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# The asymmetric aminohydroxylation route to GABOB and homoserine derivatives

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ABSTRACT

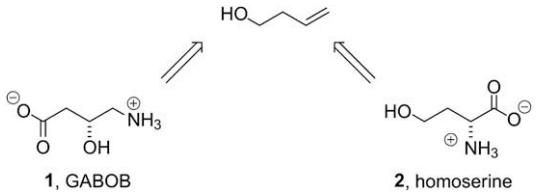
The 4-nitrophenyl ether is an efficient directing group in the asymmetric aminohydroxylation reaction of homoallylic ether derivatives. Either regioisomeric product can be obtained with useful levels of enantioselectivity allowing for the short enantioselective synthesis of GABOB and homoserine derivatives. A model based on substrate-catalyst interactions is presented to explain the regio- and enantioselectivity of the aminohydroxylation reactions.



## 1. Introduction

The osmium-catalysed asymmetric aminohydroxylation (AA) of alkenes has become a powerful tool for the synthesis of the vicinal amino alcohol functional array and has been applied to the construction of numerous biologically important targets.[1] Despite this success, the levels of regio- and enantioselectivity obtained for some alkene substitution patterns are not always synthetically useful.

Research within our laboratory[2–4] and by other groups[5–7] has shown that the interaction of substrate and catalyst plays a pivotal role in controlling selectivity in the AA reaction. In a previous study[3] we demonstrated that the AA reaction of the 4-nitrophenyl ether of but-3-en-1-ol granted selective access to either regioisomeric product, providing synthetic access to the unusual amino acids, (3*R*)-(−)-4-amino-3-hydroxybutyric acid (GABOB) **1** and homoserine **2** in protected form (Scheme 1). In this paper we provide complete experimental details of this work and extend this study to propose an explanation based on substrate-catalyst interactions for the observed changes in AA regioselectivity.




**Scheme 1.** Proposed synthesis of GABOB **1** and homoserine **2** derivatives from but-3-en-1-ol.

## 2. Results and discussion

### 2.1. Synthesis of GABOB in protected form

Our initial goal was the synthesis of the unusual amino acid GABOB **1**, which has been identified as a key fragment of the microsclerodermins, a family of marine cyclic peptides possessing anti-tumour and anti-fungal activity.[8] It is also an agonist of the γ-amino-butyric acid (GABA) receptor and is used in the treatment of epilepsy and hypertension.[9]

The proposed synthesis required aminohydroxylation of protected but-3-en-1-ol **3a–g** to give the terminal amine regioisomers **4a–g** (Table 1). Although the selective AA of styrenes to give terminal alcohol products is well documented in the literature,[10] oxidation to afford the terminal amine regioisomer usually occurs with lower levels of selectivity.[10a] The oxidation of other terminal

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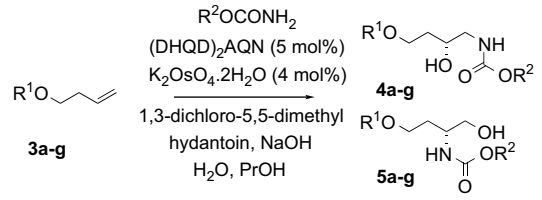
**Table 1**
The $(DHQD)_2AQN$-mediated synthesis of terminal amine regioisomers **4a–g**




| Entry | Substrate | $R^1$ | $R^2$ | Ratio[a] (**4**/**5**) | Yield of **4** (%) | ee[b] (%) |
|---|---|---|---|---|---|---|
| 1 | **3a** | 4-MeO-Ph | $^t$Bu | 6/1 | 56 | 71 |
| 2 | **3b** | 3,4-Di-MeO-Ph | $^t$Bu | 5/1 | 53[c] | 65 |
| 3 | **3c** | 4-Br-Ph | $^t$Bu | 8/1 | 66 | 63 |
| 4 | **3d** | 4-Me-Ph | $^t$Bu | 7/1 | 61 | 73 |
| 5 | **3e** | 4-$NO_2$-Ph | $^t$Bu | 9/1 | 73 | 73 |
| 6 | **3e** | 4-$NO_2$-Ph | Me | 9/1 | 61 | 79 |
| 7 | **3a** | 4-MeO-Ph | TMSE[d] | 5/1 | 61 | 79 |
| 8 | **3b** | 3,4-Di-MeO-Ph | TMSE | 5/1 | 53[c] | 78 |
| 9 | **3c** | 4-Br-Ph | TMSE | 7/1 | 63 | 76 |
| 10 | **3d** | 4-Me-Ph | TMSE | 7/1 | 62 | 75 |
| 11 | **3e** | 4-$NO_2$-Ph | TMSE | 10/1 | 67 | 81 |
| 12[e] | **3e** | 4-$NO_2$-Ph | TMSE | 9/1 | 61 | 72[f] |
| 13 | **3f** | 2,6-Di-Me-4-$NO_2$-Ph | TMSE | 9/1 | 48 | 77 |
| 14 | **3g** | TBDPS[g] | TMSE | 9/1 | 56 | 65 |

[a] Determined by integration of the 300 MHz $^1$H NMR spectrum of crude reaction mixture.
[b] Determined by chiral HPLC.
[c] Chlorination occurs to afford the 2-chloro-4,5-dimethoxyphenyl ether products.
[d] TMSE=2-(trimethylsilyl)ethyl.
[e] $(DHQ)_2AQN$ ligand used.
[f] Product formed with (*S*)-configuration.
[g] TBDPS=*tert*-butyldiphenylsilyl.

alkene substrates also typically proceeds with poor regio- or enantioselectivity.[11,11]

Previous work has demonstrated that aryl ethers are effective directing groups in the AA of structurally related unsaturated ester derivatives and AQN ligands were expected to favour the terminal amine regioisomer.[2–4] Initial studies used 4-methoxyphenyl but-3-en-yl ether **3a**[12] as substrate and *tert*-butyl carbamate[10a] as the nitrogen source in concert with the $(DHQD)_2AQN$ ligand (Fig. 1).[13] The reaction afforded a 6:1 mixture[14] of the two regioisomeric products **4a** and **5a** ($R^2$=$^t$Bu), from which the amino alcohol **4a** could be isolated in 56% yield with an enantiomeric excess of 71% (Table 1, entry 1).[15]

Different aromatic ethers (**3a–f**) and nitrogen sources were surveyed in an effort to improve the selectivity in this AA transformation. In all cases (Table 1, entries 2–13) the major product **4a–f** was that formed from addition of nitrogen to the terminal end of the alkene. The highest regioselectivities were observed with the 4-nitrophenyl ether **3e** (entries 5, 6, 11 and 12) and moderately higher enantioselectivity was obtained using the sterically undemanding methyl carbamate[3] (entry 6) or 2-(trimethylsilyl)ethyl (TMSE) carbamate[16] (entries 7–13). Thus, the best results were obtained when the 4-nitrophenyl ether was employed with TMSE carbamate to give a 67% isolated yield of regioisomer **4e** ($R^2$=TMSE) in 81% ee.

The absolute configuration of **4e** ($R^2$=TMSE) was confirmed by the formation of (*S*) and (*R*)-Mosher's esters, **6** and **7**, respectively (Table 2). Application of the modified Mosher's method[17] displayed a pattern of anisotropic shielding consistent with a (2*R*)-configuration for alcohol **4e**. Thus the facial selectivity of the aminohydroxylation reaction is consistent with the face selectivity rule for the Sharpless asymmetric dihydroxylation reaction[18] with the dihydroquinidine derived ligand $(DHQD)_2AQN$ effecting attack on the lower face of the double bond, as shown, to afford the product **4e** of (*R*)-configuration. The product of opposite configuration was successfully prepared using the pseudoenantiomeric dihydroquinine derived ligand $(DHQ)_2AQN$ (Table 1, entry 12).

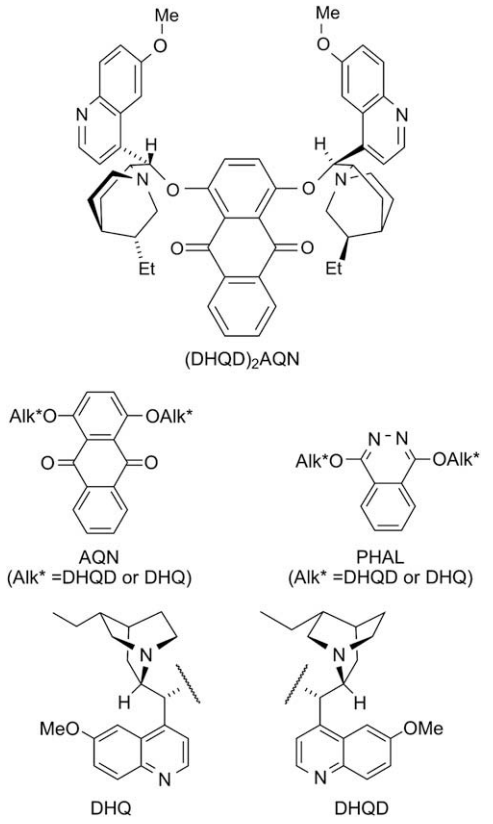
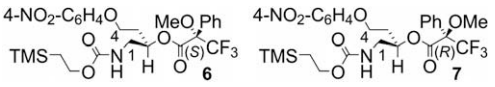



**Figure 1.** Sharpless ligands.

**Table 2**
Mosher's ester analysis of terminal amine regioisomer **4e**




| Signal | δ (*S*)-MTPA ester | δ (*R*)-MTPA ester | $\delta_{(S)}-\delta_{(R)}$ |
|---|---|---|---|
| TMS | 0.03 | 0.04 | −0.01 |
| $CH_2$TMS | 0.96 | 0.97 | −0.01 |
| $COOCH_2$ | 4.14 | 4.16 | −0.02 |
| NH | 4.61 | 4.75 | −0.14 |
| H1 | 3.47[a] | 3.51[a] | −0.04 |
| *H2* | *5.41* | *5.41* | *0.00* |
| H3 | 2.18[b] | 2.13[b] | +0.05 |
| H4 | 4.10[a] | 3.91[b] | +0.19 |
| H2′, H6′ | 6.91 | 6.84 | +0.07 |
| H3′, H5′ | 8.20 | 8.18 | +0.02 |

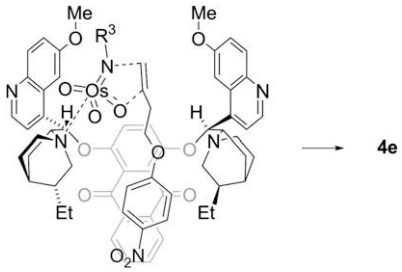
[a] Chemical shift estimate for partially overlapping or obscured multiplets.
[b] Chemical shift of central point for complex two proton multiplet.

The substrate-catalyst interactions responsible for the observed regio- and enantioselectivity of the $(DHQD)_2AQN$-mediated aminohydroxylation of substrate **3e**, to give terminal amine **4e**, are depicted in Scheme 2. This proposal builds on a similar study of substrate-catalyst interaction in the AA of structurally related unsaturated ester substrates that also contain homoallyl ether functionality.[2] Key features of the putative substrate-catalyst interaction are:

- a di-apical arrangement of the nitrogen atoms about osmium in the distorted trigonal bipyramidal osmium-ligand complex;[19]
- a geometry of the ligand based on the X-ray crystal structure of the $(DHQ)_2AQN$ ligand (see Fig. 2 below);[20]
- a face-to-face interaction of the 4-nitrophenyl ether with the anthraquinone unit of the catalyst,[21] with the but-3-en-1-yl

substituent in a low energy extended conformation and the terminal alkene carbon approaching the apical imido-substituent on osmium, and;

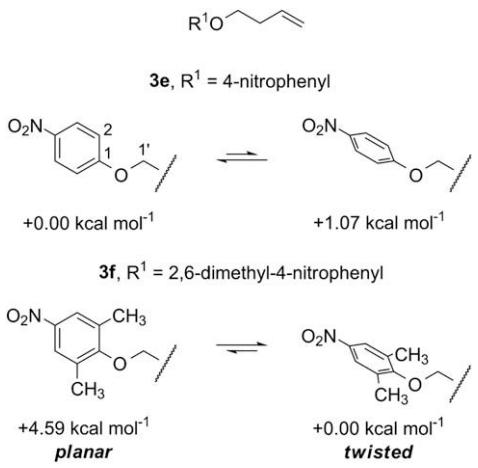
- a *syn* addition of the imidotrioxoosmium species to the *Re*-face of the alkene to give the terminal amine **4e** of (*R*)-configuration.




**Scheme 2.** Proposed substrate-catalyst interaction for the $(DHQD)_2AQN$-mediated synthesis of terminal amine regioisomer **4e** ($R^3$=Teoc). The AQN spacer unit located behind the 4-nitrophenyl ether substrate **3e** is shown in grey for clarity.

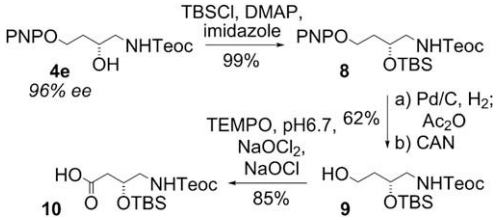
The results obtained for 2,6-dimethyl-4-nitrophenyl ether **3f** (Table 1, entry 13) and *tert*-butyldiphenylsilyl (TBDPS) ether **3g** (entry 14) lend support to the proposed binding mode. The 2,6-dimethyl substitution of substrate **3f** favours a near 90° twist of the aromatic ring relative to the 4-nitrophenyl ether analogue (Scheme 3).[22] This twist suggests a face-to-face interaction between the phenyl ether of the substrate and the anthraquinone spacer as the methyl substituents render a phenyl ether edge to anthraquinone face interaction unfavourable. For the 4-nitrophenyl ether **3e**, the relatively small energy difference between the planar and twisted conformations[22] could also allow face-to-face interactions with the catalyst.

Interestingly, silyl ether **3g** proved moderately effective, affording isomer **4g** with good regioselectivity but lower enantioselectivity (Table 1, entry 14). In this instance the steric bulk of the TBDMS ether prefers to occupy the region over the flat anthraquinone spacer unit rather than the relatively congested region adjacent to the methoxyquinoline rings.




**Scheme 3.** Conformational preferences (C2–C1–O–C1′) of phenyl ether substrates **3e** and **3f**.

The 4-nitrophenyl (PNP) ether product **4e** proved to be an effective building block for the synthesis of a protected form of GABOB **10** (Scheme 4). The crystalline amino alcohol **4e** could be optically enriched to 96% ee with 75% recovery by recrystallisation. Subsequent protection of the secondary alcohol as its TBS ether **8** was carried out in 86% yield. The phenyl ether was then removed using a two-stage procedure[23] involving reduction of the nitro group and acetylation, followed by oxidative cleavage with




**Scheme 4.** Synthesis of GABOB derivative **10**. PNP=4-nitrophenyl; Teoc=2-(trimethylsilyl)ethoxycarbonyl; TBS=*tert*-butyldimethylsilyl; TEMPO=2,2,6,6-tetramethylpiperidine 1-oxyl.

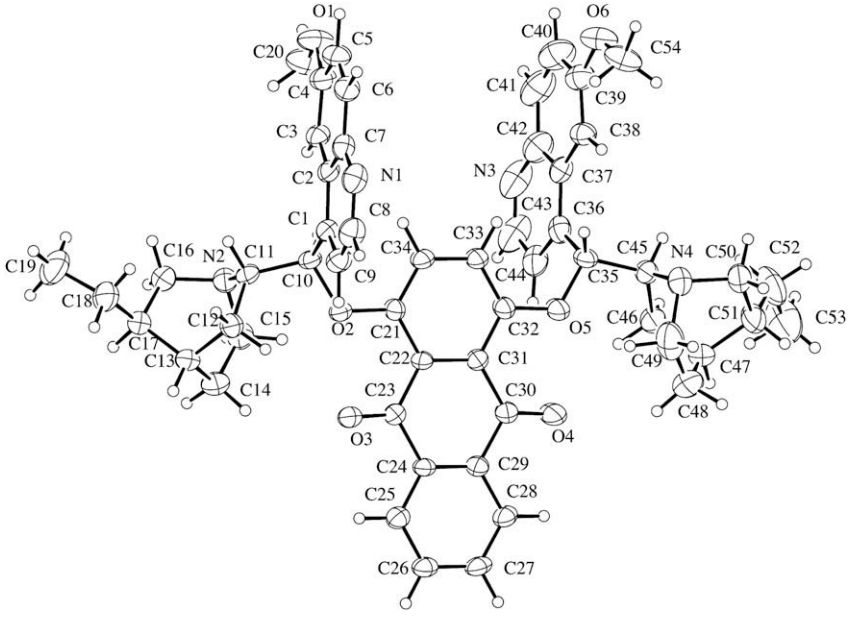


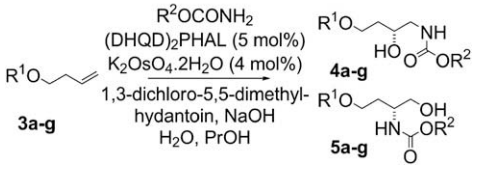

**Figure 2.** Structure of one $(DHQ)_2AQN$ molecule with labelling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

CAN. Primary alcohol **9** was obtained in 62% yield (two steps). Finally, a one-step oxidation of the alcohol to the carboxylic acid using TEMPO[24] afforded the protected GABOB derivative **10** in 85% yield.

## 2.2. Synthesis of homoserine in protected form

The application of phthalazine-derived ligands for the AA of aromatic ethers, **3** ($R^1$=Ar), was also investigated with the expectation of obtaining primary alcohol **5** as the major regioisomer.[2] The use of 4-methoxyphenyl ether **3a** in concert with phthalazine-derived ligand $(DHQD)_2PHAL$ and TMSE carbamate afforded a 1:1.9 mixture[14] of the two regioisomeric products **4a** and **5a** (Table 3, entry 1).[5] The major primary alcohol **5a** was afforded with 85% ee.[15]

**Table 3**
The $(DHQD)_2PHAL$ mediated synthesis of terminal alcohol regioisomer **5a–g**



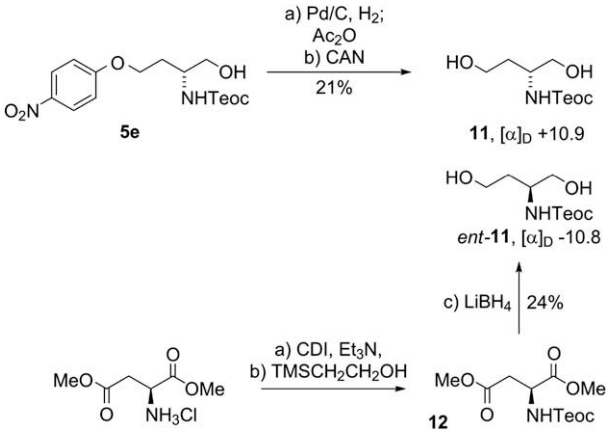

| Entry | Substrate | $R^1$ | $R^2$ | Ratio[a] (**4**/**5**) | Yield of **5** (%) | ee[b] (%) |
|---|---|---|---|---|---|---|
| 1 | **3a** | 4-MeO-Ph | TMSE[c] | 1/1.9 | 48 | 85 |
| 2 | **3c** | 4-Br-Ph | TMSE | 1/3.5 | 48 | 92 |
| 3 | **3d** | 4-Me-Ph | TMSE | 1/1.5 | 45 | 86 |
| 4 | **3e** | 4-$NO_2$-Ph | TMSE | 1/12 | 65 | 95 |
| 5[d] | **3e** | 4-$NO_2$-Ph | TMSE | 1/12 | 64 | 96[e] |
| 6 | **3e** | 4-$NO_2$-Ph | $^t$Bu | 1/6 | 71 | 96 |
| 7 | **3f** | 2,6-Di-Me-4-$NO_2$-Ph | TMSE | 5/1 | 53[f] | 67 |
| 8 | **3g** | TBDPS[g] | TMSE | 5/1 | 48[f] | 79 |

[a] Determined by integration of the 300 MHz $^1$H NMR spectrum of crude reaction mixture.
[b] Determined by chiral HPLC.
[c] TMSE=2-(trimethylsilyl)ethyl.
[d] $(DHQ)_2PHAL$ ligand used.
[e] Product formed with (*S*)-configuration.
[f] Yield of **4**.
[g] TBDPS=*tert*-butyldiphenylsilyl.

Variation of aromatic ether was investigated in an attempt to optimise the process (Table 3, entries 2–4). The 4-bromo- and 4-methyl-phenyl ethers afforded **5** with higher levels of optical purity. However, as before, the best results were obtained with the 4-nitrophenyl ether, which gave 12:1 regioselectivity providing compound **5e** in an isolated yield of 65% and with 95% ee (entry 4). The use of the pseudoenantiomeric $(DHQ)_2PHAL$ ligands gave the enantiomeric product with identical efficiency (entry 5). The substitution to *tert*-butyl carbamate gave similar isolated yield and enantioselectivity but lower regioselectivity (entry 6).

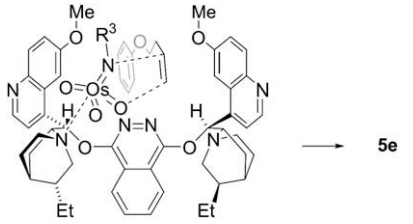
The absolute configuration of primary alcohol (*R*)-**5e** ($R^2$=TMSE) was confirmed by chemical correlation (Scheme 5). Deprotection of the 4-nitrophenyl ether was achieved by the method of Fukase[23] to give Teoc-protected diol **11** (95% ee, $[\alpha]_D$ +10.9 (*c* 1.3, $CH_2Cl_2$)). The enantiomeric diol *ent*-**11** ($[\alpha]_D$ −10.8 (*c* 1.7, $CH_2Cl_2$)) was independently prepared from L-aspartic acid dimethyl ester hydrochloride, by protection to afford carbamate **12** followed by ester reduction. The facial selectivity of the aminohydroxylation reaction is consistent with the face selectivity rule for the Sharpless asymmetric dihydroxylation reaction[18] with the dihydroquinidine derived ligand $(DHQD)_2PHAL$ effecting attack on the lower face of the double bond, as shown, to afford the product **5e** of (*R*)-configuration (Table 3).

The observed regio- and enantioselectivity observed in the $(DHQD)_2PHAL$ mediated AA of substrate **3** to give primary alcohol **5**




**Scheme 5.** Confirmation of primary alcohol **5e** ($R^2$=TMSE) absolute configuration by chemical correlation. Teoc=2-(trimethylsilyl)ethoxycarbonyl; CDI=1,1′-carbonyldiimidazole.

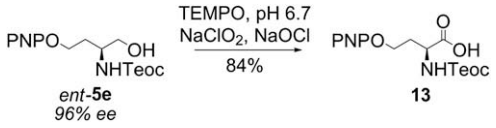
is consistent with an interaction of the aromatic ether with the face-to-face methoxyquinoline units of the catalyst depicted in Scheme 6.[25,26] The buten-3-yl substituent adopts a folded conformation[27] with the terminal alkene carbon approaching the equatorial oxo-substituent on osmium. Addition to the *Re*-face of the alkene gives the primary alcohol product of (*R*)-configuration.




**Scheme 6.** Proposed substrate-catalyst interaction for the $(DHQD)_2PHAL$-mediated synthesis of primary alcohol regioisomer **5e** ($R^3$=Teoc). The substrate **4e** phenyl ether, located above and behind the PHAL spacer, is shown in grey and with 4-nitro substituent removed for clarity.

In contrast to the effective direction observed for 4-nitrophenyl ether **3e** (Table 3, entries 4–6), the reaction of 2,6-dimethyl-4-nitrophenyl ether substrate **3f** (entry 7) and the sterically demanding silyl ether, **3g** (entry 8),[5] gave opposite regioselectivity, favouring the isomer **4** in a lower ee. In the case of the 2,6-dimethyl-4-nitrophenyl ether substrate **3f** (entry 7), the dimethyl substituents induce a near 90° twist of the aromatic ring relative to the 4-nitrophenyl ether counterpart (Scheme 3).[22] This twist of the phenyl ring would be expected to disrupt the normal mode of binding to the PHAL-derived catalyst due to the increased steric interaction between the now orthogonal aromatic ether with the methoxyquinoline rings. In contrast, the twisted conformation of the 2,6-dimethyl-4-nitrophenyl ether is well aligned to engage in face-to-face contact with the PHAL spacer of this ligand, leading to production of the terminal amine regioisomer. The silyl ether **3g**, proved reasonably effective, affording isomer **4g** with moderate regio- and enantioselectivity (entry 8).[5] As observed for the anthraquinone ligands (Table 1) the steric bulk of the TBDMS ether prefers to occupy the region over the flat phthalazine spacer unit rather than the relatively congested region adjacent to the methoxyquinoline rings.

The primary alcohol *ent*-**5e** obtained from the AA reaction of the 4-nitrophenyl ether **3e** with $(DHQ)_2PHAL$ could be efficiently transformed to a protected homoserine derivative (Scheme 7). The one-step oxidation of alcohol *ent*-**5e** with TEMPO afforded the amino acid **13** in 84% yield.[24]

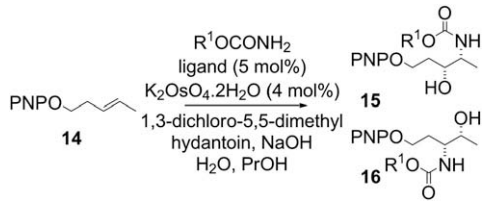



**Scheme 7.** Synthesis of homoserine derivative **13**. PNP=4-nitrophenyl; Teoc=2-(trimethylsilyl)ethoxycarbonyl; TEMPO=2,2,6,6-tetramethylpiperidine 1-oxyl.

### 2.3. Asymmetric aminohydroxylation of 4-nitrophenyl (*E*)-pent-3-enyl ether

To further explore the scope of this directing effect the AA of 4-nitrophenyl (*E*)-pent-3-enyl ether substrate **14** was briefly explored (Table 4). The experiments used the optimal 4-nitrophenyl ether as directing group and either *tert*-butyl- or TMSE-carbamate as nitrogen source. Aminohydroxylation with the AQN derived catalysts (Table 4, entries 1–4) resulted in moderate regioselectivity (2–4:1)[14] favouring the 2-amino product **15** with good levels of enantioselectivity (80–84% ee).[15] This corresponds to a lower level of regioselectivity when compared with aminohydroxylation of the terminal alkene substrate **3e**. In contrast, the PHAL mediated AA gave good levels of regiocontrol (8–10:1) in favour of 3-amino product **16**, which is similar to that observed for terminal alkene substrate **3e**. In this case the enantioselectivity of the transformation was somewhat lower than that observed for substrate **3e**. Although of limited scope, the study of (*E*)-1,2-disubstituted alkene **14** shows that PHAL catalysts in general give higher levels of regio- and enantioselectivity that the AQN counterparts and highlights the subtle interplay of substrate and catalyst characteristic of the aminohydroxylation reaction.

**Table 4**
The ligand mediated aminohydroxylation of (*E*)-1,2-disubstituted alkene **14**. PNP=4-nitrophenyl




| Entry | Ligand | $R^1$ | Ratio[a] (**15**/**16**) | Yield major (%) | ee major[b] (%) |
|---|---|---|---|---|---|
| 1 | $(DHQD)_2AQN$ | $^t$Bu | 3.7/1 | 75 | 84 |
| 2 | $(DHQ)_2AQN$ | $^t$Bu | 2.6/1 | 56 | 80[c] |
| 3 | $(DHQD)_2AQN$ | TMSE[d] | 2.6/1 | 48 | 84 |
| 4 | $(DHQ)_2AQN$ | TMSE | 2.3/1 | 43 | 81[c] |
| 5 | $(DHQD)_2PHAL$ | TMSE | 1/8 | 56 | 89 |
| 6 | $(DHQ)_2PHAL$ | TMSE | 1/10 | 38 | 91[c] |

[a] Determined by integration of the 300 MHz $^1$H NMR spectrum of the crude reaction mixture.
[b] Determined by chiral HPLC. Absolute configuration assigned by analogy with **4e** and **5e** ($R^2$=TMSE).
[c] Product formed with (*R*,*R*)-configuration.
[d] TMSE=2-(trimethylsilyl)ethyl.

### 2.4. X-ray crystal structure analysis of $(DHQ)_2AQN$

The X-ray structure of the $(DHQ)_2AQN$ ligand was solved from crystals grown in acetonitrile solution (Fig. 2).[20] Two molecules of $(DHQ)_2AQN$ were observed in the asymmetric unit. As no previous crystal structure of the AQN derived ligands exists, the structure provides a useful guide to ligand conformation in the active catalyst. The structure also permits comparison with the previously reported structure of the $(DHQD)_2PHAL$ ligand[25] to identify the structural changes associated with changing from AQN to PHAL spacer units, albeit for ligands with different alkaloid units.

Both PHAL and AQN ligands adopt a similar overall conformation, with close correlation of key torsions between the alkaloid and spacer units. The aryl ether torsion of the AQN ligand (C10–O2–C21–C34, av 1.5°) was of the same magnitude as the corresponding torsion within the PHAL ligand (av 4.6°). The alkyl ether torsion (C1–C10–O2–C21, av 75°) was of similar magnitude to the PHAL ligand (av 86°). In this instance the slightly larger torsion observed for the PHAL ligands may arise due to buttressing of the DHQD alkaloid unit ethyl substituent with the PHAL spacer and the reduced steric interaction of the C10–H of the alkaloid unit with the adjacent PHAL nitrogen lone pair when compared with the AQN C34–H atom. Changes in bond lengths and angles also result in a small increase in distance (C10–C35) between alkaloid oxymethine carbon atoms of 0.36 Å for the AQN ligand relative to its PHAL counterpart.

Overall, only small changes in ligand conformation are observed upon changing from AQN to PHAL ligands. Although the foregoing discussion cannot account for effects such as crystal packing forces or conformational mobility of ligands in solution, the analysis suggests that gross structural change in catalyst conformation is not responsible for the reversal in regioselectivity in changing from AQN to PHAL-derived ligands. Rather, changes in regioselectivity arise from changes to substrate-catalyst interaction resulting from differences in the nature of the spacer unit as depicted in Schemes 2 and 6.

## 3. Conclusion

In conclusion this work demonstrates that the 4-nitrophenyl ether is an efficient directing group in the asymmetric aminohydroxylation reaction of homoallylic ether derivatives, providing either regioisomeric product with useful levels of enantioselectivity. This finding has been applied to the short enantioselective synthesis of protected GABOB **10** and homoserine **13**. The substrate-catalyst interactions responsible for the observed regio- and enantioselectivity of the AA reactions have been proposed.

## 4. Experimental

### 4.1. General details

Melting points were determined using a Reichert heating stage with microscope and are uncorrected. Infrared absorption spectra were obtained using a Perkin–Elmer 1600 Fourier Transform Infrared spectrometer as a thin film between 0.5 cm sodium chloride plates. Absorption maxima are expressed in wavenumbers ($cm^{-1}$) and the appearance of bands are expressed as s=strong, m=medium, w=weak and br=broad. $^1$H Nuclear magnetic resonance spectra were recorded using a Bruker AC200 (200.1 MHz), Bruker AVANCE DPX200 (200 MHz), Bruker AVANCE DPX300 (300.1 MHz) or Bruker DPX400 (400.1 MHz) spectrometer at 300 K. Data is expressed as parts per million downfield shift from tetramethylsilane with either tetramethylsilane or chloroform as an internal standard and is reported as chemical shift ($\delta$), relative integral, multiplicity (s=singlet, d=doublet, t=triplet, m=multiplet with descriptor br=broad), coupling constant ($J$ in hertz) and assignment. $^{13}$C Nuclear magnetic resonance spectra were recorded using a Bruker AC200 (50.3 MHz), Bruker AVANCE DPX200 (50 MHz), Bruker AVANCE DPX300 (75.5 MHz) or Bruker DPX400 (100.4 MHz) spectrometer with complete proton decoupling at 300 K. The chemical shifts are reported relative to chloroform and are expressed as chemical shift ($\delta$). FIDs were manipulated prior to Fourier transformation applying an exponential line broadening function to improve the signal to noise ratio. Low resolution electron impact mass spectra were recorded on either an AEI model Kratos MS902 double focusing mass spectrometer with an

accelerating voltage of 8000 V and using electron impact (EI) ionisation mode at 70 eV, or a Finnegan PolarisQ ion trap mass spectrometer using electron impact ionisation mode at 40 or 70 eV. High resolution electron impact mass spectra were recorded on a VC Autospec mass spectrometer operating at 70 eV. Low resolution electrospray ($ESI^+$) mass spectra were recorded on a Finnegan LCQ mass spectrometer. High resolution electrospray mass spectra were recorded on a Bruker ApexII Fourier Transform Ion Cyclotron Resonance mass spectrometer with a 7.0 T magnet, fitted with an off-axis Analytica electrospray source (University of New South Wales, Sydney) or a Finnegan MAT 900XL (University of Queensland, Brisbane). Major fragments are quoted as *x* (assignment), where *x* is the mass to charge ratio. High resolution mass spectra were recorded at a nominal resolution of 8000–9000. Chiral Analytical High Performance Liquid Chromatography (HPLC) was carried out on a Waters Gradient system consisting of two 510 pumps, a 490E programmable multiwavelength detector at 220, 254 and 270 nm, a 410 differential refractometer, and a U6K injector. All retention times are reported at 270 nm and calculations were based on peak areas at 270 nm. Data was acquired and processed using Millenium software (Version 3.05.01). Separation was carried out using the indicated solvents on a Daicel Chiralcel OD-H (25 cm×4.6 mm ID, 5 μm particle size) or a Daicel Chiralpak AD-H (25 cm×4.6 mm ID, 5 μm particle size) column with a flow rate of 0.5 mL/min. Optical rotations α were measured using an Optical Activity PolAAr 2001 Automatic polarimeter with the sodium D line (589 nm) at ambient temperature. Optical rotations were recorded in dichloromethane, chloroform or methanol and run in a 0.25 dm cell. Specific rotations $[\alpha]_D$ are expressed in units of $dm^{-1}\ g^{-1}\ cm^3$ and concentrations (*c*) are reported as g solute/100 $cm^3$ solution. Analytical thin layer chromatography was performed using aluminium backed precoated silica gel plates (Merck Kieselgel 60 $F_{254}$). Compounds were visualised by short wave ultra-violet fluorescence or by staining with acidified ethanolic solution of anisaldehyde, alkaline potassium permanganate solution or phosphomolybdic acid and ceric sulfate in sulfuric acid. Flash chromatography was performed using Merck Kieselgel 60 (230–400 mesh) with the indicated solvents. Solvent compositions are mixed v/v as specified.

## 4.2. Experimental procedures and data

### 4.2.1. General procedure for the AA reaction

To a solution of carbamate (0.7801 mmol) in propan-1-ol (0.65 mL) at ambient temperature was added an aqueous solution of sodium hydroxide (0.4 M, 0.780 mmol). To this mixture was added 1,3-dichloro-5,5-dimethylhydantoin (0.520 mmol) followed by a solution of ligand (0.0130 mmol) in propan-1-ol (1.3 mL). The solution was sonicated to ensure homogeneity. To the reaction mixture was added a solution of substrate **3** (0.260 mmol) followed by potassium osmate dihydrate (0.0104 mmol). The reaction was left to stir at ambient temperature for 18 h and quenched upon addition of sodium sulfite (2.03 mmol). The mixture was then diluted with water (4 mL) and extracted with ethyl acetate (3×10 mL). The combined organic extract was washed with brine (10 mL), dried ($NaSO_4$) and concentrated under reduced pressure to afford the crude product. The crude product was subject to analysis by 300 MHz $^1$H NMR to determine the ratio of the regioisomers **4** and **5**, followed by purification by flash chromatography (ethyl acetate/hexane) to afford the target compounds.

### 4.2.2. (R)-tert-Butyl 2-hydroxy-4-(4-methoxyphenoxy)-butylcarbamate 4a ($R^2$=$^t$Bu)

The reaction was conducted under standard conditions using 1-(but-3-enyloxy)-4-methoxybenzene **3a**[28] (46 mg, 0.260 mmol), $(DHQD)_2AQN$ and *tert*-butyl carbamate. Analysis of the crude reaction mixture by 300 MHz $^1$H NMR identified a 6:1 ratio of the regioisomers **4a** and **5a**. Purification by flash chromatography (40% ethyl acetate/hexane) afforded the major regioisomer **4a** (45 mg, 56%; 71% ee, Chiralcel OD-H, 15% isopropyl alcohol/hexane; $t_R$: 15.6 major, 17.3 minor). $[\alpha]_D$ −1.6 (*c* 2.0, $CH_2Cl_2$); $R_f$ 0.29 (40% ethyl acetate/hexane); $^1$H NMR (300 MHz, $CDCl_3$): δ 6.82 (4H, s, ArH), 5.02 (1H, br s, NH), 4.12–4.05 (2H, m, H4), 3.98 (1H, m, H2), 3.76 (3H, s, $OCH_3$), 3.34 (1H, m, $H1_A$), 3.15 (1H, m, $H1_B$), 2.85 (1H, br s, OH), 1.93–1.87 (2H, m, H3), 1.44 (9H, s, $^t$Bu); $^{13}$C NMR (75 MHz, $CDCl_3$): δ 156.8, 154.0, 152.7, 115.5, 114.7, 79.6, 69.8, 66.2, 55.7, 46.6, 33.9 28.4; IR (thin film): 3381 (br s, OH), 2975, 2932 (m, CH), 1693 (s, C=O) $cm^{-1}$; MS ($ESI^+$): *m*/*z* 334 ($[M+Na]^+$, 100), 278 (37), 212 (16); HRMS ($ESI^+$): calcd for $C_{16}H_{25}NO_5Na$ ($[M+Na]^+$) 334.1630, found 334.1629.

### 4.2.3. (R)-2-(Trimethylsilyl)ethyl 2-hydroxy-4-(4-methoxyphenoxy)butylcarbamate **4a** ($R^2$=TMSE)

The reaction was conducted under standard conditions using 1-(but-3-enyloxy)-4-methoxybenzene **3a**[28] (46 mg, 0.260 mmol), $(DHQD)_2AQN$ and 2-(trimethylsilyl)ethyl carbamate. Analysis of the crude reaction mixture by 300 MHz $^1$H NMR identified a 5:1 ratio of the regioisomers **4a** and **5a**. Purification by flash chromatography (40% ethyl acetate/hexane) afforded the major regioisomer **4a** (56 mg, 61%; 79% ee, Chiralpak AD-H, 8% isopropyl alcohol/hexane; $t_R$: 26.2 major, 30.0 minor). $[\alpha]_D$ +10.0 (*c* 0.2, $CH_2Cl_2$); $R_f$ 0.31 (40% ethyl acetate/hexane); $^1$H NMR (300 MHz, $CDCl_3$): δ 6.82 (4H, s, ArH), 5.13 (1H, br s, NH), 4.19–4.03 (4H, m, H4, $COOCH_2$), 3.99 (1H, m, H2), 3.76 (3H, s, $OCH_3$), 3.39 (1H, m, $H1_A$), 3.18 (1H, m, $H1_B$), 2.61 (1H, br s, OH), 1.94–1.88 (2H, m, H3), 0.97 (2H, m, $CH_2TMS$), 0.03 (9H, s, TMS); $^{13}$C NMR (75 MHz, $CDCl_3$): δ 157.6, 154.1, 152.6, 115.5, 114.7, 69.8, 66.2, 63.3, 55.7, 46.8, 33.8, 17.7, −1.5; IR (thin film): 3365 (br s, OH), 2953 (s, CH), 1693 (s, C=O) $cm^{-1}$; MS ($ESI^+$): *m*/*z* 378 ($[M+Na]^+$, 100); HRMS ($ESI^+$): calcd for $C_{17}H_{29}NO_5SiNa$ ($[M+Na]^+$) 378.1713, found 378.1706.

### 4.2.4. (R)-2-(Trimethylsilyl)ethyl 1-hydroxy-4-(4-methoxyphenoxy)butan-2-ylcarbamate **5a** ($R^2$=TMSE)

The reaction was conducted under standard conditions using 1-(but-3-enyloxy)-4-methoxybenzene **3a**[28] (46 mg, 0.260 mmol), $(DHQD)_2PHAL$ and 2-(trimethylsilyl)ethyl carbamate. Analysis of the crude reaction mixture by 300 MHz $^1$H NMR identified a 1:1.9 ratio of the regioisomers **4a** and **5a**. Purification by flash chromatography (40% ethyl acetate/hexane) afforded the major regioisomer **5a** as a colourless oil (44 mg, 48%; 85% ee, Chiralpak AD-H, 8% isopropyl alcohol/hexane; $t_R$: 22.2 major, 20.0 minor). $[\alpha]_D$ +9.1 (*c* 1.1, $CH_2Cl_2$); $R_f$ 0.27 (40% ethyl acetate/hexane); $^1$H NMR (300 MHz, $CDCl_3$): δ 6.81 (4H, s, ArH), 5.16 (1H, br s, NH), 4.13 (2H, m, $COOCH_2$), 4.01 (2H, t, *J* 5.8 Hz, H4), 3.94–3.84 (1H, m, H2), 3.75 (3H, s, $OCH_3$), 3.73–3.68 (2H, m, H1), 2.34 (1H, br s, O*H*), 2.09–1.91 (2H, m, H3), 0.96 (2H, m, $CH_2TMS$), 0.02 (9H, s, TMS); $^{13}$C NMR (75 MHz, $CDCl_3$): δ 157.0, 154.1, 152.5, 115.5, 114.7, 65.7, 65.3, 63.3, 55.7, 51.2, 31.0, 17.7, −1.5; IR (thin film): 3350 (br m, OH), 2953 (m, CH), 1695 (s, C=O) $cm^{-1}$; MS ($ESI^+$): *m*/*z* 378 ($[M+Na]^+$, 100); HRMS ($ESI^+$): calcd for $C_{17}H_{29}NO_5SiNa$ ($[M+Na]^+$) 378.1713, found 378.1705.

A second fraction afforded the minor regioisomer **4a** as a colourless oil (24 mg, 26%; 70% ee, Chiralpak AD-H, 8% isopropyl alcohol/hexane; $t_R$: 25.8 major, 29.8 minor).

### 4.2.5. (R)-tert-Butyl 4-(2-chloro-4,5-dimethoxyphenoxy)-2-hydroxybutylcarbamate **4b** ($R^2$=$^t$Bu)

The reaction was conducted under standard conditions using 4-(but-3-enyloxy)-1,2-dimethoxybenzene **3b**[29] (54 mg, 0.260 mmol), $(DHQD)_2AQN$ and *tert*-butyl carbamate. Analysis of the crude reaction mixture by 300 MHz $^1$H NMR identified a 5:1 ratio of the regioisomers **4b** and **5b**. Purification by flash chromatography (55% ethyl acetate/hexane) afforded the major regioisomer **4b** (49 mg,

53%; 65% ee, Chiralcel OD-H, 5% isopropyl alcohol/hexane; $t_R$: 38.6 major, 43.7 minor). $[\alpha]_D$ −4.6 (*c* 1.2, $CH_2Cl_2$); $R_f$ 0.12 (40% ethyl acetate/hexane); $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 6.87 (1H, s, ArH), 6.58 (1H, s, ArH), 5.06 (1H, br s, NH), 4.17 (2H, m, H4), 4.03 (1H, ddt, *J* 6.3, 6.3, 3.4 Hz, H2), 3.86 (3H, s, $OCH_{3A}$), 3.82 (3H, s, $OCH_{3B}$), 3.42–3.33 (1H, m, $H1_A$), 3.24–3.12 (1H, m, $H1_B$), 2.53 (1H, br s, OH), 1.97 (2H, m, H3), 1.44 (9H, s, $^t$Bu); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 157.3, 148.9, 148.5, 144.4, 113.9, 100.7, 80.1, 70.6, 68.7, 57.0, 56.7, 47.0, 34.2, 28.8 (one carbon obscured or overlapping); IR (thin film): 3388 (br s, OH, NH), 1701 (s, C=O) cm$^{-1}$; MS (ESI$^+$): *m*/*z* 773 (2{$C_{17}H_{26}^{35}ClNO_6$}+Na, 10), 398 ([{$C_{17}H_{26}^{35}ClNO_6$}+Na]$^+$, 100); HRMS (ESI$^+$): calcd for $C_{17}H_{26}^{35}ClNO_6Na$ ([M+Na]$^+$) 398.1346, found 398.1340.

#### 4.2.6. (*R*)-2-(Trimethylsilyl)ethyl 4-(2-chloro-4,5-dimethoxyphenoxy)-2-hydroxybutylcarbamate **4b** ($R^2$=TMSE)

The reaction was conducted under standard conditions using 4-(but-3-enyloxy)-1,2-dimethoxybenzene **3b**[29] (54 mg, 0.260 mmol), $(DHQD)_2AQN$ and 2-(trimethylsilyl)ethyl carbamate. Analysis of the crude reaction mixture by 300 MHz $^1$H NMR identified a 5:1 ratio of the regioisomers **4b** and **5b**. Purification by flash chromatography (55% ethyl acetate/hexane) afforded the major regioisomer **4b** (58 mg, 53%; 78% ee, Chiralcel OD-H, 15% isopropyl alcohol/hexane; $t_R$: 27.5 major, 30.5 minor). $[\alpha]_D$ −9.9 (*c* 1.9, $CH_2Cl_2$); $R_f$ 0.30 (55% ethyl acetate/hexane); $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 6.87 (1H, s, ArH), 6.58 (1H, s, ArH), 5.16 (1H, br s, NH), 4.23–4.10 (4H, m, H4, $COOCH_2$), 4.05 (1H, m, H2), 3.86 (3H, s, $OCH_{3A}$), 3.82 (3H, s, $OCH_{3B}$), 3.25 (1H, m, $H1_A$), 3.22 (1H, m, $H1_B$), 2.97 (1H, br s, OH), 2.02–1.94 (2H, m, H3), 0.98 (2H, m, $CH_2$TMS), 0.03 (9H, s, TMS); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 157.7, 148.5, 148.1, 144.0, 113.5, 100.3, 70.1, 68.3, 63.3, 56.6, 56.3, 46.7, 33.7, 17.7, −1.5 (one carbon overlapping or obscured); IR (thin film): 3381 (br s, OH), 2953 (s, CH), 1705 (s, C=O) cm$^{-1}$; MS (ESI$^+$): *m*/*z* 864 ([2{$C_{18}H_{30}^{37}ClNO_6Si$}+Na]$^+$, 6), 862 ([$C_{18}H_{30}^{35}ClNO_6Si$+$C_{18}H_{30}^{37}ClNO_6Si$+Na]$^+$, 18), 860 ([2{$C_{18}H_{30}^{35}ClNO_6Si$}+Na]$^+$, 20), 444 ([$C_{18}H_{30}^{37}ClNO_6Si$+Na]$^+$, 43), 442 ([$C_{18}H_{30}^{35}ClNO_6Si$+Na]$^+$, 100); HRMS (ESI$^+$): calcd for $C_{18}H_{30}^{35}ClNO_6Si$Na ([M+Na]$^+$) 442.1429, found 442.1413.

#### 4.2.7. (*R*)-tert-Butyl 4-(4-bromophenoxy)-2-hydroxybutylcarbamate **4c** ($R^2$=$^t$Bu)

The reaction was conducted under standard conditions using 1-bromo-4-(but-3-enyloxy)benzene **3c**[30] (59 mg, 0.260 mmol), $(DHQD)_2AQN$ and *tert*-butyl carbamate. Analysis of the crude reaction mixture by 300 MHz $^1$H NMR identified an 8:1 ratio of the regioisomers **4c** and **5c**. Purification by flash chromatography (30% ethyl acetate/hexane) afforded the major regioisomer **4c** (62 mg, 66%; 63% ee, Chiralcel OD-H, 5% isopropyl alcohol/hexane; $t_R$: 26.5 major, 30.3 minor). $[\alpha]_D$ −1.9 (*c* 1.7, $CH_2Cl_2$); $R_f$ 0.57 (50% ethyl acetate/hexane); $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.36 (2H, m, ArH), 6.77 (2H, m, ArH), 4.98 (1H, br s, NH), 4.17–4.03 (2H, m, H4), 3.97 (1H, m, H2), 3.34 (1H, dd, *J* 13.9, 2.6 Hz, $H1_A$), 3.13 (1H, dd, *J* 14.1, 7.1 Hz, $H1_B$), 1.99–1.86 (2H, m, H3), 1.45 (9H, s, $^t$Bu); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 157.7 (C), 156.9 (C), 132.3 (CH), 116.3 (CH), 113.1 (C), 79.9 (C), 69.4 (CH), 65.4 ($CH_2$), 46.8 ($CH_2$), 33.8 ($CH_2$), 28.4 ($CH_3$); IR (thin film): 3373 (br m, OH), 2976, 2932 (m, CH), 1699 (s, C=O) cm$^{-1}$; MS (ESI$^+$): *m*/*z* 384 ([$C_{15}H_{22}^{81}BrNO_4$+Na]$^+$, 21), 382 ([$C_{15}H_{22}^{79}BrNO_4$+Na]$^+$, 18), 304 (100); HRMS (ESI$^+$): calcd for $C_{15}H_{22}^{81}BrNO_4Na$ ([M+Na]$^+$) 384.0609, found 384.0603; calcd for $C_{15}H_{22}^{79}BrNO_4Na$ ([M+Na]$^+$) 382.0630, found 382.0622.

#### 4.2.8. (*R*)-2-(Trimethylsilyl)ethyl 4-(4-bromophenoxy)-2-hydroxybutylcarbamate **4c** ($R^2$=TMSE)

The reaction was conducted under standard conditions using 1-bromo-4-(but-3-enyloxy)benzene **3c**[30] (59 mg, 0.260 mmol), $(DHQD)_2AQN$ and 2-(trimethylsilyl)ethyl carbamate. Analysis of the crude reaction mixture by 300 MHz $^1$H NMR identified a 7:1 ratio of the regioisomers **4c** and **5c**. Purification by flash chromatography (30% ethyl acetate/hexane) afforded the major regioisomer **4c** as a colourless oil (66 mg, 63%; 76% ee, Chiralcel OD-H, 2.5% isopropyl alcohol/hexane; $t_R$: 82.1 major, 93.1 minor). $[\alpha]_D$ −1.6 (*c* 0.5, $CH_2Cl_2$); $R_f$ 0.55 (50% ethyl acetate/hexane); $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.38 (2H, m, ArH), 6.78 (2H, m, ArH), 5.03 (1H, br s, NH), 4.21–4.05 (4H, m, H4, $COOCH_2$), 4.00 (1H, m, H2), 3.40 (1H, ddd, *J* 14.1, 6.2, 3.3 Hz, $H1_A$), 3.19 (1H, m, $H1_B$), 2.04–1.80 (3H, m, H3, OH), 0.98 (2H, m, $CH_2$TMS), 0.04 (9H, s, TMS); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 157.7, 132.3, 116.3, 113.2, 69.5, 65.5, 63.5, 47.0, 33.8, 17.8, −1.5 (one carbon obscured or overlapping); IR (thin film): 3360 (br m, OH), 2951 (s, CH), 1690 (s, C=O) cm$^{-1}$; MS (ESI$^+$): *m*/*z* 428 ([$C_{16}H_{26}^{81}BrNO_4Si$+Na]$^+$, 100), 426 ([$C_{16}H_{26}^{79}BrNO_4Si$+Na]$^+$, 89); HRMS (ESI$^+$): calcd for $C_{16}H_{26}^{79}BrNO_4$SiNa ([M+Na]$^+$) 426.0712, found 426.0713.

#### 4.2.9. (*R*)-2-(Trimethylsilyl)ethyl 4-(4-bromophenoxy)-1-hydroxybutan-2-ylcarbamate **5c** ($R^2$=TMSE)

The reaction was conducted under standard conditions using 1-bromo-4-(but-3-enyloxy)benzene **3c**[30] (59 mg, 0.260 mmol), $(DHQD)_2PHAL$ and 2-(trimethylsilyl)ethyl carbamate. Analysis of the crude reaction mixture by 300 MHz $^1$H NMR identified a 1:3.5 ratio of the regioisomers **4c** and **5c**. Purification by flash chromatography (40% ethyl acetate/hexane) afforded the major regioisomer **5c** as a colourless oil (50 mg, 48%; 92% ee, Chiralpak AD-H, 8% isopropyl alcohol/hexane; $t_R$: 23.8 major, 19.4 minor). $[\alpha]_D$ +12.6 (*c* 1.3, $CH_2Cl_2$); $R_f$ 0.24 (40% ethyl acetate/hexane); $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 7.37 (2H, m, ArH), 6.77 (2H, m, ArH), 5.05 (1H, br s, NH), 4.13 (2H, m, $COOCH_2$), 4.03 (2H, t, *J* 5.9 Hz, H4), 3.90 (1H, m, H2), 3.78–3.64 (2H, m, H1), 2.17–1.93 (3H, m, H3, OH), 0.94 (2H, m, $CH_2$TMS), 0.03 (9H, s, TMS); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 157.6, 157.0, 132.3, 116.3, 113.2, 65.3, 63.4, 50.9, 30.9, 17.7, −1.5 (one carbon obscured or overlapping); IR (thin film): 3337 (br m, OH), 2953 (m, CH), 1684 (s, C=O) cm$^{-1}$; MS (ESI$^+$): *m*/*z* 428 ([$C_{16}H_{26}^{81}BrNO_4Si$+Na]$^+$, 77), 426 ([$C_{16}H_{26}^{79}BrNO_4Si$+Na]$^+$, 75), 262 (28), 260 (27); HRMS (ESI$^+$): calcd for $C_{16}H_{26}^{79}BrNO_4$SiNa ([M+Na]$^+$) 426.0712, found 426.0721.

A second fraction afforded the minor regioisomer **4c** as a colourless oil (15 mg, 14%; 55% ee, Chiralpak AD-H, 8% isopropyl alcohol/hexane; $t_R$: 25.9 major, 30.7 minor).

#### 4.2.10. (*R*)-tert-Butyl 2-hydroxy-4-(4-methylphenoxy)-butylcarbamate **4d** ($R^2$=$^t$Bu)

The reaction was conducted under standard conditions using 1-(but-3-enyloxy)-4-methylbenzene **3d**[31] (42 mg, 0.260 mmol), $(DHQD)_2AQN$ and *tert*-butyl carbamate. Analysis of the crude reaction mixture by 300 MHz $^1$H NMR identified a 7:1 ratio of the regioisomers **4d** and **5d**. Purification by flash chromatography (30% ethyl acetate/hexane) afforded the major regioisomer **4d** as a colourless oil (47 mg, 61%; 73% ee, Chiralcel OD-H, 5% isopropyl alcohol/hexane; $t_R$: 28.4 major, 30.0 minor). $[\alpha]_D$ −4.4 (*c* 1.0, $CH_2Cl_2$); $R_f$ 0.21 (30% ethyl acetate/hexane); $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.07 (2H, m, ArH), 6.81 (2H, m, ArH), 4.97 (1H, br s, NH), 4.19–4.03 (2H, m, H4), 3.98 (1H, ddd, *J* 12.5, 6.8, 3.4 Hz, H2), 3.35 (1H, dd, *J* 14.1, 3.2 Hz, $H1_A$), 3.14 (1H, dd, *J* 14.1, 7.1 Hz, $H1_B$), 2.58 (1H, br s, OH), 2.28 (3H, s, $ArCH_3$), 1.96–1.86 (2H, m, H3), 1.45 (9H, s, $^t$Bu); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 156.8, 156.4, 130.3, 129.9, 114.4, 79.7, 69.9, 65.6, 46.7, 33.9, 28.4, 20.4; IR (thin film): 3366 (br m, OH), 2976, 2928, 2876 (m, CH), 1686 (s, C=O) cm$^{-1}$; MS (ESI$^+$): *m*/*z* 318 ([M+Na]$^+$, 100); HRMS (ESI$^+$): calcd for $C_{16}H_{25}NO_4Na$ ([M+Na]$^+$) 318.1681, found 318.1670.

#### 4.2.11. (*R*)-2-(Trimethylsilyl)ethyl 2-hydroxy-4-(4-methylphenoxy)-butylcarbamate **4d** ($R^2$=TMSE)

The reaction was conducted under standard conditions using 1-(but-3-enyloxy)-4-methylbenzene **3d**[31] (42 mg, 0.260 mmol), $(DHQD)_2AQN$ and 2-(trimethylsilyl)ethyl carbamate. Analysis of the crude reaction mixture by 300 MHz $^1$H NMR identified a 7:1 ratio of the regioisomers **4d** and **5d**. Purification by flash chromatography (35% ethyl acetate/hexane) afforded the major regioisomer **4d** as

a colourless oil (55 mg, 62%; 75% ee, Chiralpak AD-H, 8% isopropyl alcohol/hexane; $t_R$: 16.5 major, 19.0 minor). $[\alpha]_D$ −14.4 (*c* 0.8, $CH_2Cl_2$); $R_f$ 0.30 (35% ethyl acetate/hexane); $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 7.07 (2H, m, ArH), 6.79 (2H, m, ArH), 5.05 (1H, br s, NH), 4.21–4.08 (4H, m, H4, $COOCH_2$), 4.00 (1H, m, H2), 3.41 (1H, ddd, *J* 14.0, 6.4, 3.4 Hz, $H1_A$), 3.19 (1H, m, $H1_B$), 2.92 (1H, br s, OH), 2.28 (3H, s, $ArCH_3$), 1.97–1.88 (2H, m, H3), 0.99 (2H, m, $CH_2$TMS), 0.04 (9H, s, TMS); $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ 157.6 (C), 156.3 (C), 130.4 (C), 129.9 (CH), 114.4 (CH), 69.9 ($CH_2$), 65.7 ($CH_2$), 63.3 ($CH_2$), 46.8 (CH), 33.8 ($CH_2$), 20.4 ($CH_3$), 17.7 ($CH_2$), −1.5 ($CH_3$); IR (thin film): 3354 (br m, OH), 2953 (m, CH), 1697 (s, C=O) cm$^{-1}$; MS (ESI$^+$): *m*/*z* 362 ([M+Na]$^+$, 100); HRMS (ESI$^+$): calcd for $C_{17}H_{29}NO_4SiNa$ ([M+Na]$^+$) 362.1764, found 362.1760.

#### 4.2.12. (R)-2-(Trimethylsilyl)ethyl 1-hydroxy-4-(4-methylphenoxy)butan-2-ylcarbamate **5d** ($R^2$=TMSE)

The reaction was conducted under standard conditions using 1-(but-3-enyloxy)-4-methylbenzene **3d**[31] (42 mg, 0.260 mmol), $(DHQD)_2PHAL$ and 2-(trimethylsilyl)ethyl carbamate. Analysis of the crude reaction mixture by 300 MHz $^1$H NMR identified a 1:1.5 ratio of the regioisomers **4d** and **5d**. Purification by flash chromatography (30% ethyl acetate/hexane) afforded the major regioisomer **5d** as a colourless oil (40 mg, 45%; 86% ee, Chiralpak AD-H, 8% isopropyl alcohol/hexane; $t_R$: 18.2 major, 16.4 minor). $[\alpha]_D$ +9.1 (*c* 1.1, $CH_2Cl_2$); $R_f$ 0.38 (40% ethyl acetate/hexane); $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.08 (2H, m, ArH), 6.78 (2H, m, ArH), 5.15 (1H, br s, NH), 4.14 (2H, m, $COOCH_2$), 4.04 (2H, t, *J* 5.8 Hz, H4), 3.91 (1H, m, H2), 3.76–3.68 (2H, m, H1), 2.28 (3H, s, $ArCH_3$), 2.14–1.93 (3H, m, H3, OH), 0.96 (2H, m, $CH_2$TMS), 0.03 (9H, s, TMS); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 157.0, 156.3, 130.4, 130.0, 114.4, 65.3, 65.1, 63.3, 51.2, 30.9, 20.4, 17.7, −1.5; IR (thin film): 3331 (br m, OH), 2953, 2897 (m, CH), 1689 (s, C=O) cm$^{-1}$; MS (ESI$^+$): *m*/*z* 362 ([M+Na]$^+$, 100); HRMS (ESI$^+$): calcd for $C_{17}H_{29}NO_4SiNa$ ([M+Na]$^+$) 362.1764, found 362.1757.

A second fraction afforded the minor regioisomer **4d** as a colourless oil (25 mg, 28%; 64% ee, Chiralpak AD-H, 8% isopropyl alcohol/hexane; $t_R$: 21.4 major, 24.2 minor).

#### 4.2.13. (R)-tert-Butyl 2-hydroxy-4-(4-nitrophenoxy)-butylcarbamate **4e** ($R^2$=$^t$Bu)

The reaction was conducted under standard conditions using 1-(but-3-enyloxy)-4-nitrobenzene **3e**[32] (50 mg, 0.260 mmol), $(DHQD)_2AQN$ and *tert*-butyl carbamate. Analysis of the crude reaction mixture by 300 MHz $^1$H NMR identified a 9:1 ratio of the regioisomers **4e** and **5e**. Purification by flash chromatography (40% ethyl acetate/hexane) afforded the major regioisomer **4e** (62 mg, 73%; 73% ee, Chiralcel OD-H, 15% isopropyl alcohol/hexane; $t_R$: 13.5 major, 14.7 minor). $[\alpha]_D$ +5.1 (*c* 1.1, $CH_2Cl_2$); $R_f$ 0.20 (30% ethyl acetate/hexane); $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 8.17 (2H, m, ArH), 6.94 (2H, m, ArH), 5.01 (1H, br t, *J* 5.7 Hz, NH), 4.31–4.14 (2H, m, H4), 3.98 (1H, m, H2), 3.34 (1H, ddd, *J* 14.3, 6.2, 3.3 Hz, $H1_A$), 3.22–3.08 (1H, m, $H1_B$), 3.02 (1H, br s, OH), 1.98–1.84 (2H, m, H3), 1.44 (9H, s, $^t$Bu); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 164.2, 157.4, 142.0, 126.3, 114.9, 80.5, 69.3, 66.1, 47.3, 34.2, 28.7; IR (thin film): 3396 (br s, OH, NH), 1686 (s, C=O) cm$^{-1}$; MS (ESI$^+$): *m*/*z* 349 ([M+Na]$^+$, 100); HRMS (ESI$^+$): calcd for $C_{15}H_{22}N_2O_6Na$ ([M+Na]$^+$) 349.1376, found 349.1374.

#### 4.2.14. (R)-Methyl 2-hydroxy-4-(4-nitrophenoxy)butylcarbamate **4e** ($R^2$=Me)

The reaction was conducted under standard conditions using 1-(but-3-enyloxy)-4-nitrobenzene **3e**[32] (50 mg, 0.260 mmol), $(DHQD)_2AQN$ and methyl carbamate. Analysis of the crude reaction mixture by 300 MHz $^1$H NMR identified a 9:1 ratio of the regioisomers **4e** and **5e**. Purification by flash chromatography (35% ethyl acetate/hexane) afforded the major regioisomer **4e** (45 mg, 61%; 79% ee, Chiralcel OD-H, 15% isopropyl alcohol/hexane; $t_R$: 32.0 major, 38.1 minor). $[\alpha]_D$ +2.1 (*c* 1.0, $CH_2Cl_2$); $R_f$ 0.27 (35% ethyl acetate/hexane); $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 8.19 (2H, m, ArH), 6.96 (2H, m, ArH), 5.18 (1H, br s, NH), 4.30–4.17 (2H, m, H4), 4.02 (1H, m, H2), 3.69 (3H, s, $OCH_3$), 3.41 (1H, m, $H1_A$), 3.22 (1H, m, $H1_B$), 2.36 (1H, br s, OH), 2.06–1.87 (2H, m, H3); $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ 163.7, 155.7, 141.0, 125.9, 114.5, 68.7, 65.6, 52.4, 47.2, 33.7; IR (thin film): 3331 (br s, OH), 2951 (w, CH), 1724 (s, C=O) cm$^{-1}$; MS (ESI): *m*/*z* 285 ([M+H]$^+$, 25), 227 (19); HRMS (ESI$^+$): calcd for $C_{12}H_{17}N_2O_6$ ([M+H]$^+$) 285.1087, found 285.1081.

#### 4.2.15. (R)-2-(Trimethylsilyl)ethyl 2-hydroxy-4-(4-nitrophenoxy)-butylcarbamate **4e** ($R^2$=TMSE)

The reaction was conducted under standard conditions using 1-(but-3-enyloxy)-4-nitrobenzene **3e**[32] (434 mg, 2.25 mmol), $(DHQD)_2AQN$ and 2-(trimethylsilyl)ethyl carbamate. Analysis of the crude reaction mixture by 300 MHz $^1$H NMR identified a 10:1 ratio of the regioisomers **4e** and **5e**. Purification by flash chromatography (40% ethyl acetate/hexane) afforded the major regioisomer **4e** (558 mg, 67%; 81% ee, Chiralcel OD-H, 15% isopropyl alcohol/hexane; $t_R$: 14.3 major, 15.4 minor). The product was recrystallised from tetrahydrofuran/hexane (1:3; 24 mL) to give the product **4e** as white needles (447 mg, 54%; 96% ee, Chiralcel OD-H, 8% isopropyl alcohol/hexane; $t_R$: 39.4 major, 46.6 minor). Mp 92–93 °C; $[\alpha]_D$ +2.7 (*c* 2.2, $CH_2Cl_2$); $R_f$ 0.29 (40% ethyl acetate/hexane); $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 8.17 (2H, m, ArH), 6.94 (2H, m, ArH), 5.12 (1H, m, NH), 4.29–4.13 (4H, m, H4, $COOCH_2$), 4.00 (1H, m, H2), 3.39 (1H, m, $H1_A$), 3.21 (1H, m, $H1_B$), 2.87 (1H, br s, OH), 2.05–1.87 (2H, m, H3), 0.97 (2H, m, $CH_2$TMS), 0.03 (9H, s, TMS); $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ 163.8, 157.8, 141.5, 125.8, 114.4, 68.5, 65.6, 63.5, 47.1, 33.6, 17.7, −1.6; IR (thin film): 3398 (br s, OH), 2953, 2894 (m, CH), 1701 (s, C=O) cm$^{-1}$; MS (ESI$^+$): *m*/*z* 762 ([2M+Na]$^+$, 100), 393 ([M+Na]$^+$, 83); HRMS (ESI$^+$): calcd for $C_{16}H_{26}N_2O_6SiNa$ ([M+Na]$^+$) 393.1458, found 393.1449.

#### 4.2.16. (S)-2-(Trimethylsilyl)ethyl 2-hydroxy-4-(4-nitrophenoxy)-butylcarbamate ent-**4e** ($R^2$=TMSE)

The reaction was conducted under standard conditions using 1-(but-3-enyloxy)-4-nitrobenzene **3e**[32] (50 mg, 0.260 mmol), $(DHQ)_2AQN$ and 2-(trimethylsilyl)ethyl carbamate. Analysis of the crude reaction mixture by 300 MHz $^1$H NMR identified a 9:1 ratio of the regioisomers *ent*-**4e** and *ent*-**5e**. Purification by flash chromatography (40% ethyl acetate/hexane) afforded the major regioisomer *ent*-**4e** (59 mg, 61%; 72% ee, Chiralcel OD-H, 15% isopropyl alcohol/hexane; $t_R$: 13.7 minor, 14.8 major).

#### 4.2.17. (R)-tert-Butyl 1-hydroxy-4-(4-nitrophenoxy)butan-2-ylcarbamate **4e** ($R^2$=$^t$Bu)

The reaction was conducted under standard conditions using 1-(but-3-enyloxy)-4-nitrobenzene **3e**[32] (30 mg, 0.154 mmol), $(DHQD)_2AQN$ and *tert*-butyl carbamate. Analysis of the crude reaction mixture by 300 MHz $^1$H NMR identified a 1:6 ratio of the regioisomers **4e** and **5e**. Purification by flash chromatography (5% methanol/dichloromethane) afforded the major regioisomer **5e** (36 mg, 71%; 96% ee, Chiralcel OD-H, 12% isopropyl alcohol/hexane; $t_R$: 20.3 major, 19.1 minor). $[\alpha]_D$ +29 (*c* 1.8, $CH_2Cl_2$); $R_f$ 0.063 (30% ethyl acetate/hexane); $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 8.17 (2H, m, 2ArH), 6.94 (2H, m, 2ArH), 4.96 (1H, d, *J* 8.4 Hz, NH), 4.15 (2H, t, *J* 6.3 Hz, H4), 3.88 (1H, m, H2), 3.80–3.61 (2H, m, H1), 2.66 (1H, br s, OH), 2.12–1.97 (2H, m, H3), 1.40 (9H, s, $^t$Bu); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 164.1, 156.5, 141.9, 126.2, 114.8, 80.2, 66.3, 65.6, 50.5, 31.4, 28.6; IR (thin film): 3398 (br s, OH, NH), 2975 (CH), 1703 (s, C=O) cm$^{-1}$; MS (ESI$^+$): *m*/*z* 349 ([M+Na]$^+$, 48%); HRMS (ESI$^+$): calcd for $C_{15}H_{22}N_2O_6Na$ 349.1376, found 349.1377.

#### 4.2.18. (R)-2-(Trimethylsilyl)ethyl 1-hydroxy-4-(4-nitrophenoxy)-butan-2-ylcarbamate **3e** ($R^2$=TMSE)

The reaction was conducted under standard conditions using 1-(but-3-enyloxy)-4-nitrobenzene **3e**[32] (50 mg, 0.260 mmol),

$(DHQD)_2PHAL$ and 2-(trimethylsilyl)ethyl carbamate. Analysis of the crude reaction mixture by 300 MHz $^1H$ NMR identified a 1:12 ratio of the regioisomers **4e** and **5e**. Purification by flash chromatography (45% ethyl acetate/hexane) afforded the major regioisomer **5e** (63 mg, 65%, 95% ee, Chiralpak AD-H, 12% isopropyl alcohol/hexane; $t_R$: 30.8 minor, 39.7 major) $[\alpha]_D$ −27.5 (*c* 1.3, $CH_2Cl_2$); $R_f$ 0.29 (40% ethyl acetate/hexane); $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 8.18 (2H, m, ArH), 6.94 (2H, m, ArH), 5.03 (1H, br d, *J* 7.3 Hz, NH), 4.18–4.09 (4H, m, H4, $COOCH_2$), 3.93 (1H, m, H3), 3.79–3.66 (2H, m, H2), 2.31 (1H, br s, OH), 2.18–1.93 (2H, m, H2), 0.94 (2H, m, $CH_2TMS$), 0.01 (9H, s, TMS); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 163.6, 156.9, 141.7, 125.9, 114.5, 65.9, 65.1, 63.4, 50.5, 31.0, 17.7, −1.5; IR (thin film): 3396 (br m, OH), 2953, 2894 (m, CH), 1693 (s, C=O) $cm^{-1}$; MS ($ESI^+$): *m*/*z* 393 ($[M+Na]^+$, 12), 227 (100); HRMS ($ESI^+$): calcd for $C_{16}H_{26}N_2O_6SiNa$ ($[M+Na]^+$) 393.1458, found 393.1439.

#### 4.2.19. (S)-2-(Trimethylsilyl)ethyl 1-hydroxy-4-(4-nitrophenoxy)-butan-2-ylcarbamate ent-5e ($R^2$=TMSE)

The reaction was conducted under standard conditions using 1-(but-3-enyloxy)-4-nitrobenzene **3e**[32] (575 mg, 2.98 mmol), $(DHQ)_2PHAL$ and 2-(trimethylsilyl)ethyl carbamate. Analysis of the crude reaction mixture by 300 MHz $^1H$ NMR identified a 1:12 ratio of the regioisomers *ent*-**4e** and *ent*-**5e**. Purification by flash chromatography (45% ethyl acetate/hexane) afforded the major regioisomer *ent*-**5e** (706 mg, 64%, 96% ee, Chiralpak AD-H, 25% isopropyl alcohol/hexane; $t_R$: 19.6 major, 27.0 minor).

#### 4.2.20. 2-(But-3-enyloxy)-1,3-dimethyl-5-nitrobenzene 3f

To a stirred solution of but-3-en-1-ol (1.00 g, 13.9 mmol) in tetrahydrofuran (35 mL) at room temperature was added 2,6-dimethyl-4-nitrophenol (3.01 g, 18.0 mmol) and triphenylphosphine (3.92 g, 14.9 mmol). Following addition of diethyl azodicarboxylate (3.06 mL, 19.4 mmol), the mixture was heated at reflux for 30 min then cooled and concentrated to afford a brown oil. Purification by flash chromatography (15% ethyl acetate/hexane) afforded pure ether **3f** as a colourless oil (2.21 g, 72%). $R_f$ 0.40 (15% ethyl acetate/hexane); $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 7.80 (2H, s, ArH), 5.90 (1H, m, H3), 5.20–5.05 (2H, m, H4), 3.83 (2H, t, *J* 6.6 Hz, H1), 2.54 (2H, qt, *J* 6.7, 1.3 Hz, H2), 2.27 (6H, s, ArMe); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 161.5, 143.4, 134.3, 132.4, 124.2, 117.5, 71.9, 34.8, 16.6; IR (thin film): 2979, 2959, 2927 (w, CH), 1519 (s, C=C), 1346 (s, $NO_2$) $cm^{-1}$; MS (EI): *m*/*z* 222 (45), 221 ($M^{+\bullet}$, 30), 55 (100); HRMS (EI): calcd for $C_{12}H_{15}NO_3$ ($M^{+\bullet}$) 221.1052, found 221.1051.

#### 4.2.21. (R)-2-(Trimethylsilyl)ethyl 4-(2,6-dimethyl-4-nitrophenoxy)-2-hydroxybutylcarbamate 4f ($R^2$=TMSE)

The reaction was conducted under standard conditions using substrate **3f** (58 mg, 0.260 mmol), $(DHQD)_2AQN$ and 2-(trimethylsilyl)ethyl carbamate. Analysis of the crude reaction mixture by 300 MHz $^1H$ NMR identified a 9:1 ratio of the regioisomers **4f** and **5f**. Purification by flash chromatography (30% ethyl acetate/hexane) afforded the major regioisomer **4f** as a pale yellow oil (50 mg, 48%; 77% ee, Chiralcel OD-H, 12% isopropyl alcohol/hexane; $t_R$: 14.0 major, 15.2 minor). $[\alpha]_D$ +0.4 (*c* 1.1, $CH_2Cl_2$); $R_f$ 0.18 (30% ethyl acetate/hexane); $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 7.91 (2H, s, ArH), 5.11 (1H, br s, NH), 4.19–3.95 (5H, m, H4, H2, $COOCH_2$), 3.42 (1H, m, $H1_A$), 3.26 (1H, m, $H1_B$), 2.51 (1H, br s, OH), 2.35 (6H, s, $ArCH_3$), 1.99–1.92 (2H, m, H3), 0.98 (2H, m, $CH_2TMS$), 0.03 (9H, s, TMS); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 161.0, 157.7, 143.6, 132.3, 124.3, 70.0, 69.4, 63.5, 47.2, 34.7, 17.7, 16.5, −1.5; IR (thin film): 3412 (br m, OH), 2953 (m, CH), 1701 (s, C=O) $cm^{-1}$; MS ($ESI^+$): *m*/*z* 421 ($[M+Na]^+$, 15); HRMS ($ESI^+$): calcd for $C_{18}H_{30}N_2O_6SiNa$ ($[M+Na]^+$) 421.1771, found 421.1759.

The reaction was conducted under standard conditions using substrate **4f** (58 mg, 0.260 mmol), $(DHQD)_2PHAL$ and 2-(trimethylsilyl)ethyl carbamate. Analysis of the crude reaction mixture by 300 MHz $^1H$ NMR identified a 5:1 ratio of the regioisomers **4f** and **5f**. Purification by flash chromatography (30% ethyl acetate/hexane) afforded the major regioisomer **4f** as a pale yellow oil (55 mg, 53%; 67% ee, Chiralpak AD-H, 12% isopropyl alcohol/hexane; $t_R$: 14.0 major, 15.1 minor).

#### 4.2.22. (R)-2-(Trimethylsilyl)ethyl 4-(tert-butyldiphenylsilyloxy)-2-hydroxybutylcarbamate 4g ($R^2$=TMSE)

The reaction was conducted under standard conditions using (but-3-enyloxy)(*tert*-butyl)diphenylsilane **3g**[33] (81 mg, 0.260 mmol), $(DHQD)_2AQN$ and 2-(trimethylsilyl)ethyl carbamate. Analysis of the crude reaction mixture by 300 MHz $^1H$ NMR identified a 9:1 ratio of the regioisomers **4g** and **5g**. Purification by flash chromatography (35% ethyl acetate/hexane) afforded the major regioisomer **4g** as a pale yellow oil (71 mg, 56%; 65% ee, Chiralpak AD-H, 2% isopropyl alcohol/hexane; $t_R$: 35.2 major, 39.6 minor). $[\alpha]_D$ −3.2 (*c* 1.0, $CH_2Cl_2$); $R_f$ 0.30 (30% ethyl acetate/hexane); $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 7.66 (4H, m, ArH), 7.45–7.40 (6H, m, ArH), 5.08 (1H, br s, NH), 4.16 (2H, m, $COOCH_2$), 3.99 (1H, m, H2), 3.88 (2H, t, *J* 5.5 Hz, H4), 3.37 (1H, m, $H1_A$), 3.14 (1H, m, $H1_B$), 1.85–1.59 (2H, m, H3), 1.06 (9H, s, $^tBu$), 0.98 (2H, m, $CH_2TMS$), 0.04 (9H, s, TMS) (OH overlapping or obscured); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 157.3, 135.5, 132.8, 129.9, 127.8, 71.1, 63.1, 46.7, 35.7, 26.8, 19.0, 17.8, −1.5 (one carbon overlapping or obscured); IR (thin film): 3346 (br m, OH), 2956, 2893 (s, CH), 1703 (s, C=O) $cm^{-1}$; MS ($ESI^+$): *m*/*z* 510 ($[M+Na]^+$, 100); HRMS ($ESI^+$): calcd for $C_{26}H_{41}NO_4Si_2Na$ ($[M+Na]^+$) 510.2472, found 510.2465.

The reaction was conducted under standard conditions using (but-3-enyloxy)(*tert*-butyl)diphenylsilane **3g**[33] (81 mg, 0.260 mmol), $(DHQD)_2PHAL$ and 2-(trimethylsilyl)ethyl carbamate. Analysis of the crude reaction mixture by 300 MHz $^1H$ NMR identified a 5:1 ratio of the regioisomers **4g** and **5g**. Purification by flash chromatography (35% ethyl acetate/hexane) afforded the major regioisomer **4g** as a pale yellow oil (61 mg, 48%; 79% ee, Chiralpak AD-H, 2% isopropyl alcohol/hexane; $t_R$: 35.2 major, 39.6 minor).

#### 4.2.23. (S)-((R)-4-(4-Nitrophenoxy)-1-((2-(trimethylsilyl)ethoxy)-carbonylamino)butan-2-yl)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate ((S)-MTPA derivative) 6

Alcohol **4e** ($R^2$=TMSE, 10 mg, 0.0270 mmol) and (*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoic acid (8.2 mg, 0.0350 mmol) were stirred in dichloromethane (1.0 mL) at room temperature. To this solution was added *N*,*N*′-dicyclohexylcarbodiimide (57 μL, 1 M, 0.0567 mmol) and 4-(dimethylamino)pyridine (0.3 mg, 0.0027 mmol). The mixture was sonicated at 0 °C for 5 h, during which time a white precipitate formed. The mixture was filtered through Celite and concentrated. Purification by flash chromatography (25% ethyl acetate/hexane) afforded pure (*S*)-MTPA derivative **6** as a pale yellow oil (12 mg, 76%). $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 8.20 (2H, m, H3′, H5′), 7.48–7.28 (5H, m, Ph), 6.91 (2H, m, H2′, H6′), 5.41 (1H, m, H2), 4.61 (1H, m, NH), 4.14 (2H, m, $COOCH_2$), 4.18–4.01 (2H, m, H4), 3.53–3.41 (2H, m, H1), 3.49 (3H, s, OMe), 2.23–2.13 (2H, m, H3), 0.96 (2H, m, $CH_2TMS$), 0.03 (9H, s, TMS).

#### 4.2.24. (R)-((R)-4-(4-Nitrophenoxy)-1-((2-(trimethylsilyl)ethoxy)-carbonylamino)butan-2-yl)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate ((R)-MTPA derivative) 7

Alcohol **4e** (10 mg, 0.0270 mmol) and (*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoic acid (8.2 mg, 0.0350 mmol) were stirred in dichloromethane (1.0 mL) at room temperature. To this solution was added *N*,*N*′-dicyclohexylcarbodiimide (57 μL, 1 M, 0.0567 mmol) and 4-(dimethylamino)pyridine (0.3 mg, 0.0027 mmol). The mixture was sonicated at 0 °C for 5 h, during which time a white precipitate formed. The mixture was filtered through Celite and concentrated. Purification by flash

chromatography (25% ethyl acetate/hexane) afforded pure (*R*)-MTPA derivative **7** as a pale yellow oil (12 mg, 76%). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 8.18 (2H, m, H3′, H5′), 7.49–7.27 (5H, m, Ph), 6.84 (2H, m, H2′, H6′), 5.41 (1H, m, H2), 4.75 (1H, m, NH), 4.16 (2H, m, $COOCH_2$), 4.01–3.81 (2H, m, H4), 3.55–3.47 (2H, m, H1), 3.51 (3H, s, OMe), 2.19–2.07 (2H, m, H3), 0.97 (2H, m, $CH_2TMS$), 0.04 (9H, s, TMS).

#### 4.2.25. (R)-2-(Trimethylsilyl)ethyl 2-(tert-butyldimethylsilyloxy)-4-(4-nitrophenoxy)butylcarbamate **8**

To a solution of alcohol **4e** ($R^2$=TMSE, 216 mg, 0.583 mmol) in dimethylformamide (2.0 mL) at ambient temperature was added *tert*-butyldimethylsilyl chloride (263 mg, 1.75 mmol) followed by imidazole (159 mg, 2.33 mmol) and 4-dimethylaminopyridine (21 mg, 0.172 mmol). The reaction mixture was heated to 40 °C. After 14 h the reaction was quenched upon addition of a saturated aqueous solution of sodium hydrogen carbonate (5 mL). Ethyl acetate (10 mL) was added and the organic layer was separated. The aqueous layer was then extracted with ethyl acetate (2×10 mL) and the combined organic extract was washed with water (10 mL), brine (10 mL), dried ($NaSO_4$) and concentrated under reduced pressure to leave a brown oil, which was purified by flash chromatography (10% ethyl acetate/hexane). The product **8** was isolated as a pale yellow oil (281 mg, 99%). $[\alpha]_D$ +16.0 (*c* 2.6, $CH_2Cl_2$); $R_f$ 0.27 (10% ethyl acetate/hexane); $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 8.18 (2H, m, ArH), 6.93 (2H, m, ArH), 4.86 (1H, m, NH), 4.20–4.00 (5H, m, H4, H2, $COOCH_2$), 3.30–3.23 (2H, m, H1), 2.05–1.85 (2H, m, H3), 0.97 (2H, m, $CH_2TMS$), 0.87 (9H, m, $^t$Bu), 0.07, (3H, s, $SiMe_A$), 0.03 (9H, s, TMS), −0.02 (3H, s, $SiMe_B$); $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ 163.8, 156.9, 141.5, 125.9, 114.3, 67.8, 64.8, 63.1, 46.3, 33.8, 25.7, 17.9, 17.7, −1.6, −4.6, −4.9; IR (thin film): 3342 (br w, NH), 2953, 2930, 2894, 2856 (m, CH), 1718 (s, C=O) cm$^{-1}$; MS (ESI$^+$): *m*/*z* 991 ([2M+Na]$^+$, 10), 940 (16), 507 ([M+Na]$^+$, 100), 457 (21), 341 (23); HRMS (ESI$^+$): calcd for $C_{22}H_{40}N_2O_6Si_2Na$ ([M+Na]$^+$) 507.2323, found 507.2321.

#### 4.2.26. (R)-2-(Trimethylsilyl)ethyl 2-(tert-butyldimethylsilyloxy)-4-hydroxybutylcarbamate **9**

A suspension of *p*-nitrophenyl ether **8** (140 mg, 0.290 mmol) and palladium on charcoal (15 mg) in ethyl acetate (2 mL) was submitted to an atmosphere of hydrogen gas. After complete consumption of starting material was observed by TLC, acetic anhydride (1 mL) was added and the reaction was stirred for 1 h. The mixture was then filtered through a 1 cm pad of Celite® and the residue was washed with ethyl acetate (1 mL). The combined filtrate was evaporated under reduced pressure to leave a pale brown oil. The crude product was dissolved in acetonitrile/water (10:1; 3.3 mL) cooled to 0 °C and ammonium cerium(IV) nitrate (238 mg, 0.434 mmol) was added. After 15 min the reaction was quenched upon addition of a saturated aqueous solution of sodium thiosulfate (5 mL). The mixture was extracted with ethyl acetate (3×10 mL) and the combined organic extract was washed with brine (10 mL), dried ($NaSO_4$) and concentrated under reduced pressure to leave a brown oil. The crude material was purified by flash chromatography (30% ethyl acetate/hexane) to give the desired product **9** as a colourless oil (65 mg, 62%). $[\alpha]_D$ +6.5 (*c* 1.1, $CH_2Cl_2$); $R_f$ 0.45 (40% ethyl acetate/hexane); $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 4.86 (1H, br s, NH), 4.15 (2H, br t, *J* 8.4 Hz, $COOCH_2$), 3.99 (1H, quin, *J* 5.9 Hz, H2), 3.74 (2H, t, *J* 5.9 Hz, H4), 3.33–3.16 (2H, m, H1), 2.03 (1H, br s, OH), 1.82–1.64 (2H, m, H3), 0.97 (2H, t, *J* 8.3 Hz, $CH_2TMS$), 0.89 (9H, s, $^t$Bu), 0.09 (6H, s, $SiMe_2$), 0.03 (9H, s, TMS); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 157.0 (C), 69.6 (CH), 63.1 ($CH_2$), 59.5 ($CH_2$), 46.3 ($CH_2$), 36.7 ($CH_2$), 25.8 ($CH_3$), 18.0 (C), 17.8 ($CH_2$), −1.5 ($CH_3$), −4.6 ($CH_3$), −4.8 ($CH_3$); IR (thin film): 3352 (br s, OH), 2953, 2894, 2856 (s, CH), 1705 (s, C=O) cm$^{-1}$; MS (ESI$^+$): *m*/*z* 386 ([M+Na]$^+$, 100), 336 (24); HRMS (ESI$^+$): calcd for $C_{16}H_{37}NO_4Si_2Na$ ([M+Na]$^+$) 386.2159, found 386.2149.

#### 4.2.27. (R)-3-(tert-Butyldimethylsilyloxy)-4-((2-(trimethylsilyl)-ethoxy)carbonylamino)butanoic acid **10**

To a solution of alcohol **9** (31 mg, 0.0852 mmol) and TEMPO (1.3 mg, 0.0083 mmol) in acetonitrile (1 mL) and pH 6.7 potassium phosphate buffer (0.6 mL) was added simultaneously an aqueous solution of $NaClO_2$ (84 μL, 2 M, 0.168 mmol) and a solution of sodium hypochlorite (10 μL, 1.4 M, 14 μM). After stirring for 15 h at 35 °C the reaction mixture was adjusted to pH 3 upon addition of citric acid. The reaction was diluted with water (5 mL) and the aqueous layer was extracted ethyl acetate (3×10 mL). The combined organic extract was washed with brine (5 mL), dried ($NaSO_4$) and concentrated under reduced pressure to leave the crude product as a pale brown oil. Purification by flash chromatography (5% methanol/dichloromethane) gave the product **10** as a colourless oil (27 mg, 85%). $[\alpha]_D$ +9.3 (*c* 0.6, MeOH); $R_f$ 0.29 (40% ethyl acetate/hexane); $^1$H NMR (300 MHz, MeOH-$d_4$): $\delta$ 6.75 (1H, m, NH), 4.25–4.12 (3H, m, H3, $COOCH_2$), 3.23 (1H, m, $H4_A$), 3.09 (1H, m, $H4_B$), 2.51 (1H, dd, *J* 14.9, 4.3 Hz, $H2_A$), 2.33 (1H, dd, *J* 14.9, 7.9 Hz, $H2_B$), 1.01 (2H, m, $CH_2TMS$), 0.90 (9H, s, $^t$Bu), 0.12 (3H, s, $SiMe_A$), 0.10 (3H, s, $SiMe_B$), 0.07 (9H, s, TMS); $^{13}$C NMR (50 MHz, MeOH-$d_4$): $\delta$ 175.2 (C), 159.3 (C), 70.1 (CH), 63.9 ($CH_2$), 47.6 ($CH_2$), 41.8 ($CH_2$), 26.3 ($CH_3$), 18.9 ($CH_2$), 18.7 (C), −1.5 ($CH_3$), −4.4 ($CH_3$), −4.8 ($CH_3$); IR (thin film): 3339 (w, NH), 2953, 2895, 2858 (m, CH), 1710 (s, C=O) cm$^{-1}$; MS (ESI$^+$): *m*/*z* 422 ([M−H+2Na]$^+$, 41), 400 ([M+Na]$^+$, 100); HRMS (ESI$^+$): calcd for $C_{16}H_{35}NO_5Si_2Na$ ([M+Na]$^+$) 400.1952, found 400.1965.

#### 4.2.28. (R)-2-(Trimethylsilyl)ethyl 1,4-dihydroxybutan-2-ylcarbamate **11**

A suspension of *p*-nitrophenyl ether **5e** ($R^2$=TMSE, 135 mg, 0.364 mmol) and palladium on charcoal (20 mg) in ethyl acetate (3 mL) was submitted to an atmosphere of hydrogen gas. After complete consumption of starting material was observed by TLC, acetic anhydride (1 mL) was added and the reaction was stirred for 1 h. The mixture was then filtered through a 1 cm pad of Celite® and the residue was washed with ethyl acetate (1 mL). The combined filtrate was evaporated under reduced pressure to leave a pale brown oil. The crude product was dissolved in acetonitrile/water (10:1; 3.3 mL), cooled to 0 °C and ammonium cerium(IV) nitrate (395 mg, 0.721 mmol) was added. After 10 min the reaction was quenched upon addition of a saturated aqueous solution of sodium thiosulfate (5 mL). The mixture was extracted with ethyl acetate (3×10 mL) and the combined organic extract was washed with brine (10 mL), dried ($NaSO_4$) and concentrated under reduced pressure to leave a brown oil. The crude product was purified by flash chromatography (10% methanol/dichloromethane) to give the diol product **11** as a pale yellow oil (18.5 mg, 20%). $[\alpha]_D$ +10.9 (*c* 1.3, $CH_2Cl_2$); $R_f$ 0.44 (90% ethyl acetate/hexane); $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 5.33 (1H, br d, *J* 6.4 Hz, NH), 4.13 (2H, m, $COOCH_2$), 3.84 (1H, m, H2), 3.72–3.59 (4H, m, H1, H4), 3.16 (2H, br s, OH), 1.80 (1H, m, $H3_A$), 1.64 (1H, m, $H3_B$), 0.96 (2H, m, $CH_2TMS$), 0.03 (9H, s, TMS); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 157.6, 65.0, 63.5, 58.7, 50.0, 34.6, 17.7, −1.5; IR (thin film): 3339 (br m, OH), 2953, 2895 (m, CH), 1689 (s, C=O) cm$^{-1}$; MS (ESI$^+$): *m*/*z* 272 ([M+Na]$^+$, 17), 250 ([M+H]$^+$, 11), 222 (15), 204 (15); HRMS (ESI$^+$): calcd for $C_{10}H_{23}NO_4SiNa$ ([M+Na]$^+$) 272.1294, found 272.1289.

#### 4.2.29. (S)-2-(Trimethylsilyl)ethyl 1,4-dihydroxybutan-2-ylcarbamate ent-**11**

To a solution of L-aspartic acid, 1,4-dimethyl ester, hydrochloride (452 mg, 2.29 mmol) and triethylamine (0.64 mL, 4.60 mmol) in dichloromethane (11 mL) was added carbonyldiimidazole (745 mg, 4.60 mmol) and the reaction was stirred for 30 min followed by the addition of 2-(trimethylsilyl)ethanol (0.66 mL, 4.60 mmol). After 14 h the reaction was quenched upon addition of a saturated aqueous solution of sodium hydrogen carbonate (20 mL). Ethyl

acetate (20 mL) was added and the organic layer was separated. The aqueous layer was then extracted with ethyl acetate (2×10 mL) and the combined organic extract was washed with water (10 mL), brine (10 mL), dried ($NaSO_4$) and concentrated under reduced pressure to leave a colourless oil, which was purified by flash chromatography (20% ethyl acetate/hexane) to give the *N*-((2-(trimethylsilyl)ethoxy)carbonyl)-L-aspartic acid, dimethyl ester **12** as a colourless oil (180 mg). This was dissolved in tetrahydrofuran (4 mL) and added via cannula to a suspension of lithium borohydride (76 mg, 3.50 mmol) in tetrahydrofuran (4 mL). After 12 h the reaction was quenched upon addition of a saturated aqueous solution of sodium hydrogen carbonate (10 mL). Ethyl acetate (10 mL) was added and the organic layer was separated. The aqueous layer was then extracted with ethyl acetate (2×10 mL) and the combined organic extract was washed with water (10 mL), brine (10 mL), dried ($NaSO_4$) and concentrated under reduced pressure to leave a colourless oil, which was purified by flash chromatography (7% methanol/dichloromethane) to give the (*S*)-2-(trimethylsilyl)ethyl 1,4-dihydroxybutan-2-ylcarbamate *ent*-**11** as a colourless oil (135 mg, 24%). $[\alpha]_D$ −10.8 (*c* 1.7, $CH_2Cl_2$).

#### 4.2.30. (S)-4-(4-Nitrophenoxy)-2-((2-(trimethylsilyl)ethoxy)-carbonylamino)butanoic acid **13**

To a solution of alcohol *ent*-**5e** ($R^2$=TMSE, 524 mg, 1.42 mmol) and TEMPO (22 mg, 0.141 mmol) in acetonitrile (7.1 mL) and pH 6.7 potassium phosphate buffer (5.3 mL) was added simultaneously an aqueous solution of sodium chlorite (1.42 mL, 2 M, 2.84 mmol) and a solution of sodium hypochlorite (20 μL, 1.4 M, 28 μmol). After stirring for 17 h at 35 °C the reaction mixture was taken to pH 3 upon addition of citric acid. The reaction was diluted with water (5 mL) and the aqueous layer was extracted ethyl acetate (3×15 mL). The combined organic extract was washed with brine (5 mL) and concentrated under reduced pressure to leave the crude product, which was redissolved in water/diethyl ether (1:1; 50 mL) and the aqueous layer was taken to pH 10 upon addition of sodium hydroxide (2 M). The ether layer was separated and the aqueous layer extracted with diethyl ether (2×10 mL). The aqueous layer was then converted to pH 3 upon addition of an aqueous solution of hydrochloric acid and extracted with ethyl acetate (3×15 mL). The combined organics were washed with brine (15 mL), dried ($NaSO_4$) and concentrated under reduced pressure to leave the product **13** as a pale yellow oil (455 mg, 84%). $[\alpha]_D$ −6.4 (*c* 1.4, MeOH); $R_f$ 0.30 (10% methanol/dichloromethane); $^1$H NMR (200 MHz, MeOH-$d_4$): $\delta$ 8.19 (2H, m, ArH), 7.08 (2H, m, ArH), 4.49–4.39 (1H, m, H2), 4.27–4.08 (4H, m, H4, $COOCH_2$), 2.46–2.09 (2H, m, H3), 0.95 (2H, m, $CH_2TMS$), 0.02 (9H, s, TMS); $^{13}$C NMR (50 MHz, MeOH-$d_4$): $\delta$ 176.9, 166.8, 144.4, 128.3, 117.3, 67.8, 65.7, 53.7, 33.6, 20.1, 0.0 (one carbon obscured or overlapping); IR (thin film): 3330 (br s, OH), 2953 (m, CH), 1712 (s, C=O) $cm^{-1}$; MS ($ESI^+$): *m*/*z* 407 ($[M+Na]^+$, 75), 241 (100); HRMS ($ESI^+$): calcd for $C_{16}H_{24}N_2O_7SiNa$ ($[M+Na]^+$) 407.1251, found 407.1246.

#### 4.2.31. (E)-1-Nitro-4-(pent-3-enyloxy)benzene **14**

To a stirred solution of (*E*)-pent-3-en-1-ol[34] (0.990 g, 11.5 mmol) in tetrahydrofuran (41 mL) at room temperature was added *p*-nitrophenol (1.65 g, 11.9 mmol) and triphenylphosphine (3.92 g, 14.9 mmol). Following addition of diethyl azodicarboxylate (2.53 mL, 16.1 mmol), the mixture was heated at reflux for 30 min then cooled and concentrated to afford a brown oil. Purification by flash chromatography (10% ethyl acetate/hexane) afforded pure ether **14** as a colourless oil (1.20 g, 50%). $R_f$ 0.50 (10% ethyl acetate/hexane); $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 8.19 (2H, m, ArH), 6.94 (2H, m, ArH), 5.65–5.43 (2H, m, H3, H4), 4.05 (2H, t, *J* 6.8 Hz, H1), 2.50 (2H, q, *J* 6.8 Hz, H2), 1.69 (3H, d, *J* 6.0 Hz, H5); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 164.1 (C), 141.4 (C), 128.4 (CH), 125.9 (CH), 114.4 (CH), 68.6 ($CH_2$), 32.2 ($CH_2$), 18.0 ($CH_3$) (one carbon obscured or overlapping); IR (thin film): 3026 (w, CH=CH), 2951, 2922 (w, CH), 1595 (s, C=C), 1510, 1339 (s, $NO_2$) $cm^{-1}$; MS (EI): *m*/*z* 207 ($M^{+\bullet}$, 100), 191 (10); HRMS (EI): calcd for $C_{11}H_{13}NO_3$ ($M^{+\bullet}$) 207.0895, found 207.0893.

#### 4.2.32. tert-Butyl (2R,3R)-3-hydroxy-5-(4-nitrophenoxy)pentan-2-ylcarbamate **15** ($R^1$=$^t$Bu)

The reaction was conducted under standard conditions using substrate **14** (100 mg, 0.48 mmol), $(DHQD)_2AQN$ and *tert*-butyl carbamate. Analysis of the crude reaction mixture by 300 MHz $^1$H NMR identified a 3.7:1 ratio of the regioisomers **15** and **16**. Purification by flash chromatography (40% ethyl acetate/hexane) afforded the major regioisomer **15** as a pale yellow oil (124 mg, 75%; 84% ee, Chiralpak AD-H, 20% isopropyl alcohol/hexane; $t_R$: 21.8 major, 25.8 minor). Data for *ent*-**15** ($R^1$=$^t$Bu) below.

#### 4.2.33. tert-Butyl (2S,3S)-3-hydroxy-5-(4-nitrophenoxy)pentan-2-ylcarbamate *ent*-**15** ($R^1$=$^t$Bu)

The reaction was conducted under standard conditions using substrate **14** (200 mg, 0.97 mmol), $(DHQ)_2AQN$ and *tert*-butyl carbamate. Analysis of the crude reaction mixture by 300 MHz $^1$H NMR identified a 2.6:1 ratio of the regioisomers *ent*-**15** and *ent*-**16**. Purification by flash chromatography (40% ethyl acetate/hexane) afforded the major regioisomer *ent*-**15** as a pale yellow oil (185 mg, 56%; 80% ee, Chiralpak AD-H, 20% isopropyl alcohol/hexane; $t_R$: 25.5 major, 21.7 minor). $[\alpha]_D$ −25.3 (*c* 1.5, $CHCl_3$); $R_f$ 0.34 (40% ethyl acetate/hexane); $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 8.16 (2H, m, ArH), 6.94 (2H, m, ArH), 4.75 (1H, br s, NH), 4.30–4.17 (2H, m, H5), 3.79 (1H, dt, *J* 8.9, 3.9 Hz, H3), 3.69 (1H, br s, H2), 2.40 (1H, br s, OH), 2.02–1.88 (2H, m, H4), 1.43 (9H, s, $^t$Bu), 1.21 (3H, d, *J* 6.8 Hz, H1); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 163.8 (C), 156.4 (C), 141.5 (C), 125.9 (CH), 114.4 (CH), 79.8 (C), 72.1 (CH), 66.0 ($CH_2$), 50.8 (CH), 33.5 ($CH_2$), 28.3 ($CH_3$), 18.1 ($CH_3$); IR (thin film): 3400 (br s, OH), 2975, 2931 (w, CH), 1691 (s, C=O) $cm^{-1}$; MS ($ESI^+$): *m*/*z* 363 ($[M+Na]^+$, 100), 285 (18), 241 (30); HRMS ($ESI^+$): calcd for $C_{16}H_{24}N_2O_6Na$ ($[M+Na]^+$) 363.1532, found 363.1514.

A second fraction afforded the minor regioisomer *ent*-**16** as a pale yellow oil (30 mg, 9%; ee not determined). $[\alpha]_D$ −23.4 (*c* 0.53, $CHCl_3$); $R_f$ 0.17 (40% ethyl acetate/hexane); $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 8.18 (2H, m, ArH), 6.94 (2H, m, ArH), 4.81 (1H, d, *J* 8.5 Hz, NH), 4.14 (2H, t, *J* 6.2 Hz, H1), 3.90 (1H, m, H4), 3.71 (1H, m, H3), 2.11–2.00 (3H, m, H2, OH), 1.40 (9H, s, $^t$Bu), 1.24 (3H, d, *J* 6.3 Hz, H5); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 163.8 (C), 156.4 (C), 141.6 (C), 125.9 (CH), 114.5 (CH), 79.6 (C), 69.4 (CH), 66.1 ($CH_2$), 53.0 (CH), 32.1 ($CH_2$), 28.3 ($CH_3$), 20.5 ($CH_3$); IR (thin film): 3404 (br s, OH), 2974, 2931 (w, CH), 1683 (s, C=O) $cm^{-1}$; MS ($ESI^+$): *m*/*z* 363 ($[M+Na]^+$, 100), 285 (41), 241 (63); HRMS ($ESI^+$): calcd for $C_{16}H_{24}N_2O_6Na$ ($[M+Na]^+$) 363.1532, found 363.1516.

#### 4.2.34. 2-(Trimethylsilyl)ethyl (2R,3R)-3-hydroxy-5-(4-nitrophenoxy)pentan-2-ylcarbamate **15** ($R^1$=TMSE)

The reaction was conducted under standard conditions using substrate **14** (100 mg, 0.48 mmol), $(DHQD)_2AQN$ and 2-(trimethylsilyl)ethyl carbamate. Analysis of the crude reaction mixture by 300 MHz $^1$H NMR identified a 2.6:1 ratio of the regioisomers **15** and **16**. Purification by flash chromatography (40% ethyl acetate/hexane) afforded the major regioisomer **15** as a pale yellow oil (90 mg, 48%; 84% ee, Chiralpak AD-H, 20% isopropyl alcohol/hexane; $t_R$: 15.6 major, 19.4 minor). Data for *ent*-**15** ($R^1$=TMSE) below.

A second fraction afforded the minor regioisomer **16** as a pale yellow oil (35 mg, 19%; 34% ee, Chiralpak AD-H, 20% isopropyl alcohol/hexane; $t_R$: 14.5 major, 11.9 minor). Data for *ent*-**16** ($R^1$=TMSE) below.

#### 4.2.35. 2-(Trimethylsilyl)ethyl (2S,3S)-3-hydroxy-5-(4-nitrophenoxy)pentan-2-ylcarbamate *ent*-**15** ($R^1$=TMSE)

The reaction was conducted under standard conditions using substrate **14** (100 mg, 0.48 mmol), $(DHQ)_2AQN$ and 2-

(trimethylsilyl)ethyl carbamate. Analysis of the crude reaction mixture by 300 MHz $^1$H NMR identified a 2.3:1 ratio of the regioisomers *ent*-**15** and *ent*-**16**. Purification by flash chromatography (40% ethyl acetate/hexane) afforded the major regioisomer *ent*-**15** as a pale yellow oil (79 mg, 43%; 81% ee, Chiralpak AD-H, 20% isopropyl alcohol/hexane; $t_R$: 19.3 major, 15.9 minor). $[\alpha]_D$ −18.9 (*c* 1.4, $CHCl_3$); $R_f$ 0.36 (40% ethyl acetate/hexane); $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 8.15 (2H, m, ArH), 6.93 (2H, m, ArH), 4.94 (1H, d, *J* 8.7 Hz, NH), 4.30–4.09 (4H, m, H5, $COOCH_2$), 3.85–3.65 (2H, m, H2, H3), 2.55 (1H, br s, OH), 1.97 (2H, m, H4), 1.22 (3H, d, *J* 6.7 Hz, H1), 0.95 (2H, m, $CH_2TMS$), 0.02 (9H, s, TMS); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 163.8 (C), 157.0 (C), 141.3 (C), 125.8 (CH), 114.3 (CH), 71.3 (CH), 65.8 ($CH_2$), 63.1 ($CH_2$), 50.8 (CH), 33.4 ($CH_2$), 18.1 ($CH_3$), 17.6 ($CH_2$), −1.6 ($CH_3$); IR (thin film): 3425 (br s, OH), 2952, 2896 (w, CH), 1691 (s, C=O) cm$^{-1}$; MS (ESI$^+$): *m*/*z* 407 ([M+Na]$^+$, 100), 357 (19), 241 (100); HRMS (ESI$^+$): calcd for $C_{17}H_{28}N_2O_6SiNa$ ([M+Na]$^+$) 407.1614, found 407.1617.

A second fraction afforded the minor regioisomer *ent*-**16** as a pale yellow oil (35 mg, 19%; 25% ee, Chiralpak AD-H, 20% isopropyl alcohol/hexane; $t_R$: 11.9 major, 14.6 minor). Data below.

#### 4.2.36. 2-(Trimethylsilyl)ethyl (3R,4R)-4-hydroxy-1-(4-nitrophenoxy)pentan-3-ylcarbamate **16** ($R^1$=TMSE)

The reaction was conducted under standard conditions using substrate **14** (100 mg, 0.48 mmol), $(DHQD)_2PHAL$ and 2-(trimethylsilyl)ethyl carbamate. Analysis of the crude reaction mixture by 300 MHz $^1$H NMR identified a 1:8 ratio of the regioisomers **15** and **16**. Purification by flash chromatography (40% ethyl acetate/hexane) afforded the major regioisomer **16** as a pale yellow oil (103 mg, 56%; 89% ee, Chiralpak AD-H, 20% isopropyl alcohol/hexane; $t_R$: 14.1 major, 11.6 minor). Data for *ent*-**16** ($R^1$=TMSE) below.

A second fraction afforded the minor regioisomer **15** as a pale yellow oil (12.5 mg, 7%; 33% ee, Chiralpak AD-H, 20% isopropyl alcohol/hexane; $t_R$: 15.0 major, 18.1 minor).

#### 4.2.37. 2-(Trimethylsilyl)ethyl (3S,4S)-4-hydroxy-1-(4-nitrophenoxy)pentan-3-ylcarbamate *ent*-**16** ($R^1$=TMSE)

The reaction was conducted under standard conditions using substrate **14** (100 mg, 0.48 mmol), $(DHQ)_2PHAL$ and 2-(trimethylsilyl)ethyl carbamate. Analysis of the crude reaction mixture by 300 MHz $^1$H NMR identified a 1:10 ratio of the regioisomers *ent*-**15** and *ent*-**16**. Purification by flash chromatography (40% ethyl acetate/hexane) afforded the major regioisomer *ent*-**16** as a pale yellow oil (71 mg, 38%; 91% ee, Chiralpak AD-H, 20% isopropyl alcohol/hexane; $t_R$: 11.6 major, 14.2 minor). $[\alpha]_D$ −29.8 (*c* 1.7, $CHCl_3$); $R_f$ 0.22 (40% ethyl acetate/hexane); $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 8.17 (2H, m, ArH), 6.94 (2H, m, ArH), 5.00 (1H, d, *J* 9.4, NH), 4.17–4.06 (4H, m, H1, $COOCH_2$), 3.92 (1H, m, H4), 3.76 (1H, m, H3), 2.16–2.07 (3H, m, H2, OH), 1.24 (3H, d, *J* 6.3 Hz, H5), 0.93 (2H, m, $CH_2TMS$), 0.01 (9H, s, TMS); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 163.7 (C), 157.2 (C), 141.5 (C), 125.9 (CH), 114.5 (CH), 69.3 (CH), 66.0 ($CH_2$), 63.3 ($CH_2$), 53.4 (CH), 32.2 ($CH_2$), 20.5 ($CH_3$), 17.7 ($CH_2$), −1.5 ($CH_3$); IR (thin film): 3400 (br s, OH), 2952, 2897 (w, CH), 1691 (s, C=O) cm$^{-1}$; MS (ESI$^+$): *m*/*z* 407 ([M+Na]$^+$, 100), 357 (23), 241 (55); HRMS (ESI$^+$): calcd for $C_{17}H_{28}N_2O_6SiNa$ ([M+Na]$^+$) 407.1614, found 407.1597.

A second fraction afforded the minor regioisomer *ent*-**15** as a pale yellow oil (6.9 mg, 4%; 8% ee, Chiralpak AD-H, 20% isopropyl alcohol/hexane; $t_R$: 18.2 major, 15.1 minor).

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## Supplementary data

CIF file for the $(DHQ)_2AQN$ crystal structure. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.11.037.

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