy-2-methylbutylcarbamate.¹²

***rac*-1-Methoxy-4-[(2-methylpent-1-en-3-yloxy)-methyl]-benzene (8b)**

To a stirred solution of *rac*-2-methylpent-1-en-3-ol (**10b**)²⁴ (800 mg, 7.99 mmol) and sodium hydride (383 mg, 16.0 mmol) in dichloromethane (5.0 ml) at 0 °C under nitrogen was added *p*-methoxybenzyl chloride (1.38 g, 8.81 mmol). The reaction mixture was stirred at room temperature until the reaction was complete (24 h). The reaction was quenched with aqueous sodium hydrogen carbonate (5.0 ml, 1.0 M), and the layers were separated. The aqueous layer was further extracted with dichloromethane (3 × 5 ml). The combined organic extract was washed with brine (10 ml), dried over sodium sulfate and concentrated under reduced pressure to afford the crude product. Purification by flash chromatography (2% ethyl acetate/*n*-hexane) afforded the title compound **8b** as a colorless oil (1.18 mg, 67%), R_f 0.27 (5% ethyl acetate/*n*-hexane). IR (thin film, cm^{-1}) 3071, 3034, 2963, 2936, 2874, 2836 (C–H), 1649, 1613 (C=C), 1586, 1513. ^1H -NMR (400 MHz, CDCl_3) 7.23–7.26 (2H, m, ArH), 6.84–6.87 (2H, m, ArH), 4.96–4.95 (1H, m, H1A), 4.89 (1H, m, H1B), 4.43 (1H, d, J 11.2 Hz, $\text{CH}_\text{A}\text{H}_\text{B}\text{Ar}$), 4.18 (1H, d, J 11.6 Hz, $\text{CH}_\text{A}\text{H}_\text{B}\text{Ar}$), 3.79 (3H, s, OCH_3), 3.59 (1H, t, J 6.8 Hz, H3), 1.42–1.68 (5H, m, H4 and CH_3), 0.89 (3H, t, J 7.6 Hz, H5). ^{13}C -NMR (100 MHz, CDCl_3) 158.99, 144.55, 130.99, 129.31, 113.72, 113.69, 84.55, 69.48, 55.24, 26.45, 16.46, 10.22. LRMS (EI⁺) 220 (M^+ , 5%), 137 (62), 121 (100), 109 (8), 91 (6), 84 (20), 77 (15), 69 (19), 65 (4), 55 (10). HRMS (EI⁺) calcd for $\text{C}_{14}\text{H}_{20}\text{O}_2$ (M^+) 220.1463, found 220.1466.

***rac*-Benzyl (2*S*,3*R*)-2-hydroxy-3-(4-methoxybenzyloxy)-2-methylpentylcarbamate (11b) and *rac*-benzyl (2*R*,3*R*)-2-hydroxy-3-(4-methoxybenzyloxy)-2-methylpentylcarbamate (14b)**

The reaction was conducted according to general procedure 1 with *rac*-1-methoxy-4-[(2-methylpent-1-en-3-yloxy)methyl]benzene (**8b**) (65.0 mg, 0.30 mmol), potassium osmate dihydrate (4.40 mg, 0.01 mmol) and benzyl *N*-(4-tosyloxy)carbamate (**1**) (114 mg, 0.35 mmol). Integration of the $\text{C2}-\text{CH}_3$ signal of the 400 MHz ^1H -NMR spectrum of the crude reaction mixture showed a 4.9:1 ratio of *rac*-benzyl (2*S*,3*R*)-2-hydroxy-3-(4-methoxybenzyloxy)-2-methylpentylcarbamate (**11b**) [δ 1.14 (3H, s, CH_3)] and *rac*-benzyl (2*R*,3*R*)-2-hydroxy-3-(4-methoxybenzyloxy)-2-methylpentylcarbamate (**14b**) [δ 1.11* (3H, s, CH_3^*)]. Purification by flash chromatography (20% ethyl acetate/*n*-hexane) afforded an inseparable mixture of two diastereomers as a colorless oil (49.9 mg, 44%), R_f 0.33 (40% ethyl acetate/*n*-hexane). IR (thin film, cm^{-1}) 3401 (O–H, N–H), 3066, 3033, 2966, 2932, 2877 (C–H), 1697 (C=O), 1529. ^1H -NMR (400 MHz, CDCl_3) 7.27–7.37 (5H, m, ArH), 7.25 (2H, d, J 8.4 Hz, ArH), 6.86 (2H, d, J 8.8 Hz, ArH), 5.21 (1H, s, NH), 5.09–5.12 (2H,

m, ArCH₂), 4.65 (1H, d, *J* 10.4 Hz, CH_AH_B), 4.50 (1H, d, *J* 11.2 Hz, CH_AH_B), 3.78 (3H, s, OCH₃), 3.35 (1H, dd, *J* 14.0, 8.0 Hz, H1A), 3.26 (1H, dd, *J* 8.8, 3.6 Hz, H3), 3.21 (1H, dd, *J* 13.6, 3.6 Hz, H1B), 2.69 (1H, s, OH), 1.69 (1H, m, H4A), 1.55 (1H, m, H4B), 1.14 (3H, s, CH₃) and 1.11* (3H, s, CH₃*), 1.07 (3H, t, *J* 7.6 Hz, H5) and 1.04* (3H, t, *J* 7.6 Hz, H5*). ¹³C-NMR (100 MHz, CDCl₃) 159.34, 157.31, 136.57, 130.39, 129.39, 128.47, 128.03, 127.97, 113.94, 86.90 (84.54*), 74.51, 74.42, 66.73 (66.94*), 55.24, 47.30 (48.08*), 23.69 (23.48*), 21.93 (20.70*), 11.82 (11.29*). LRMS (ESI+) 410 ([M+Na]⁺, 100%), 121 (16). HRMS (ESI+) calcd for C₂₂H₂₉NO₅Na ([M+Na]⁺) 410.1943, found 410.1938. (*Indicates signals of the minor diastereomer)

***rac*-(2*S*,3*R*)-1-(benzyloxycarbonylamino)-2-hydroxy-2-methylpentan-3-yl acetate (12b) and *rac*-(2*R*,3*R*)-1-(benzyloxycarbonylamino)-2-hydroxy-2-methylpentan-3-yl acetate (15b)**

The reaction was conducted according to general procedure 1 with *rac*-2-methylpent-1-en-3-yl acetate (**9b**)²⁵ (56.0 mg, 0.39 mmol), potassium osmate dihydrate (5.80 mg, 0.02 mmol) and benzyl *N*-(4-tosyloxy)carbamate (**1**) (190 mg, 0.59 mmol). Purification by flash chromatography (30% ethyl acetate/*n*-hexane) afforded *rac*-(2*S*,3*R*)-1-(benzyloxycarbonylamino)-2-hydroxy-2-methylpentan-3-yl acetate (**12b**) as a colorless oil (67.0 mg, 55%). *R*_f 0.33 (50% ethyl acetate/*n*-hexane). IR (thin film, cm⁻¹) 3744 (O–H), 3414 (N–H), 3066, 3033, 2974, 2938, 2879 (C–H), 1722 (C=O), 1524. ¹H-NMR (400 MHz, CDCl₃) 7.29–7.36 (5H, m, ArH), 5.44 (1H, s, NH), 5.07–5.16 (2H, m, CH₂Ar), 4.80 (1H, dd, *J* 10.4, 2.0 Hz, H3), 3.38 (1H, dd, *J* 14.0, 8.0 Hz, H1A), 3.01 (1H, dd, *J* 14.4, 4.8 Hz, H1B), 2.82 (1H, s, OH), 2.09 (3H, s, CH₃), 1.80 (1H, m, H4A), 1.54 (1H, m, H4B), 1.15 (3H, s, CH₃), 0.90 (3H, t, *J* 7.6 Hz, H5). ¹³C-NMR (100 MHz, CDCl₃) 171.68, 158.03, 136.28, 128.51, 128.14, 128.09, 78.16, 73.99, 67.08, 47.60, 21.66, 20.99, 20.92, 10.70. LRMS (ESI+) 332 ([M+Na]⁺, 100%), 272 (5), 91 (34). HRMS (ESI+) calcd for C₁₆H₂₃NO₅Na ([M+Na]⁺) 332.1474, found 332.1487; calcd for C₁₆H₂₄NO₅ ([M+H]⁺) 310.1654, found 310.1654.

A second fraction afforded *rac*-(2*R*,3*R*)-1-(benzyloxycarbonylamino)-2-hydroxy-2-methylpentan-3-yl acetate (**15b**) as a colorless oil (23.8 mg, 20%), *R*_f 0.26 (50% ethyl acetate/*n*-hexane). IR (thin film, cm⁻¹) 3748 (O–H), 3401 (N–H), 3066, 3033, 2973, 2936, 2879 (C–H), 1717 (C=O), 1529. ¹H-NMR (400 MHz, CDCl₃) 7.30–7.36 (5H, m, ArH), 5.23 (1H, s, NH), 5.11 (2H, s, CH₂Ar), 4.82 (1H, dd, *J* 10.4, 2.4 Hz, H3), 3.34 (1H, dd, *J* 14.0, 6.8 Hz, H1A), 3.11 (1H, dd, *J* 14.0, 6.4 Hz, H1B), 2.43 (1H, s, OH), 2.13 (3H, s, CH₃), 1.71 (1H, m, H4A), 1.58 (1H, m, H4B), 1.15 (3H, s, CH₃), 0.89 (3H, t, *J* 7.2 Hz, H5). ¹³C-NMR (100 MHz, CDCl₃) 171.78, 157.06, 136.37, 128.51, 128.13, 128.06, 79.05, 74.45, 66.93, 48.08, 22.16, 20.92, 20.63, 10.48. LRMS (ESI+) 332 ([M+Na]⁺, 100%), 284 (4), 272 (4), 91 (30). HRMS (ESI+) calcd for C₁₆H₂₃NO₅K ([M+K]⁺) 348.1213, found 348.1214; calcd for C₁₆H₂₃NO₅Na ([M+Na]⁺) 332.1474, found 332.1474.

***rac*-Benzyl (2*S*,3*R*)-2,3-dihydroxy-2-methylpentylcarbamate (**13b**) and *rac*-benzyl (2*R*,3*R*)-2,3-dihydroxy-2-methylpentylcarbamate (**16b**)**

Procedure 1: The reaction was conducted according to general procedure 1 with *rac*-2-methylpent-1-en-3-ol (**10b**)²⁴ (63.5 mg, 0.63 mmol), potassium osmate dihydrate (9.40 mg, 0.03 mmol) and benzyl *N*-(4-tosyloxy)carbamate (**1**) (245 mg, 0.76 mmol). Integration of C2–CH₃ signal of the 400 MHz ¹H-NMR spectrum of the crude reaction mixture showed a 2.7:1 ratio of *rac*-benzyl (2*S*,3*R*)-2,3-dihydroxy-2-methylpentylcarbamate (**13b**) [δ 1.12 (3H, s, CH₃)] and *rac*-benzyl (2*R*,3*R*)-2,3-dihydroxy-2-methylpentylcarbamate (**16b**) [δ 1.09 (3H, s, CH₃)]. Purification by flash chromatography (30% ethyl acetate/*n*-hexane) afforded an inseparable mixture of diastereomers as a colorless oil (67.2 mg, 40%), *R*_f 0.36 (70% ethyl acetate/*n*-hexane). HRMS (ESI+) calcd for C₁₄H₂₁NO₄Na ([M+Na]⁺) 290.1368, found 290.1368; calcd for C₁₄H₂₁NO₄K (M+K)⁺ 306.1108, found 306.1108.

Procedure 2: To *rac*-(2*S*,3*R*)-1-(benzyloxycarbonylamino)-2-hydroxy-2-methylpentan-3-yl acetate (**12b**) (25.0 mg, 0.08 mmol) was added a freshly prepared solution of potassium carbonate (22.4 mg, 0.16 mmol) in methanol (3 ml) and water (1 ml) at 20 °C. The reaction mixture was stirred until the reaction was complete (1 h). The reaction was quenched with aqueous hydrochloric acid (5.0 ml, 1.0 M), and extracted with dichloromethane (3 × 10 ml). The combined dichloromethane extract was washed with brine (10 ml), dried over sodium sulfate and concentrated under reduced pressure to afford *rac*-benzyl (2*S*,3*R*)-2,3-dihydroxy-2-methylpentylcarbamate (**13b**) as a colorless oil (21.6 mg, 100%), *R*_f 0.37 (70% ethyl acetate/*n*-hexane). IR (thin film, cm⁻¹) 3405 (broad, N–H, O–H), 3065, 3033, 2966, 2933, 2877 (C–H), 1696 (C=O), 1530. ¹H-NMR (400 MHz, CDCl₃) 7.30–7.37 (5H, m, ArH), 5.28 (1H, s, NH), 5.09–5.16 (2H, m, CH₂Ar), 3.50 (1H, dd, *J* 14.8, 6.4 Hz, H3), 3.31 (1H, d, *J* 10.0 Hz, H1A), 3.09 (1H, dd, *J* 14.4, 6.0 Hz, H1B), 2.96 (1H, s, OH), 2.40 (1H, s, OH), 1.60 (1H, m, H4A), 1.35 (1H, m, H4B), 1.12 (3H, s, CH₃), 1.03 (3H, t, *J* 8.0 Hz, H5). ¹³C-NMR (100 MHz, CDCl₃) 158.08, 136.22, 128.54, 128.23, 128.10, 77.24, 74.62, 67.13, 47.50, 23.51, 20.75, 11.48. LRMS (ESI+) 290 ([M+Na]⁺, 100%), 204 (7), 91 (9). HRMS (ESI+) calcd for C₁₄H₂₁NO₄Na ([M+Na]⁺) 290.1368, found 290.1360; calcd for C₁₄H₂₂NO₄ ([M+H]⁺) 268.1549, found 268.1544.

Procedure 3: To *rac*-(2*R*,3*R*)-1-(benzyloxycarbonylamino)-2-hydroxy-2-methylpentan-3-yl acetate (**15b**) (20.0 mg, 0.065 mmol) was added a freshly prepared solution potassium carbonate (17.9 mg, 0.129 mmol) in methanol (3 ml) and water (1 ml) at 20 °C. The reaction mixture was stirred until the reaction was complete (1 h). The reaction was quenched with aqueous hydrochloric acid

(5.0 ml, 1.0 M) and extracted with dichloromethane (3×10 ml). The combined dichloromethane extract was washed with brine (10 ml), dried over sodium sulfate and concentrated under reduced pressure to afford *rac*-benzyl (2*R*,3*R*)-2,3-dihydroxy-2-methylpentylcarbamate (**16b**) as a colorless oil (16.7 mg, 97%), R_f 0.36 (70% ethyl acetate/*n*-hexane). IR (thin film, cm^{-1}) 3400 (broad, N–H, O–H), 3066, 3033, 2964, 2931, 2876 (C–H), 1697 (C=O), 1530. ^1H -NMR (400 MHz, CDCl_3) 7.30–7.38 (5H, m, ArH), 5.22 (1H, s, NH), 5.11 (2H, s, CH_2Ar), 3.37 (1H, dd, J 14.0, 6.8 Hz, H3), 3.32 (1H, d, J 10.8 Hz, H1A), 3.12 (1H, dd, J 14.4, 6.0 Hz, H1B), 2.91 (1H, s, OH), 2.77 (1H, s, OH), 1.54 (1H, m, H4A), 1.40 (1H, m, H4B), 1.09 (3H, s, CH_3), 1.00 (3H, t, J 7.2 Hz, H5). ^{13}C -NMR (100 MHz, CDCl_3) 157.65, 136.22, 128.54, 128.24, 128.10, 75.85, 74.45, 67.12, 48.60, 23.45, 20.24, 11.03. LRMS (ESI+) 290 ($[\text{M}+\text{Na}]^+$, 100%), 204 (4), 91 (5). HRMS (ESI+) calcd for $\text{C}_{14}\text{H}_{22}\text{NO}_4$ ($[\text{M}+\text{H}]^+$) 268.1549, found 268.1541; calcd for $\text{C}_{14}\text{H}_{21}\text{NO}_4\text{Na}$ ($[\text{M}+\text{Na}]^+$) 290.1368, found 290.1364.

***rac*-Benzyl [(4*S*,5*R*)-5-ethyl-2,2,4-trimethyl-1,3-dioxolan-4-yl]methylcarbamate (18)**

The reaction was conducted according to general procedure 2 with *rac*-benzyl (2*S*,3*R*)-2,3-dihydroxy-2-methylpentylcarbamate (**13b**) (21.8 mg, 0.08 mmol), 2,2-dimethoxypropane (42.5 mg, 0.41 mmol), camphorsulfonic acid (0.800 mg, 0.003 mmol) and *p*-toluenesulfonic acid (0.600 mg, 0.003 mmol). The title compound **18** was isolated without further purification as a yellow oil (25.1 mg, 100%), R_f 0.51 (40% ethyl acetate/*n*-hexane). IR (thin film, cm^{-1}) 3350 (N–H), 3066, 3033, 2981, 2935, 2878 (C–H), 1725 (C=O), 1513. ^1H -NMR (400 MHz, CDCl_3) 7.30–7.37 (5H, m, ArH), 5.11 (2H, s, CH_2Ar), 5.07 (1H, s, NH), 3.73 (1H, dd, J 8.8, 4.0 Hz, H5), 3.31 (1H, dd, J 13.2, 8.8 Hz, H8A), 3.09 (1H, dd, J 13.6, 2.0 Hz, H8B), 1.46–1.65 (2H, m, H9), 1.40 (3H, s, CH_3), 1.35 (3H, s, CH_3), 1.23 (3H, s, CH_3), 1.05 (3H, t, J 7.2 Hz, H10). ^{13}C -NMR (100 MHz, CDCl_3) 156.81, 136.60, 128.46, 128.10, 128.03, 107.25, 84.62, 81.05, 66.73, 45.23, 28.32, 26.50, 21.70, 21.08, 11.44. LRMS (ESI+) 330 ($[\text{M}+\text{Na}]^+$, 100%), 91 (9). HRMS (ESI+) calcd for $\text{C}_{17}\text{H}_{26}\text{NO}_4$ ($[\text{M}+\text{H}]^+$) 308.1862, found 308.1865; calcd for $\text{C}_{17}\text{H}_{25}\text{NO}_4\text{Na}$ ($[\text{M}+\text{Na}]^+$) 330.1681, found 330.1678.

***rac*-Benzyl [(4*R*,5*R*)-5-ethyl-2,2,4-trimethyl-1,3-dioxolan-4-yl]methylcarbamate (19)**

The reaction was conducted according to general procedure 2 with *rac*-benzyl (2*R*,3*R*)-2,3-dihydroxy-2-methylpentylcarbamate (**16b**) (16.7 mg, 0.06 mmol), 2,2-dimethoxypropane (32.5 mg, 0.31 mmol), camphorsulfonic acid (0.600 mg, 0.003 mmol) and *p*-toluenesulfonic acid (0.500 mg, 0.003 mmol). The title compound **19** was isolated without further purification as a yellow oil (19.2 mg, 100%), R_f 0.46 (40% ethyl acetate/*n*-hexane). IR (thin film, cm^{-1}) 3350 (N–H), 3066, 3034, 2981, 2933, 2879 (C–H), 1725 (C=O), 1516. ^1H -NMR (400 MHz, CDCl_3) 7.30–7.37 (5H, m,

ArH), 5.11 (3H, s, broad, NH and CH₂Ar), 3.66 (1H, dd, *J* 9.2, 4.0 Hz, H5), 3.31 (1H, dd, *J* 14.0, 6.8 Hz, H8A), 3.20 (1H, dd, *J* 14.4, 5.6 Hz, H8B), 1.57 (1H, m, H9A), 1.47 (1H, m, H9B), 1.41 (3H, s, CH₃), 1.31 (3H, s, CH₃), 1.07 (3H, s, CH₃), 1.01 (3H, t, *J* 7.2 Hz, H10). ¹³C-NMR (100 MHz, CDCl₃) 156.60, 136.57, 128.47, 128.09, 128.01, 106.96, 81.83, 80.56, 66.77, 46.69, 28.60, 26.69, 22.42, 19.68, 11.18. LRMS (ESI+) 330 ([M+Na]⁺, 100%), 91 (52). HRMS (ESI+) calcd for C₁₇H₂₆NO₄ ([M+H]⁺) 308.1862, found 308.1861; calcd for C₁₇H₂₅NO₄Na ([M+Na]⁺) 330.1681, found 330.1681; calcd for C₁₇H₂₅NO₄K ([M+K]⁺) 346.1421, found 346.1420.

***rac*-1-[(2,4-Dimethylpent-1-en-3-yloxy)methyl]-4-methoxybenzene (8c)**

To a stirred suspension of *rac*-2,4-dimethylpent-1-en-3-ol (**10c**)²⁵ (480 mg, 4.20 mmol) and sodium hydride (202 mg, 8.41 mmol) in dimethylformamide (3.0 ml) was added *p*-methoxybenzyl chloride (988 mg, 6.31 mmol) at room temperature under nitrogen. This reaction mixture was stirred until the reaction was complete. The reaction was quenched with aqueous sodium hydrogen carbonate (5.0 ml, 1.0 M) and extracted with dichloromethane (3 × 10 ml). The combined organic extract was washed with brine (10 ml), dried over sodium sulfate and concentrated under reduced pressure to afford the crude product. Purification by flash chromatography (2% ethyl acetate/*n*-hexane) afforded the title compound **8c** as a colorless oil (243 mg, 25%), *R*_f 0.23 (5% ethyl acetate/*n*-hexane). IR (thin film, cm⁻¹) 3070, 2957, 2870, 2836 (C–H), 1649, 1613, 1586 (C=C), 1514. ¹H-NMR (400 MHz, CDCl₃) 7.23 (2H, m, ArH), 6.85 (2H, m, ArH), 4.98 (1H, m, H1A), 4.85 (1H, m, H1B), 4.42 (1H, d, *J* 11.6 Hz, CH_AH_BAr), 4.13 (1H, d, *J* 11.6 Hz, CH_AH_BAr), 3.79 (3H, s, OCH₃), 3.20 (1H, d, *J* 8.8 Hz, H3), 1.76 (1H, m, H4), 1.66 (3H, s, CH₃), 0.99 (3H, d, *J* 6.4 Hz, CH₃), 0.74 (3H, d, *J* 6.8 Hz, CH₃). ¹³C-NMR (100 MHz, CDCl₃) 143.78, 142.33, 131.06, 129.36, 114.82, 113.62, 89.30, 69.63, 55.23, 30.12, 19.51, 19.13, 16.61. LRMS (EI+) 234 (M⁺•, 100%), 228 (80), 213 (12), 204 (22), 197 (54), 191 (70). HRMS (EI+) calcd for C₁₅H₂₂O₂ (M⁺•) 234.1620, found 234.1619.

***rac*-Benzyl (2*S*,3*R*)-2-hydroxy-3-(4-methoxybenzyloxy)-2,4-dimethylpentylcarbamate (11c) and *rac*-benzyl (2*R*,3*R*)-2-hydroxy-3-(4-methoxybenzyloxy)-2,4-dimethylpentylcarbamate (14c)**

The reaction was conducted according to general procedure 1 with *rac*-1-[(2,4-dimethylpent-1-en-3-yloxy)methyl]-4-methoxybenzene (**8c**) (84.5 mg, 0.36 mmol), potassium osmate dihydrate (5.30 mg, 0.02 mmol) and benzyl *N*-(4-tosyloxy)carbamate (**1**) (139 mg, 0.43 mmol). Purification by flash chromatography (30% ethyl acetate/*n*-hexane) afforded an inseparable mixture of two diastereomers as a colorless oil (25.2 mg, 17%), *R*_f 0.28 (40% ethyl acetate/*n*-hexane). Purification

by preparative HPLC (μ Porasil silica 10 μ m, 3.9 $\times$ 300 mm, 1% isopropanol/*n*-hexane, flow rate 0.7 ml/min) gave a 12:1 ratio of diastereomers **11c** and **14c** and afforded *rac*-benzyl (2*S*,3*R*)-2-hydroxy-3-(4-methoxybenzyloxy)-2,4-dimethylpentylcarbamate (**11c**) (t_R 23.7 min) as a colorless oil (21.8 mg, 15%). IR (thin film, cm^{-1}) 3421 (O–H, N–H), 3065, 3032, 2959, 2874, 2837 (C–H), 1702 (C=O), 1612, 1586 (C=C), 1514. ^1H -NMR (400 MHz, CDCl_3) 7.29–7.38 (5H, m, ArH), 7.26 (2H, d, J 8.4 Hz, ArH), 6.86 (2H, d, J 8.4 Hz, ArH), 5.16 (1H, s, NH), 5.09 (2H, s, CH_2Ar), 4.68 (1H, d, J 10.8 Hz, $\text{CH}_\text{A}\text{H}_\text{B}\text{Ar}$), 4.46 (1H, d, J 10.8 Hz, $\text{CH}_\text{A}\text{H}_\text{B}\text{Ar}$), 3.78 (3H, s, OCH_3), 3.37 (1H, dd, J 13.6, 8.0 Hz, H1A), 3.21 (1H, d, J 2.8 Hz, H3), 3.19 (1H, dd, J 11.6, 3.6 Hz, H1B), 2.68 (1H, s, OH), 1.99 (1H, m, H4), 1.17 (3H, s, CH_3), 1.12 (3H, d, J 6.8 Hz, CH_3), 1.03 (3H, d, J 6.8 Hz, H5). ^{13}C -NMR (100 MHz, CDCl_3) 159.32, 157.28, 136.58, 130.36, 129.27, 128.47, 128.02, 127.96, 113.92, 89.27, 75.34, 74.90, 66.72, 55.23, 47.56, 28.96, 24.07, 22.18, 17.65. LRMS (ESI+) 424 ($[\text{M}+\text{Na}]^+$, 100%), 121 (90). HRMS (ESI+) calcd for $\text{C}_{23}\text{H}_{31}\text{NO}_5\text{Na}$ ($[\text{M}+\text{Na}]^+$) 424.2100, found 424.2102; calcd for $\text{C}_{23}\text{H}_{32}\text{NO}_5$ ($[\text{M}+\text{H}]^+$) 402.2280, found 424.2290.

A second fraction afforded *rac*-benzyl (2*R*,3*R*)-2-hydroxy-3-(4-methoxybenzyloxy)-2,4-dimethylpentylcarbamate (**14c**) (t_R 21.3 min) as a colorless oil (1.8 mg, 1.2%). IR (thin film, cm^{-1}) 3401 (O–H, N–H), 3031, 2958, 2925, 2872, 2852 (C–H), 1705 (C=O), 1612, 1587 (C=C), 1514. LRMS (ESI+) 424 ($[\text{M}+\text{Na}]^+$, 100%), 413 (11), 302 (32), 181 (8), 149 (18), 121 (65), 91 (42). HRMS (ESI+) calcd for $\text{C}_{23}\text{H}_{31}\text{NO}_5\text{Na}$ ($[\text{M}+\text{Na}]^+$) 424.2100, found 424.2099.

***rac*-(2*S*,3*R*)-1-(Benzyloxycarbonylamino)-2-hydroxy-2,4-dimethylpentan-3-yl acetate (**12c**) and *rac*-(2*R*,3*R*)-1-(benzyloxycarbonylamino)-2-hydroxy-2,4-dimethylpentan-3-yl acetate (**15c**)**

The reaction was conducted according to general procedure 1 with *rac*-2,4-dimethylpent-1-en-3-yl acetate (**9c**)²⁵ (60.0 mg, 0.38 mmol), potassium osmate dihydrate (5.70 mg, 15.5 μ mol) and benzyl *N*-(4-tosyloxy)carbamate (**1**) (148 mg, 0.46 mmol). Purification by flash chromatography (30% ethyl acetate/*n*-hexane) afforded *rac*-(2*S*,3*R*)-1-(benzyloxycarbonylamino)-2-hydroxy-2,4-dimethylpentan-3-yl acetate (**12c**) as a colorless oil (31.0 mg, 25%), R_f 0.34 (40% ethyl acetate/*n*-hexane). IR (thin film, cm^{-1}) 3416 (O–H, N–H), 3064, 3033, 2965, 2936, 2877 (C–H), 1722 (C=O), 1525. ^1H -NMR (400 MHz, CDCl_3) 7.29–7.37 (5H, m, ArH), 5.36 (1H, s, NH), 5.08–5.16 (2H, m, CH_2Ar), 4.70 (1H, d, J 4.4 Hz, H3), 3.36 (1H, dd, J 14.4, 8.0 Hz, H1A), 3.04 (1H, dd, J 14.4, 4.4 Hz, H1B), 2.70 (1H, s, OH), 2.10–2.16 (4H, m, CH_3 and H4), 1.19 (3H, s, CH_3), 1.00 (3H, d, J 6.8 Hz, CH_3), 0.94 (3H, d, J 6.4 Hz, H5). ^{13}C -NMR (100 MHz, CDCl_3) 171.35, 157.87, 136.34, 128.48, 128.11, 128.04, 79.95, 74.67, 67.03, 48.37, 28.14, 21.91, 21.53, 20.85, 18.27. LRMS (ESI+) 346

($[M+Na]^+$, 100%), 286 (5), 91 (11). HRMS (ESI+) calcd for $C_{17}H_{25}NO_5Na$ ($[M+Na]^+$) 346.1630, found 346.1623.

A second fraction afforded *rac*-(2*R*,3*R*)-1-(benzyloxycarbonylamino)-2-hydroxy-2,4-dimethylpentan-3-yl acetate (**15c**) as a colorless oil (8.9 mg, 7%), R_f 0.20 (40% ethyl acetate/*n*-hexane). IR (thin film, cm^{-1}) 3400 (O–H, N–H), 3066, 3033, 2963, 2929, 2874 (C–H), 1721 (C=O), 1522. 1H -NMR (400 MHz, $CDCl_3$) 7.30–7.36 (5H, m, ArH), 5.24 (1H, s, NH), 5.11 (2H, s, CH_2Ar), 4.76 (1H, d, J 3.2 Hz, H3), 3.31 (1H, dd, J 14.0, 6.4 Hz, H1A), 3.02 (1H, dd, J 14.4, 6.4 Hz, H1B), 2.27 (1H, s, OH), 2.08–2.14 (4H, m, CH_3 and H4), 1.21 (3H, s, CH_3), 0.99 (3H, d, J 7.2 Hz, CH_3), 0.94 (3H, d, J 6.4 Hz, H5). ^{13}C -NMR (100 MHz, $CDCl_3$) 171.45, 157.04, 136.40, 128.50, 128.12, 128.07, 79.95, 74.95, 66.89, 48.56, 28.32, 21.90, 21.31, 20.77, 17.04. LRMS (ESI+) 346 ($[M+Na]^+$, 100%), 286 (7), 260 (5), 91 (8). HRMS (ESI+) calcd for $C_{17}H_{25}NO_5Na$ ($[M+Na]^+$) 346.1630, found 346.1630.

***rac*-(3*S*,4*R*)-Benzyl 2,4-dihydroxy-2-methylpentan-3-ylcarbamate (**25a**)¹⁰**

The reaction was conducted according to general procedure 1 with *rac*-4-methylpent-3-en-2-ol (**20a**)²⁶ (45.0 mg, 0.45 mmol), potassium osmate dihydrate (6.60 mg, 0.02 mmol) and benzyl *N*-(4-tosyloxy)carbamate (**1**) (173 mg, 0.54 mmol). Purification by flash chromatography (80% diethyl ether/*n*-hexane) afforded the title compound **25a** as a brown oil (11.3 mg, 9.4%), R_f 0.14 (80% diethyl ether/*n*-hexane). IR (thin film, cm^{-1}) 3414 (broad, O–H, N–H), 3067, 3033, 2956, 2923, 2852 (C–H), 1721 (C=O), 1699, 1513. 1H -NMR (400 MHz, $CDCl_3$) 7.31–7.37 (5H, m, ArH), 5.56 (1H, d, J 9.6 Hz, NH), 5.14 (2H, s, CH_2Ar), 4.42 (1H, q, J 5.6 Hz, H4), 3.37 (1H, d, J 9.2 Hz, H3), 2.59 (2H, s, broad, 2 $\times$ OH), 1.38 (3H, s, CH_3), 1.24 (3H, s, H1), 1.18 (3H, d, J 6.4 Hz, H5). ^{13}C -NMR (100 MHz, $CDCl_3$) 157.35, 136.57, 128.50, 128.06, 127.86, 74.49, 67.16, 66.84, 60.54, 27.87, 27.65, 20.56. LRMS (ESI+) 290 ($[M+Na]^+$, 85%), 272 (28), 245 (11), 232 (5), 177 (5), 149 (6), 132 (10), 91 (100), 89 (9), 57 (5). HRMS (ESI+) calcd for $C_{14}H_{21}NO_4Na$ ($[M+Na]^+$) 290.1368, found 290.1367.

***rac*-(3*S*,4*R*)-Benzyl 2,4-dihydroxy-2-methylhexan-3-ylcarbamate (**25b**)**

The reaction was conducted according to general procedure 1 with *rac*-5-methylhex-4-en-3-ol (**20b**)²⁶ (50.0 mg, 0.44 mmol), potassium osmate dihydrate (6.50 mg, 0.02 mmol) and benzyl *N*-(4-tosyloxy)carbamate **1** (169 mg, 0.53 mmol). Purification by flash chromatography (80% diethyl ether/*n*-hexane) afforded the title compound **25b** as a brown oil (8.2 mg, 6.7%), R_f 0.33 (80% diethyl ether/*n*-hexane). IR (thin film, cm^{-1}) 3406 (broad, O–H, N–H), 2970, 2934 (C–H), 1694 (C=O), 1515. 1H -NMR (400 MHz, $CDCl_3$) 7.29–7.36 (5H, m, ArH), 5.52 (1H, d, J 10.0 Hz, NH),

5.09–5.16 (2H, m, CH₂Ar), 4.08 (1H, t, *J* 7.2 Hz, H4), 3.47 (1H, dd, *J* 9.6, 1.6 Hz, H3), 2.67 (1H, s, OH), 2.54 (1H, s, OH), 1.54–1.47 (2H, m, H5), 1.38 (3H, s, CH₃), 1.25 (3H, s, H1), 0.95 (3H, t, *J* 7.6 Hz, H6). ¹³C-NMR (100 MHz, CDCl₃) 157.22, 136.57, 128.48, 128.05, 127.87, 74.60, 72.92, 66.82, 58.84, 27.84, 27.67, 27.32, 9.98. LRMS (ESI⁺) 304 ([M+Na]⁺, 100%), 286 (4), 145 (5), 91 (84), 85 (5). HRMS (ESI⁺) calcd for C₁₅H₂₃NO₄Na ([M+Na]⁺) 304.1525, found 304.1526.

Results

The choice of substrates was influenced by practical considerations. In the absence of ligand control, the intermolecular oxyamination of unsymmetrically substituted alkenes by pre-formed nitrogen sources typically gives high selectivity for products where the nitrogen adds to the less substituted end of the double bond.^{4,9–12} High regioselectivity in the oxyamination reaction would significantly simplify product analysis of the diastereomeric mixtures. On this basis, the oxyamination reaction of mono-, 1,1-di- and tri-substituted alkenes expected to display high regioselectivity was investigated.

A similar procedure was employed for the oxyamination of all allylic alcohol derivatives.¹² This involved reaction of the allylic alcohol or its derivative (1.0 equiv) and benzyl *N*-(4-tosyloxy)carbamate **1** (1.2 equiv) with potassium osmate dihydrate (0.04 equiv) in acetonitrile/water (3:1). The reaction diastereoselectivity was determined by 400 MHz ¹H NMR integration of the crude reaction mixture, or where this was not possible by HPLC-UV integration or by product isolation after careful purification by flash chromatography.

The yields and diastereoselectivities for the oxyamination of a range allylic alcohol derivatives **2**, **3**, **8–10** containing mono- and 1,1-di-substituted double bonds are presented in Tables I and II respectively. Several trends were observed. The amino alcohol products **4–7** and **11–16** were afforded in moderate to good combined yield but long reaction times were normally required. Lower yields were afforded from more highly substituted substrates and also those bearing unprotected allylic hydroxyl groups. While the oxyamination of allylic alcohol **10c** failed to afford product under the standard conditions, reaction of the corresponding *para*-methoxybenzyl and acetate protected derivatives **8c** and **9c** did afford amino-alcohol products, albeit in low yields (Table II, Entries 3, 6 and 9). High regioselectivity was achieved as expected, with the terminal amine product produced exclusively from both protected and unprotected allylic alcohol derivatives.

In all cases examined, the *anti* diastereomers **4**, **5** and **11–13** were the major products of the oxyamination reaction, with *anti:syn* selectivities ranging from 1.2:1 to 12:1. Increasing the size of the alkyl substituent appended to the allylic alcohol-bearing stereogenic center was observed to modestly increase selectivity for the *anti* diastereomer. For example, allylic alcohol **3a** with methyl-substituent provided a 1.8:1 / *anti:syn* ratio while the reaction of allylic alcohol **3c** with isopropyl substituent gave a 3.1:1 / *anti:syn* ratio (Table I, Entries 4–6). The 1,1-disubstituted alkenes **8–10** (Table II, Entries 4–8) afforded higher selectivity than their corresponding monosubstituted counterparts **2**, **3** (Table I, Entries 1–5). No significant change in diastereoselectivity was observed on protection of the alcohols as the corresponding acetate esters (Table I, Entries 1–6 and Table II, Entries 4–8). However, improved *anti* selectivity was observed for the *para*-methoxybenzyl ethers examined (Table II, Entries 1–3).

<Table I here>

<Table II here>

The relative configuration of *anti* acetate **4a** and *anti* diol **5a** was confirmed by a sequence of deacetylation followed by acetonide formation (Scheme 2). The 400 MHz ¹H NMR spectrum revealed two acetonide methyl signals at δ 1.44 and δ 1.33 consistent with a *cis*-4,5-disubstituted-2,2-dimethyldioxolane **17**.²⁷ In addition, irradiation of H5 (δ 4.33, dq, *J* 6.3, 6.3 Hz) showed nOes to H4 (δ 4.11, m) and the α -oriented acetonide methyl signal (δ 1.33, s).²⁷

<Scheme 2 here>

Scheme 2. Stereochemical proof for acetate **4a** and diol **5a**.

The relative configuration of acetates **12b** and **15b** and their corresponding diols **13b** and **16b** were confirmed by a sequence of deacetylation followed by acetonide formation (Scheme 3). The *anti* acetate **12b** afforded *anti* diol **13b** and acetonide **18**. For the acetonide **18**, irradiation of H5 (δ 3.73, dd, *J* 8.8, 4.0 Hz) showed nOes to the C4-methyl (δ 1.23, s) and the α -oriented acetonide methyl signal (δ 1.35, s). The diastereomeric *syn* acetate **15b** afforded *syn* diol **16b** and acetonide **19**. For the acetonide **19**, irradiation of H5 (δ 3.66, dd, *J* 9.2, 4.0 Hz) showed nOes to H8A (δ 3.31, dd, *J* 14.0, 6.8 Hz) and the α -oriented acetonide methyl signal (δ 1.31, s). The relative configuration of *anti* benzyl ether **11a** was confirmed through selective deprotection of the *para*-methoxybenzyl ether and comparison with the previously described *anti* diol **13a** (Scheme 4).¹²

<Scheme 3 here>

Scheme 3. Stereochemical proof for acetates **12b**, **15b** and diols **13b**, **16b**.

<Scheme 4 here>

Scheme 4. Stereochemical proof for PMB ether **11a**.

The reactivity of a range of trisubstituted alkenes **20–23** is presented in Table III. In contrast to the allylic alcohol derivatives bearing mono- and 1,1-disubstituted double bonds, the oxyamination reaction compounds bearing trisubstituted double bonds failed to afford the products **24–31** in the majority of cases investigated. In two cases examined oxyamination products were observed in low yields to give the *syn* diastereomer **25a,b** (Table III, Entries 1 and 2) as the major product isolated. The identity and relative configuration of compound **25a** was confirmed by comparison with the literature.¹⁰ The reactions of these alkenes were characterised by the formation of a number of unidentified by-products. Longer reaction times did not afford higher yields of product.

<Table III here>

Discussion

The pioneering work conducted by Kishi and co-workers provided an empirical rule for the observed diastereoselectivity of the osmium tetroxide mediated dihydroxylation of allylic alcohol derivatives.^{18,19,28} Since this time, several important experimental studies delineating the scope and limitations of this phenomenon have been reported,^{29–31} and a series of refined models have been advanced to explain the observed diastereoselectivity.^{20,29–31} The model advanced by Houk and co-workers and developed with the aid of DFT computation predicts the *anti* diastereomer as the major product of the dihydroxylation of (*E*)-3-buten-2-ol with ligated osmium tetroxide.²⁰ Adapting this model to the oxyamination reaction of allylic alcohol derivatives bearing mono- and 1,1-disubstituted double bonds is shown in Scheme 5. The imidoosmium catalyst approaches the alkene with the large imido-group directed toward the unsubstituted and sterically unencumbered terminus of the double bond leading to high regioselectivity. The favored approach of the imidoosmium catalyst to the *si*-face of the double bond positions the allylic oxygen substituent (OP) in the inside position to avoid unfavorable electrostatic and stereoelectronic effects²⁰ and the large alkyl substituent (R) in the sterically unencumbered *anti* position giving transition structure **A** and leading to the *anti* diastereomer. In contrast, approach of the imidoosmium catalyst to the *re*-face of the double bond with the allylic oxygen substituent (OP) in the inside position leaves the large alkyl substituent (R) in the more sterically encumbered outside position giving transition structure **B** and leading to the *syn* diastereomer. Consistent with this proposal, the results show a modest but

consistent and systematic trend of increasing selectivity for the *anti* diastereomer as the alkyl substituent (R) on the allylic stereocenter increases in size from methyl to isopropyl, reinforcing the preference for the less sterically encumbered transition structure **A** (Tables I and II). Furthermore, the introduction of a methyl substituent (R') on the double bond also leads to an increase in *anti* selectivity due to increased steric interactions between this substituent (R') and the alkyl substituent (R) on the allylic stereocenter in transition structure **B** (compare Table I, Entries 1–5 and Table II, Entries 4–8 respectively).

<Scheme 5 here>

Scheme 5. Proposed transition structures for the oxyamination of allylic alcohol derivatives bearing mono- and 1,1-disubstituted double bonds.

Similar trends in stereoselectivity have been observed for the osmium catalyzed dihydroxylation of allylic alcohol derivatives.^{18,19,28,30,31} In particular, the sense and magnitude of diastereoselectivity noted by Evans and Kaldor³¹ for the osmium-catalyzed dihydroxylation of allylic benzyl ether substrates **26b,c** bearing 1,1-disubstituted double bonds (Scheme 6) parallels the results of this work for the oxyamination of structurally related *para*-methoxybenzyl ether derivatives (Table II, Entries 1–3). The isopropyl derivative **8c** gave the highest *anti* selectivity of the terminal alkene substrates examined.

<Scheme 6 here>

Scheme 6. Evans dihydroxylation³¹ and oxyamination of allylic benzyl ether derivatives bearing 1,1-disubstituted double bonds.

The osmium-catalyzed oxyamination of alkene **20a** (Table III, Entry 1) unexpectedly afforded the *syn* diastereoisomer **25a** as the major product identified in low yield in contrast to the *anti* diastereoisomers observed for the terminal alkene substrates (Tables I and II). A related oxyamination protocol was recently reported to afford the same product.¹⁰ The *anti* diastereomer **24a** was not observed. Kishi's empirical rule for the dihydroxylation of allylic alcohol derivatives with *cis*-substituted double bonds predicts *anti* selectivity, as do other models of diastereoselectivity,^{18,19,29,30} including the aforementioned model advanced by Houk and co-workers which predicts the *anti* diastereomer as the major product of the dihydroxylation of (*Z*)-3-buten-2-ol with ligated osmium tetroxide.²⁰ Several features of this oxyamination reaction are noteworthy. The double bond substitution pattern of the trisubstituted alkenes **20a,b** favor addition of the large *N*-(benzyloxycarbonyl)imido-osmium grouping to the least substituted carbon of the double bond, in

close proximity to the allylic stereocenter. This contrasts with the oxyamination of terminal alkenes where a smaller oxo-osmium group occupies this proximal position (Scheme 5). Furthermore, the oxyamination reactions of trisubstituted alkenes occurred in low yields^{10,12} and in most cases examined in this study failed to afford product under the standard conditions. Given the low reactivity observed and the limited data available, further experimentation is warranted before drawing conclusions on the basis for, and generality of, this stereochemical outcome.

Conclusion

In conclusion, the diastereoselective oxyamination reaction of chiral allylic alcohol derivatives bearing mono- or 1,1-di-substituted double bonds was observed to occur in moderate to good yield, excellent regioselectivity, and with moderate substrate controlled *anti* diastereoselectivity. The observed stereoselectivity shows a clear and systematic trend with *anti:syn* ratios increasing in line with substituent size at both the allylic stereocenter and double bond α -carbon. The stereoinduction is in accord with the sense of diastereoselectivity predicted by Kishi's empirical rule, and a previously reported transition state model for the osmium-catalyzed dihydroxylation of allylic alcohol derivatives. In contrast, the osmium mediated oxyamination of allylic alcohol derivatives bearing trisubstituted double bonds displayed low or no reactivity and provided the *syn* diastereoisomer in two examples. These results highlight the potential for the use of substrate-controlled oxyamination in the synthesis of stereochemically complex natural products and other amino alcohol containing compounds.

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