

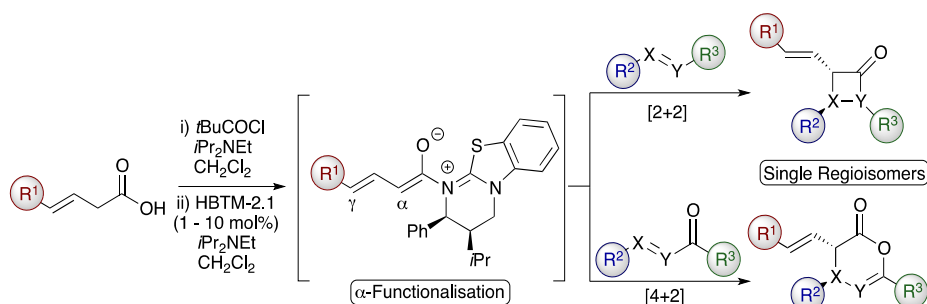
# Isothiourea-Mediated Asymmetric Functionalization of 3-Alkenoic Acids

Louis C. Morrill, Samuel M. Smith, Alexandra M. Z. Slawin and Andrew D. Smith\*

EaStCHEM, School of Chemistry, University of St Andrews, North Haugh, St Andrews, KY16 9ST,

U.K.

e-mail: [ads10@st-andrews.ac.uk](mailto:ads10@st-andrews.ac.uk)

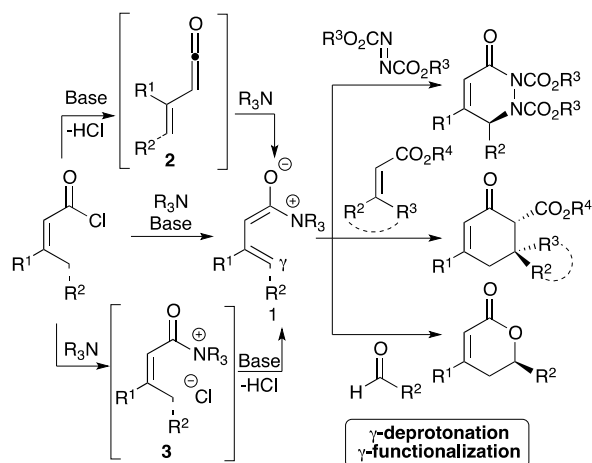


## Abstract:

Isothiourea HBTM-2.1 promotes the catalytic asymmetric  $\alpha$ -functionalization of 3-alkenoic acids through formal [2+2] cycloadditions with  $N$ -tosyl aldimines and formal [4+2] cycloadditions with either 4-aryltrifluoromethyl enones or  $N$ -aryl- $N$ -royl diazenes, providing useful synthetic building blocks in good yield and with excellent enantiocontrol (up to >99% ee). Stereodefined products are amenable to further synthetic elaboration through manipulation of the olefinic functionality.

## Introduction

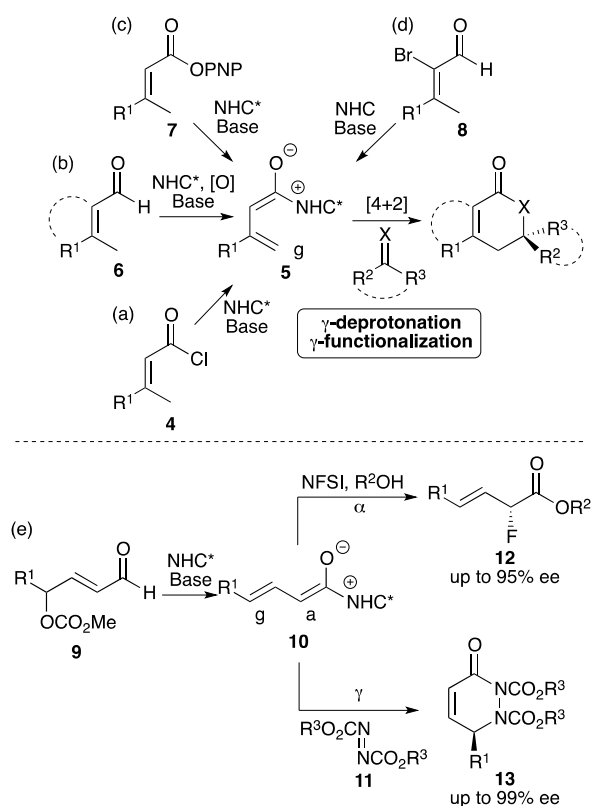
The organocatalytic generation of dienolates or their dienamine equivalents is an increasingly popular area of research.<sup>1</sup> These intermediates have powerful synthetic potential due to their ability to react regio- and enantioselectively through either  $\alpha$ - or  $\gamma$ -positions, allowing rapid access to diverse molecular scaffolds. In particular, recent research has demonstrated the ability of ammonium and azolium dienolates to participate in asymmetric transformations.<sup>2-11</sup> For example, Peters<sup>2</sup> and Ye<sup>3</sup> have accessed cinchona alkaloid and norephedrine derived C1-ammonium dienolates from  $\alpha,\beta$ -unsaturated acid chloride starting materials and applied these towards the synthesis of a range of stereodefined products (Scheme 1). C1-ammonium dienolate **1** may form either *via* initial dehydrohalogenation to form vinyl ketene **2** which is intercepted by the Lewis base, or from initial attack of the Lewis base to form  $\alpha,\beta$ -acyl ammonium **3** followed by  $\gamma$ -deprotonation. To the best of our knowledge, all catalytically generated  $\beta,\beta$ -disubstituted C1-ammonium dienolates documented in the literature react to give  $\gamma$ -functionalized products.



**Scheme 1:** Generation and utility of C1-ammonium dienolates.

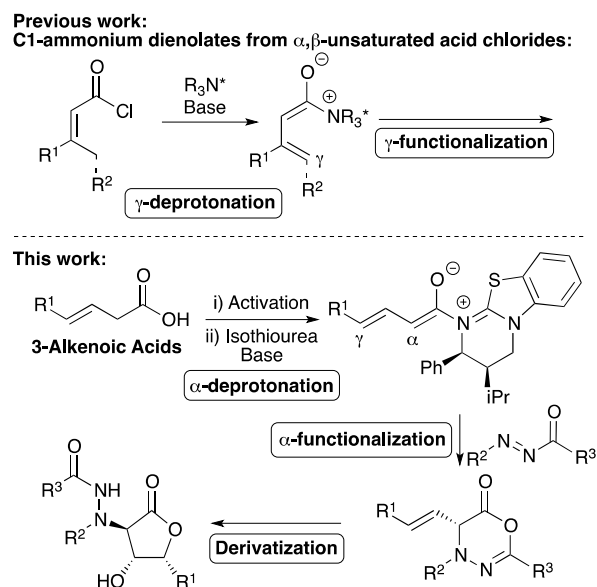
C1-azolium dienolates have also received considerable attention within the past two years. For example, Ye demonstrated that  $\alpha,\beta$ -unsaturated acid chlorides **4**, in the presence of an N-heterocyclic carbene (NHC) and base, afford C1-azolium dienolates **5** that react *via* the  $\gamma$ -centre in asymmetric formal [4+2]

cycloadditions with  $2\pi$  electrophiles (Scheme 2a).<sup>4</sup> Chi subsequently disclosed the ability to access the same dienolate *via* both enals **6** (in presence of a stoichiometric oxidant)<sup>5,6</sup> and  $\alpha,\beta$ -unsaturated esters **7** (Scheme 2b,c).<sup>7</sup> Alternatively, enals bearing an  $\alpha$ -bromo leaving group such as **8** have also been demonstrated as suitable azolium dienolate precursors (Scheme 2d).<sup>8</sup> In examples a-d, each process is postulated to involve  $\gamma$ -deprotonation of the corresponding  $\beta,\beta$ -disubstituted- $\alpha,\beta$ -acyl azolium intermediate to generate the corresponding dienolate, often depicted in both (*E*)- and (*Z*)-configurations, followed by  $\gamma$ -functionalization of the resulting azolium dienolate.<sup>9</sup> Alternatively, aldehydes that contain a  $\gamma$ -leaving group such as **9** have been used to access C1-azolium dienolates **10** (Scheme 2e). Interestingly, these dienolates give  $\alpha$ -functionalization *via* fluorination with NFSI, and  $\gamma$ -functionalization in the formal [4+2] cycloaddition with diazodicarboxylates **11**, affording esters **12**<sup>10</sup> and lactams **13**<sup>11</sup> respectively.



**Scheme 2:** Generation and utility of C1-azolium dienolates.

Building upon the elegant nucleophile catalysed aldol-lactonisation (NCAL) reaction developed by Romo,<sup>12</sup> we have recently shown that isothioureas<sup>13,14</sup> can generate ammonium enolates<sup>15</sup> *in situ* from carboxylic acids that subsequently undergo a range of intra- and intermolecular Michael addition-lactonization/lactamization reactions to generate stereodefined products.<sup>16</sup> Although powerful, the success of the intermolecular processes often relies upon using arylacetic acids as starting materials,<sup>17,18</sup> which constitutes a limitation of this organocatalytic strategy. To broaden the substrate scope of such processes, the use of 3-alkenoic acids would allow access to extended ammonium dienolates that could give rise to either  $\alpha$ - or  $\gamma$ -functionalized products in a stereodefined manner (Scheme 3). In this manuscript, a range of 3-alkenoic acids are shown to act as suitable precursors to isothiourea derived ammonium dienolates that react in a variety of formal [2+2] and [4+2] cycloadditions. In contrast to previously accessed C1-ammonium dienolates formed *via*  $\gamma$ -deprotonation, these ammonium dienolates are formed *via*  $\alpha$ -deprotonation and provide exclusively  $\alpha$ -functionalized products. This strategy introduces an additional exocyclic olefin functional handle, allowing for further product functionalization into useful synthetic building blocks.

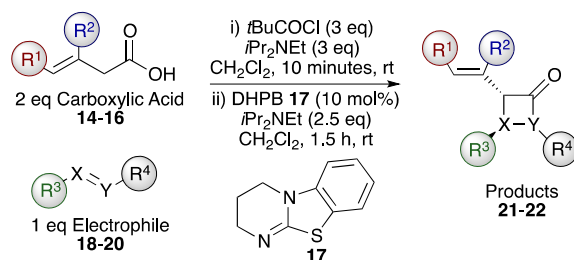


**Scheme 3:** Proposed asymmetric transformations of 3-alkenoic acids *via* either  $\alpha$ - or  $\gamma$ -functionalization.

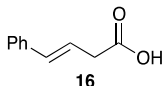
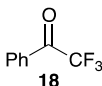
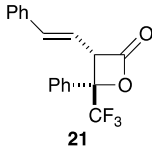
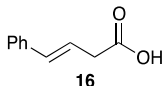

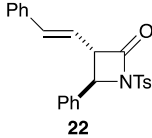
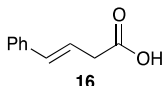
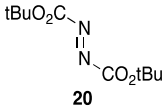
## Results and Discussion

## Generation of isothiurea derived ammonium dienolates and reaction with 2π electrophiles

Initial studies probed the ability of isothiureas to generate an ammonium dienolate from a 3-alkenoic acid, with subsequent reaction with a reactive 2π component used to test if α- or γ-selectivity is observed. Encouraged by Ye's report demonstrating diazodicarboxylates as suitable reaction partners with C1-ammonium dienolates,<sup>3a</sup> along with both Ye and Chi who showed that trifluoromethyl ketones are suitable partners in [4+2] cycloadditions with C1-azolium dienolates,<sup>4,5</sup> these 2π components were evaluated. Following our report in the previous manuscript we also evaluated *N*-tosyl aldimines 2π electrophiles.<sup>19</sup> Using 3-methylbut-3-enoic acid **14** or 2-(cyclopent-1-en-1-yl)acetic acid **15** with pivaloyl chloride as activating agent, achiral DHPB **17** (3,4-dihydro-2*H*-pyrimido[2,1-*b*]benzothiazole) as catalyst and trifluoromethyl ketone **18** as the 2π electrophile,<sup>20</sup> no distinguishable cycloaddition products were observed (Table 1). Under the same reaction conditions, (*E*)-4-phenylbut-3-enoic acid **16** reacted with trifluoromethyl ketone **18**, giving solely the [2+2] cycloaddition product β-lactone **21** (60:40 dr *anti:syn*) derived from α-functionalization<sup>21</sup> in 71% combined yield whilst reaction with *N*-tosyl aldimine **19** gave β-lactam **22** (83:17 dr *anti:syn*) in 68% yield (*anti* diastereoisomer).<sup>22-24</sup> Unfortunately, diazodicarboxylate **20** proved incompatible with this system giving no distinguishable product despite full consumption of **20**.

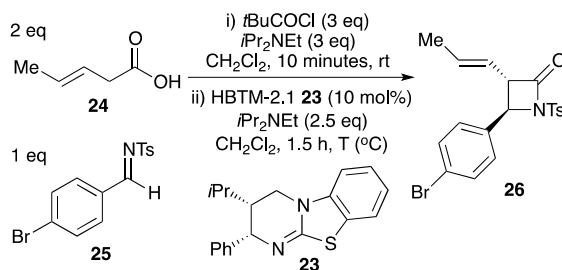


Entry	Carboxylic Acid	Electrophile	Product (major)	dr <sup>a</sup> ( <i>anti:syn</i> )	Yield <sup>b</sup> (% <i>anti,syn</i> )
1			None	N/A	N/A
2			None	N/A	N/A

3				60:40	43,29
4				83:17	68,-
5			None	N/A	N/A

**Table 1:** Initial studies: <sup>a</sup> Determined by <sup>1</sup>H NMR spectroscopic analysis of the crude reaction mixture; <sup>b</sup> Isolated yield ( $\geq 95:5$  dr).

Encouraged by the promising diastereoselectivities observed in the reaction with *N*-tosyl aldimine **19**, further optimization studies focused upon finding a suitable asymmetric variant. Screening of a range of isothiourea catalysts and C(4)-substituted alkenoic acids revealed that chiral isothiourea HBTM-2.1 **23** efficiently promotes the formal [2+2] cycloaddition of (*E*)-pent-3-enoic acid **24** and imine **25** at rt, affording  $\beta$ -lactam **26** in moderate diastereoselectivity (68:32 dr *anti:syn*), with each separable diastereoisomer isolated in good yield (53% *anti*, 27% *syn*) and enantioselectivity (*anti* 79% ee, *syn* 72% ee) (Table 2). Lowering the temperature to  $-78$  °C resulted in similar diastereoselectivity (71:29 dr *anti:syn*), but with each separable diastereoisomer formed in excellent enantioselectivity (*anti* 97% ee, *syn* >99% ee).<sup>25</sup>

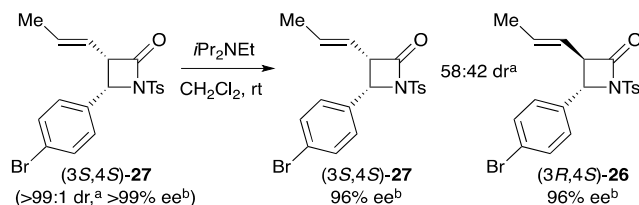


Entry	T (°C)	dr <sup>a</sup> ( <i>anti:syn</i> )	Yield <sup>b</sup> (% <i>anti,syn</i> )	ee <sup>c</sup> (% <i>anti,syn</i> )
-------	--------	-------------------------------------	---	--------------------------------------

1	23	68:32	53,27	79,72
2	-78	71:29	53,11	97,>99

**Table 2:** Formal [2+2] cycloaddition using *N*-tosyl aldimine **25**: <sup>a</sup> Determined by <sup>1</sup>H NMR spectroscopic analysis of the crude reaction mixture; <sup>b</sup> Isolated yield ( $\geq 95:5$  dr); <sup>c</sup> Determined by chiral HPLC analysis.

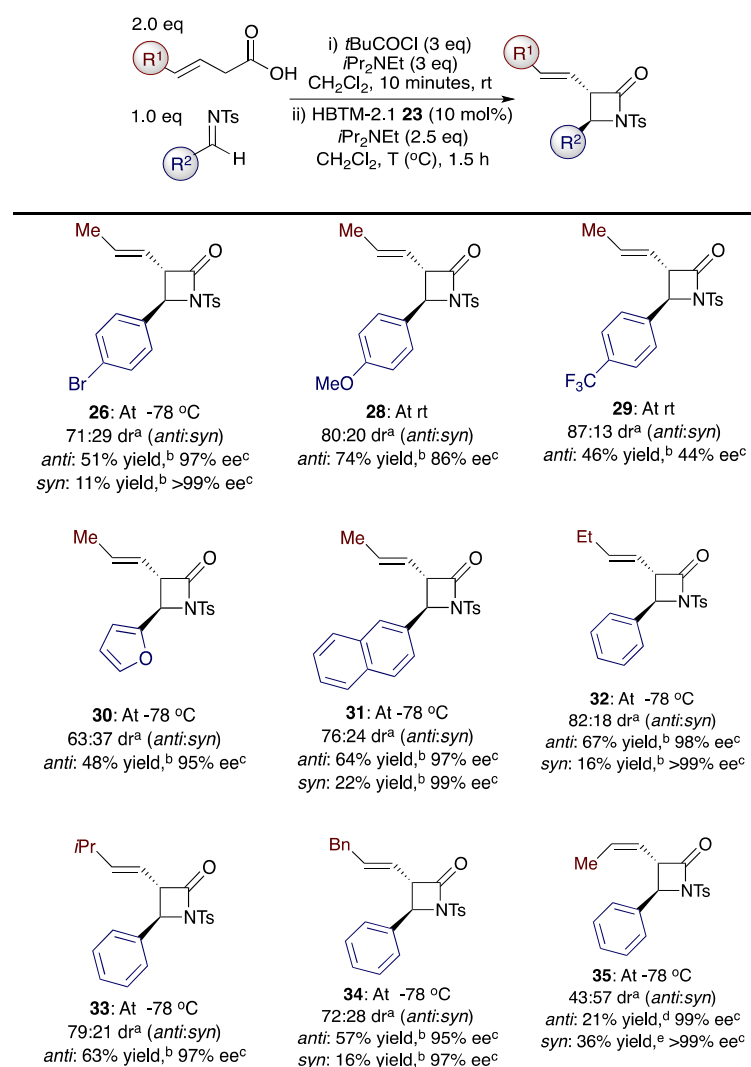
The absolute configuration of *syn*- $\beta$ -lactam **27** was confirmed unambiguously by X-ray crystallography as (3*S*,4*S*),<sup>26</sup> while that of the *anti*- $\beta$ -lactam **26** was confirmed by an epimerization experiment (Scheme 4). Treatment of *syn*- $\beta$ -lactam (3*S*,4*S*)-**27** (>99:1 dr, >99% ee) using *i*Pr<sub>2</sub>NEt at rt for 16 h gave a (58:42 *syn:anti*) mixture comprising of *syn*- $\beta$ -lactam (3*S*,4*S*)-**27** (96% ee) and *anti*- $\beta$ -lactam (3*R*,4*S*)-**26** (96% ee) as determined by Chiral HPLC. The absolute configuration of the *anti*- $\beta$ -lactam formed by epimerization is opposite to that observed experimentally in the catalytic process. Assuming epimerization occurs solely at C(3), this allows the absolute configuration of the *anti*- $\beta$ -lactam formed in Table 2 to be assigned (3*S*,4*R*).<sup>27</sup>



**Scheme 4:** Epimerization experiment; <sup>a</sup> Determined by <sup>1</sup>H NMR spectroscopic analysis of the crude reaction mixture; <sup>b</sup> Determined by HPLC analysis.

The generality of this protocol was next investigated by variation of both the acid and aldimine components (Table 3). Within the aldimine, electron-donating and withdrawing groups can be incorporated provided the reactions are carried out at rt.<sup>28</sup> 4-OMe Substituted  $\beta$ -lactam **28** is formed in good diastereo- and enantioselectivity, whilst incorporation of the 4-CF<sub>3</sub> group results in a significant reduction in enantioselectivity (44% ee). Heteroaryl substituents (2-furyl) and extended aromatics (2-naphthyl) are tolerated within the aldimine, giving  $\beta$ -lactams **30** and **31** in modest diastereoselectivity with

the major (*anti*) diastereoisomer formed in excellent ee (95% and 97% respectively). In cases where the minor (*syn*) diastereoisomer can be isolated, it is always formed in excellent enantioselectivity (>96% ee). Both the 4-position substituent and the configuration within the acid component can also be varied; for example (*E*)-4-ethyl, (*E*)-4-isopropyl and (*E*)-4-benzyl alkenoic acids give the corresponding  $\beta$ -lactams **32-34** in high yields and good diastereo- and enantioselectivities. Finally, (*Z*)-pent-3-enoic acid was used as a starting material, giving the usual  $\alpha$ -functionalization under the reaction conditions, but generating  $\beta$ -lactam **35** with negligible diastereoselectivity at  $-78$  °C (43:57 dr, *anti:syn*), despite both diastereoisomers being formed in exquisite enantioselectivity (>99% ee).<sup>29</sup>

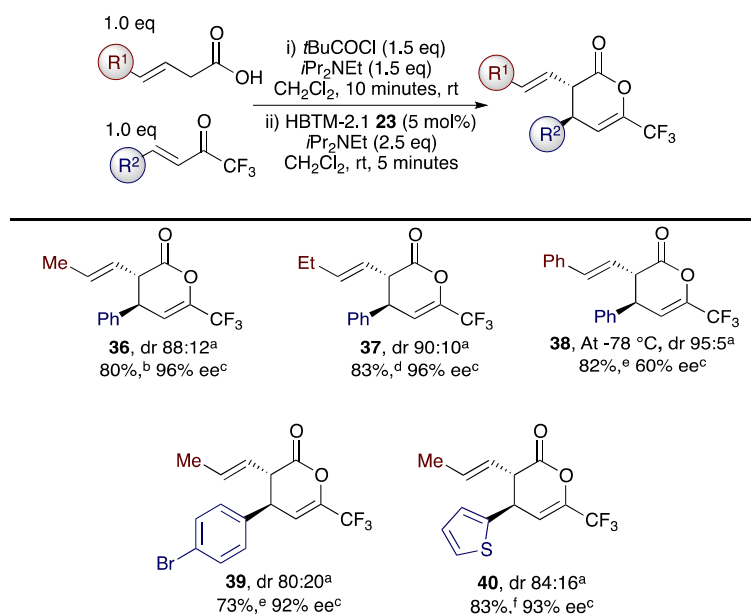




**Table 3:** Formal [2+2] cycloaddition scope. <sup>a</sup> Determined by <sup>1</sup>H NMR spectroscopic analysis of the crude reaction mixture; <sup>b</sup> Isolated yield ( $\geq 95:5$  dr); <sup>c</sup> Determined by chiral HPLC analysis; <sup>d</sup> Isolated yield (92:8 dr); <sup>e</sup> Isolated yield (88:12 dr);

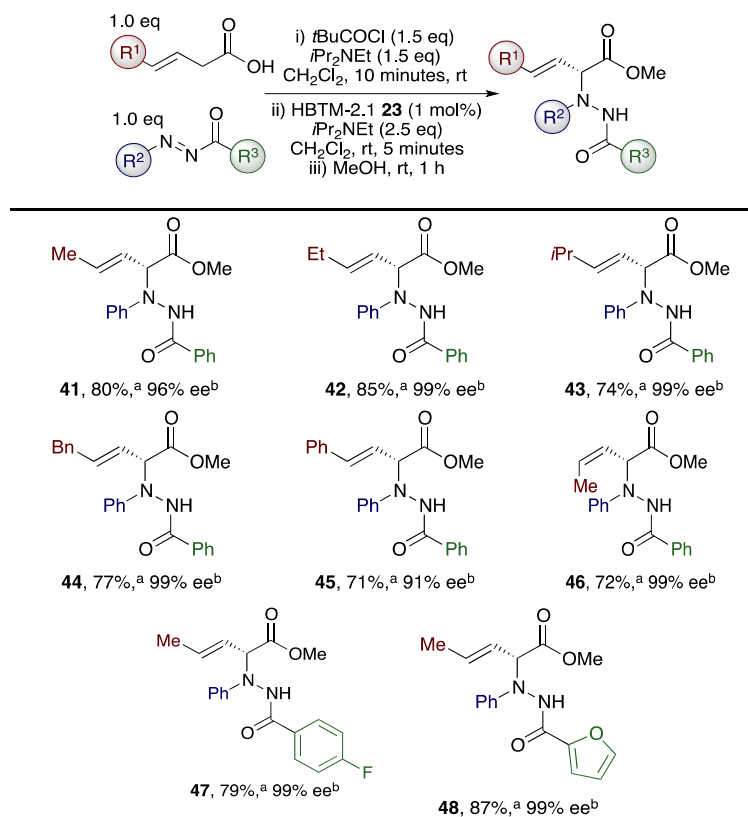
### [4+2] cycloadditions of isothiurea derived ammonium dienolates with 4 $\pi$ electrophiles

Having established the propensity of these ammonium dienolates to react at the  $\alpha$ -position with 2 $\pi$  electrophiles, their ability to partake in formal [4+2] cycloadditions with electron deficient 4 $\pi$  Michael acceptors was investigated. HBTM-2.1 **23** efficiently catalyzes the reaction between (*E*)-pent-3-enoic and (*E*)-1,1,1-trifluoro-4-phenyl-3-buten-2-one in only 5 minutes at rt, giving  $\delta$ -lactone **36** in 80% yield with good diastereoselectivity (88:12 dr) and excellent enantioselectivity (96% ee).<sup>30-32</sup> The reaction proceeds efficiently using (*E*)-3-hexenoic acid, giving  $\delta$ -lactone **37**, although when using (*E*)-styrylacetic acid the reaction has to be carried out at  $-78$  °C to prevent product decomposition and gives the major diastereoisomer of  $\delta$ -lactone **38** in reduced enantioselectivity (60% ee). Heteroaryl and 4-bromophenyl substituted trifluoromethyl enones are also tolerated giving  $\delta$ -lactones **39** and **40** in good yields and high diastereo- and enantioselectivity (Table 4).



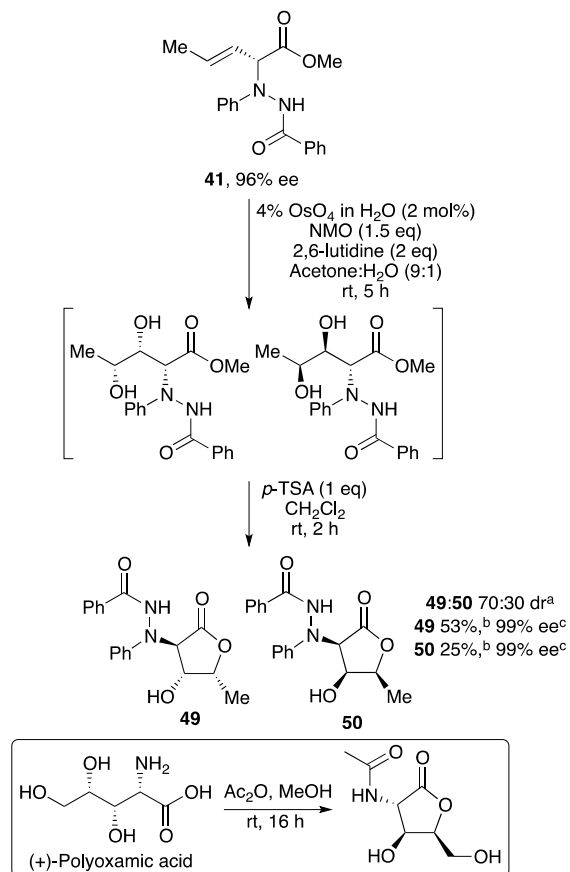
**Table 4:** Formal [4+2] cycloadditions with 4-aryltrifluoromethyl enones; <sup>a</sup> Determined by <sup>1</sup>H NMR spectroscopic analysis of the crude reaction mixture; <sup>b</sup> Isolated yield (88:12 dr); <sup>c</sup> Determined by HPLC analysis; <sup>d</sup> Isolated yield (93:7 dr); <sup>e</sup> Isolated yield ( $\geq 95:5$  dr); <sup>f</sup> Isolated yield (84:16 dr).

The generality of this asymmetric Michael addition-lactonization process was next investigated using *N*-aryl-*N*-aroyldiazenes as Michael acceptors, followed by *in situ* ring opening of the intermediate 1,3,4-oxadiazin-6-one formal [4+2] cycloaddition adduct with MeOH. Examples including the use of 3-alkenoic acids bearing 4-alkyl (Me, Et, *i*Pr), 4-benzyl and 4-phenyl substituents, in addition to (*E*)- and (*Z*)-alkene configurations are all readily incorporated giving, after *in situ* ring-opening with methanol,<sup>33</sup> a range of hydrazides **41-46** in high yields (71-85 %) and excellent enantioselectivity (91-99 % ee) (Table 5).<sup>34,35</sup> Diazenes bearing electron deficient (4-FC<sub>6</sub>H<sub>4</sub>) and heteroaryl (2-furyl) *N*-aroyl substituents are also tolerated giving products **47** and **48** in excellent ee.



**Table 5:** Formal [4+2] cycloaddition/ring opening with *N*-aryl-*N*-aroyldiazenes; <sup>a</sup> Isolated yield. <sup>b</sup> Determined by HPLC analysis.

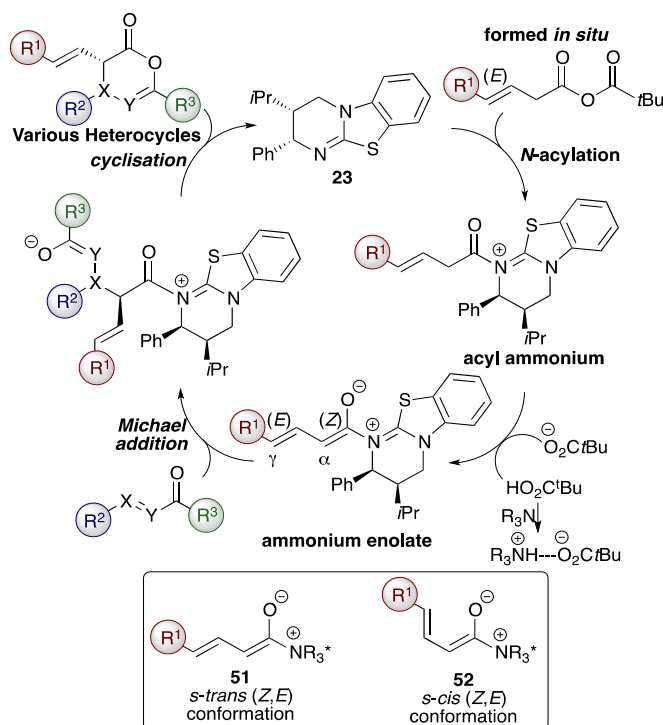
Having developed a highly enantioselective route to hydrazides **41-48**, their potential for further elaboration through functionalization of the olefin was probed. Treatment of hydrazide **41** under Upjohn dihydroxylation conditions, followed by acid catalysed cyclisation, gave a 70:30 mixture of separable diastereomeric 5-membered lactones **49** and **50** in 85% combined yield, both in 99% ee (Scheme 5).<sup>36</sup> These interesting aza-sugar derivatives structurally resemble the cyclized form of (+)-polyoxamic acid, indicating their potential biological significance.



**Scheme 5:** Conversion of hydrazide **41** to lactones **49** and **50**; <sup>a</sup> Determined by <sup>1</sup>H NMR spectroscopic analysis of the crude reaction mixture; <sup>b</sup> Isolated yield (>98:2 dr); <sup>c</sup> Determined by HPLC analysis.

We propose that the catalytic cycle for these transformations proceeds *via* initial *N*-acylation of HBTM-2.1 **23** with the pre-formed mixed anhydride to form the corresponding acyl ammonium ion.  $\alpha$ -Deprotonation generates the (*Z,E*)-enolate (from the (*E*)-alkenoic acid), which undergoes stereoselective Michael addition *via*  $\alpha$ -functionalization with electron deficient 4 $\pi$  Michael acceptors, followed by intramolecular

cyclisation, to generate the corresponding heterocyclic species (Figure 1). The sense of stereoinduction in these transformations is consistent with our previous rationale.<sup>16a,c</sup> We tentatively assign the origin of the observed  $\alpha$ -functionalization in these processes to preferential reaction *via* the assumed *s-trans* (*Z,E*)-dienolate conformation **51**, in preference to the *s-cis* (*Z,E*)-dienolate conformation **52** that is presumably necessary to participate in  $\gamma$ -functionalization.



**Figure 1:** Proposed mechanism of asymmetric heterocycle formation.

**Conclusion:** Isothiourea-mediated functionalization of 3-alkenoic acids occurs regioselectively, giving products derived from  $\alpha$ -functionalization of an intermediate ammonium enolate in a range of formal [2+2] and [4+2] cycloadditions. Formal [2+2] cycloadditions with *N*-tosyl aldimines proceed readily using HBTM-2.1 (10 mol%) with moderate diastereocontrol (up to 87:13 dr) and excellent enantiocontrol (up to >99% ee). Formal [4+2] cycloadditions with either 4-aryl-trifluoromethylenones or *N*-aryl-*N*-aroyldiazenes are also catalyzed by HBTM-2.1 (1-5 mol%), with products obtained in high diastereo- and enantiocontrol (up to 95:5 dr, up to 99% ee). The simple, two-step elaboration of stereodefined hydrazides into aza-sugar analogues without erosion of enantiopurity has also been demonstrated. Current research

from this laboratory is directed toward developing alternative applications of isothioureas in asymmetric catalysis.

## **Experimental:**

### **General Information**

Reactions involving moisture sensitive reagents were carried out under an argon atmosphere using standard vacuum line techniques in addition to dry solvents. In these cases, all glassware used was flame dried and cooled under vacuum.

For moisture sensitive reactions, solvents (THF, CH<sub>2</sub>Cl<sub>2</sub>, toluene, hexane and Et<sub>2</sub>O) were obtained anhydrous and purified by an alumina column. Petrol is defined as petroleum ether 40-60 °C. All other solvents and commercial reagents were used as supplied without further purification unless stated otherwise. Room temperature (rt) refers to 20–25 °C, with temperatures of 0 and –78 °C obtained using ice/water and CO<sub>2</sub>(s)/acetone baths, respectively. <sup>1</sup>H NMR spectra were acquired at 300, 400, or 500 MHz, <sup>13</sup>C{<sup>1</sup>H} NMR spectra were acquired at 75, 100, or 125 MHz, and <sup>19</sup>F{<sup>1</sup>H} NMR spectra were acquired at 282, 376, or 471 MHz. Chemical shifts are quoted in parts per million (ppm) relative to the residual solvent peak. Coupling constants, J, are quoted in Hertz (Hz). NMR peak assignments were confirmed using 2D <sup>1</sup>H correlated spectroscopy (COSY), 2D <sup>1</sup>H nuclear Overhauser effect spectroscopy (NOESY), 2D <sup>1</sup>H–<sup>13</sup>C heteronuclear multiple-bond correlation spectroscopy (HMBC), and 2D <sup>1</sup>H–<sup>13</sup>C heteronuclear single quantum coherence (HSQC) where necessary. Infrared spectra were recorded as thin films using an attenuated total reflectance (ATR) accessory. Mass spectrometry (m/z) data was acquired using electrospray ionization (ESI), electron impact (EI), chemical ionization (CI), atmospheric solids analysis probe (ASAP), atmospheric pressure chemical ionization (APCI), or nanospray ionization (NSI) using a time of flight (TOF) mass analyzer. Optical rotations were recorded with a path length of 1 dm and concentrations, c, are quoted in g/100 mL. All chiral high-performance liquid chromatography (HPLC) traces were compared with an authentic racemic trace. Racemic compounds were prepared using general procedure A, employing either DHPB **17** or (±)-HBTM-2.1 **23** as catalyst.

### Isothiourea catalysts used

DHPB **17**, HBTM-2.1 ( $\pm$ )-**23** and HBTM-2.1 (2*S*,3*R*)-**23** were made to literature procedures.<sup>16d</sup>

### *N*-tosyl aldimines used

4-methyl-*N*-[(1*E*)-phenylmethylidene]benzene-1-sulfonamide **19**, 4-methyl-*N*-[(1*E*)-4-(bromophenyl)methylidene]benzene-1-sulfonamide **25**, 4-methyl-*N*-[(1*E*)-4-(methoxyphenyl)methylidene]benzene-1-sulfonamide **53**, 4-methyl-*N*-[(1*E*)-4-(trifluoromethylphenyl)methylidene]benzene-1-sulfonamide **54**, *N*-[(1*E*)-furan-2-ylmethylidene]-4-methylbenzene-1-sulfonamide **55** and 4-methyl-*N*-[(1*E*)-naphthalen-2-ylmethylidene]benzene-1-sulfonamide **56** were made according to literature procedures.<sup>37</sup>

### Trifluoromethyl enones used

(*E*)-1,1,1-trifluoro-4-phenyl-3-buten-2-one **57**, (*E*)-1,1,1-trifluoro-4-(4-bromophenyl)-3-buten-2-one **58** and (*E*)-1,1,1-trifluoro-4-(2-thienyl)-3-buten-2-one **59** were made according to literature procedures.<sup>16d</sup>

### *N*-aryl-*N*-aroyldiazenes used

(*NE*)-*N*-(phenylimino)benzamide **60**, (*NE*)-4-fluoro-*N*-(phenylimino)benzamide **61** and (*NE*)-*N*-(phenylimino)furan-2-carboxamide **62** were made according to literature procedures.<sup>16c</sup>

### Carboxylic acids used

(*E*)-4-phenylbut-3-enoic acid **16**, (*E*)-pent-3-enoic acid **24** and (*E*)-hex-3-enoic acid **81** were used as purchased.

### 3-methylbut-3-enoic acid **14**

Following a literature procedure,<sup>38</sup> to a solution of 3-methylbut-3-en-1-ol (2.00 mL, 19.8 mmol) in acetone (100 mL) at 0 °C was added 2.68 M Jones' reagent (10.4 mL, 27.7 mmol) and the reaction mixture was stirred at 0 °C for 1 h. The reaction mixture was washed with 2M NaOH and then the aqueous layer acidified with conc HCl and extracted with Et<sub>2</sub>O (x 3). The combined organic extracts were dried (MgSO<sub>4</sub>), filtered and concentrated *in vacuo*. The residual oil was purified by distillation to give acid 3-

methylbut-3-enoic acid **14** as a colourless oil (1.50 g, 76%); bp 88-90 °C (20 mmHg); {lit.<sup>38</sup> bp 67-70 °C (10 mmHg)};  $\delta_{\text{H}}$  (500 MHz,  $\text{CDCl}_3$ ) 1.87 (3H, s,  $\text{CH}_3$ ), 3.11 (2H, s,  $\text{CH}_2$ ), 4.92 (1H, s, = $\text{CHH}$ ), 4.99 (1H, s, = $\text{CHH}$ ). Data are in accordance with the literature.<sup>38</sup>

### ethyl 2-cyclopentylideneacetate **63**

Following a literature procedure,<sup>39</sup> to a suspension of 60% NaH in mineral oil (1.23 g, 51.4 mmol) in  $\text{Et}_2\text{O}$  (120 mL) at 0 °C was added ethyl 2-(diethoxyphosphoryl)acetate (10.2 mL, 51.4 mmol) and the reaction mixture was stirred for 5 minutes at 0 °C. A solution of cyclopentanone (4.42 mL, 50.0 mmol) in  $\text{Et}_2\text{O}$  (10 mL) was added and the reaction mixture was allowed to stir at rt for 4 h. The reaction mixture was diluted with water and extracted with  $\text{Et}_2\text{O}$  (x 3). The combined organic extracts were dried ( $\text{MgSO}_4$ ), filtered and concentrated *in vacuo*. Chromatographic purification (eluent  $\text{Et}_2\text{O}$ :petrol 10:90) gave ethyl 2-cyclopentylideneacetate **63** as a colourless oil (7.00 g, 91%);  $\delta_{\text{H}}$  (500 MHz,  $\text{CDCl}_3$ ) 1.30 (3H, t,  $J$  7.1,  $\text{CH}_3$ ), 1.68 (2H, quintet,  $J$  6.8,  $\text{CH}_2$ ), 1.77 (2H, quintet,  $J$  7.0,  $\text{CH}_2$ ), 2.44-2.47 (2H, m,  $\text{CH}_2\text{C=}$ ), 2.78-2.81 (2H, m,  $\text{CH}_2\text{C=}$ ), 4.17 (2H, q,  $J$  7.1,  $\text{CH}_2\text{CH}_3$ ), 5.82 (1H, quintet,  $J$  2.2, = $\text{CH}$ ). Data are in accordance with the literature.<sup>39</sup>

### ethyl 2-(cyclopent-1-en-1-yl)acetate **64**

Following a literature procedure,<sup>40</sup> To a solution of DIPA (5.82 mL, 41.2 mmol) in THF (80 mL) at 0 °C was added 2.5 M *n*-BuLi (16.5 mL, 41.2 mmol) and the reaction mixture was stirred at that temperature for 30 minutes. The reaction mixture was cooled to -78 °C and a solution of ethyl 2-(cyclopent-1-en-1-yl)acetate **63** (5.88 g, 38.2 mmol) in THF (25 mL) was added dropwise over 15 minutes before stirring for a further 20 minutes. The reaction mixture was quenched by addition of sat. aq.  $\text{NH}_4\text{Cl}$  and the reaction mixture was warmed to rt before being poured into water and extracted with  $\text{Et}_2\text{O}$  (x 3). The combined organic extracts were dried ( $\text{MgSO}_4$ ), filtered and concentrated *in vacuo* to give ethyl 2-(cyclopent-1-en-1-yl)acetate **64** as a light yellow oil (5.68 g, 97%);  $\delta_{\text{H}}$  (500 MHz,  $\text{CDCl}_3$ ) 1.29 (3H, t,  $J$  7.1,  $\text{CH}_3$ ), 1.93 (2H,

quintet,  $J$  7.5,  $\text{CH}_2$ ), 2.33-2.38 (4H, m,  $\text{CH}_2$  and  $\text{CH}_2$ ), 3.14 (2H, s,  $\text{CH}_2\text{CO}_2\text{Et}$ ), 4.17 (2H, q,  $J$  7.1,  $\text{CH}_2\text{CH}_3$ ), 5.55-5.57 (1H, m,  $=\text{CH}$ ). Data are in accordance with the literature.<sup>40</sup>

### **2-(cyclopent-1-en-1-yl)acetic acid 15**

Following a literature procedure,<sup>41</sup> a solution of ethyl 2-(cyclopent-1-en-1-yl)acetate **64** (4.15 g, 27.0 mmol) in 0.5 M KOH (80.8 mL, 40.4 mmol) was heated at reflux for 16 h. Once cooled to rt the reaction mixture was extracted with  $\text{Et}_2\text{O}$  (x 3). The combined organic extracts were dried ( $\text{MgSO}_4$ ), filtered and concentrated *in vacuo*. Recrystallisation from petrol gave 2-(cyclopent-1-en-1-yl)acetic acid **15** as a white solid (2.74 g, 59%); mp 44-46 °C; {lit.<sup>41</sup> mp 48-51 °C};  $\delta_{\text{H}}$  (300 MHz,  $\text{CDCl}_3$ ) 1.90-2.00 (2H, m,  $\text{CH}_2$ ), 2.37-2.42 (4H, m,  $\text{CH}_2$  and  $\text{CH}_2$ ), 3.21 (2H, s,  $\text{CH}_2\text{CO}_2\text{H}$ ), 5.63 (1H, m,  $=\text{CH}$ ). Data are in accordance with the literature.<sup>41</sup>

### **(E)-5-methylhex-3-enoic acid 65**

Following a literature procedure,<sup>42</sup> a solution of piperidine (39.5  $\mu\text{L}$ , 0.40 mmol) and acetic acid (22.9  $\mu\text{L}$ , 0.40 mmol) in DMSO (1 mL) was stirred at rt for 5 minutes after which time a solution of malonic acid (4.16 g, 40.0 mmol) and isovaleraldehyde (4.29 mL, 40.0 mmol) in DMSO (20 mL) was added. The reaction mixture was stirred at rt for 20 minutes and then at 100 °C for 16 h. Once cooled to rt, the reaction mixture was diluted with  $\text{H}_2\text{O}$  and extracted with  $\text{Et}_2\text{O}$  (x 3). The combined organic fractions were washed with  $\text{H}_2\text{O}$ , dried ( $\text{MgSO}_4$ ), filtered and concentrated *in vacuo*. Chromatographic purification (eluent  $\text{Et}_2\text{O}$ :petrol 30:70) gave (E)-5-methylhex-3-enoic acid **65** as a colourless oil (2.93 g, 57%);  $\delta_{\text{H}}$  (400 MHz,  $\text{CDCl}_3$ ) 0.99 (6H, d,  $J$  6.8,  $\text{CH}(\text{CH}_3)_2$ ), 2.26-2.34 (1H, m, C(5) $H$ ), 3.07 (2H, dt,  $J$  6.6, 0.9, C(2) $H_2$ ), 5.47 (1H, dtd,  $J$  15.4, 6.7, 1.1, C(3) $H$ ), 5.54-5.60 (1H, m, C(4) $H$ ). Data are in accordance with the literature.<sup>42</sup>

### **(E)-5-phenylpent-3-enoic acid 66**

Following a literature procedure,<sup>42</sup> a solution of piperidine (39.5  $\mu\text{L}$ , 0.40 mmol) and acetic acid (22.9  $\mu\text{L}$ , 0.40 mmol) in DMSO (1 mL) was stirred at rt for 5 minutes after which time a solution of malonic acid



(4.16 g, 40.0 mmol) and 3-phenylpropionaldehyde (5.28 mL, 40.0 mmol) in DMSO (20 mL) was added. The reaction mixture was stirred at rt for 20 minutes and then at 100 °C for 16 h. Once cooled to rt, the reaction mixture was diluted with H<sub>2</sub>O and extracted with Et<sub>2</sub>O (x 3). The combined organic fractions were washed with H<sub>2</sub>O, dried (MgSO<sub>4</sub>), filtered and concentrated *in vacuo*. Chromatographic purification (eluent Et<sub>2</sub>O:petrol 25:75) gave (*E*)-5-phenylpent-3-enoic acid **66** as a colourless oil (4.15 g, 59%);  $\delta_{\text{H}}$  (400 MHz, CDCl<sub>3</sub>) 3.13 (2H, dq, *J* 6.8, 1.1, C(5)H<sub>2</sub>), 3.40 (2H, d, *J* 6.7, C(2)H<sub>2</sub>), 5.63 (1H, dtt, *J* 15.3, 6.9, 1.4, C(3)H), 5.77 (1H, dtt, *J* 15.3, 6.7, 1.3, C(4)H), 7.18-7.23 (3H, m, Ar(2,6)H and Ar(4)H), 7.28-7.32 (2H, m, Ar(3,5)H). Data are in accordance with the literature.<sup>43</sup>

### **(*Z*)-pent-3-en-1-ol 67**

Following a literature procedure,<sup>44</sup> lindlar's catalyst (5% on CaCO<sub>3</sub>, Pb poisoned, 900 mg (45 mg Pd), 0.43 mmol) was degassed in a RB flask. Quinoline (0.72 mL, 6.04 mmol), Et<sub>2</sub>O (150 mL) and pent-3-yn-1-ol (2.74 mL, 29.7 mmol) were added and a balloon of H<sub>2</sub> gas was appended to the reaction flask. H<sub>2</sub> gas was bubbled through the reaction mixture at rt for 20 h. The reaction mixture was filtered through Celite concentrated *in vacuo* and the residual oil was purified by distillation to give alcohol (*Z*)-pent-3-en-1-ol **67** (94:6 (*Z*):(*E*)) as a colourless oil (1.64 g, 64%); bp 140-141 °C (760 mmHg); {lit.<sup>44</sup> bp 140 °C (760 mmHg)}; Data for (*Z*)-isomer:  $\delta_{\text{H}}$  (500 MHz, CDCl<sub>3</sub>) 1.65-1.68 (3H, m, CH<sub>3</sub>), 2.32-2.37 (2H, m, C(2)H<sub>2</sub>), 3.66 (2H, q, *J* 6.2, C(1)H<sub>2</sub>), 5.37-5.43 (1H, m, C(4)H), 5.62-5.68 (1H, m, C(3)H); Selected data for (*E*)-isomer:  $\delta_{\text{H}}$  (500 MHz, CDCl<sub>3</sub>) 1.68-1.70 (3H, m, CH<sub>3</sub>), 2.23-2.28 (2H, m, C(2)H<sub>2</sub>). Data are in accordance with the literature.<sup>44</sup>

### **(*Z*)-pent-3-enoic acid 68**

Following a literature procedure,<sup>44</sup> to K<sub>2</sub>Cr<sub>2</sub>O<sub>7</sub> (56.1 mg, 0.19 mmol), HNO<sub>3</sub> (343 mg, 3.81 mmol) and NaIO<sub>4</sub> (8.97 g, 42.0 mmol) in H<sub>2</sub>O (25 mL) was added a solution of (*Z*)-pent-3-en-1-ol **67** (1.64 g, 19.1 mmol) in MeCN (50 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 8 h followed by rt for 16 h. The inorganic salts were filtered and washed with Et<sub>2</sub>O. H<sub>2</sub>O was added and the reaction mixture was

extracted with Et<sub>2</sub>O (x 3). The combined organic fractions were dried (MgSO<sub>4</sub>), filtered and concentrated *in vacuo*. The residual oil was purified by distillation to give (*Z*)-pent-3-enoic acid **68** (94:6 (*Z*):(*E*)) as a colourless oil (0.69 g, 36%); bp 100-102 °C (22 mmHg); {lit.<sup>44</sup> bp 100 °C (20 mmHg)}; Data for (*Z*)-isomer: δ<sub>H</sub> (500 MHz, CDCl<sub>3</sub>) 1.64 (3H, dt, *J* 6.8, 0.8, CH<sub>3</sub>), 3.14 (2H, dd, *J* 7.2, 0.4, C(2)H<sub>2</sub>), 3.66 (2H, q, *J* 6.2, C(1)H<sub>2</sub>), 5.56 (1H, dtq, *J* 10.7, 7.1, 1.8, C(3)H), 5.66-5.73 (1H, m, C(4)H); Selected data for (*E*)-isomer: δ<sub>H</sub> (500 MHz, CDCl<sub>3</sub>) 1.70 (3H, dt, *J* 6.3, 1.3, CH<sub>3</sub>), 3.06 (2H, dt, *J* 6.7, 1.2, C(2)H<sub>2</sub>). Data are in accordance with the literature.<sup>44</sup>

### **(*E*)-ethyl 3-phenylbut-2-enoate 69**

Following a literature procedure,<sup>45</sup> to a suspension of 60% NaH in mineral oil (1.00 g, 41.6 mmol) in THF (35 mL) at 0 °C was added ethyl 2-(diethoxyphosphoryl)acetate (8.26 mL, 41.6 mmol) dropwise over 30 minutes and the reaction mixture was stirred for 30 minutes at rt. A solution of acetophenone (4.85 mL, 41.6 mmol) in THF (15 mL) was added dropwise and the reaction mixture was allowed to stir at rt for 4 h. The reaction mixture was diluted with water and extracted with Et<sub>2</sub>O (x 3). The combined organic extracts were dried (MgSO<sub>4</sub>), filtered and concentrated *in vacuo*. Chromatographic purification (eluent Et<sub>2</sub>O:petrol 5:95) gave (*E*)-ethyl 3-phenylbut-2-enoate **69** as a colourless oil (2.35 g, 30%); δ<sub>H</sub> (500 MHz, CDCl<sub>3</sub>) 1.35 (3H, t, *J* 7.1, CH<sub>2</sub>CH<sub>3</sub>), 2.61 (3H, d, *J* 1.3, CH<sub>3</sub>), 4.25 (2H, q, *J* 7.1, CH<sub>2</sub>CH<sub>3</sub>), 6.16 (1H, q, *J* 1.2, =CH), 7.38-7.42 (3H, m, ArH), 7.50-7.52 (2H, m, ArH). Data are in accordance with the literature.<sup>45</sup>

### **(*E*)-3-phenylbut-2-enoic acid 70**

Following a literature procedure,<sup>41</sup> a solution of (*E*)-ethyl 3-phenylbut-2-enoate **69** (2.35 g, 12.4 mmol) in 0.5 M KOH (37.1 mL, 18.6 mmol) was heated at reflux for 16 h. Once cooled to rt the reaction mixture was extracted with Et<sub>2</sub>O (x 3). The reaction mixture was treated with 1M H<sub>2</sub>SO<sub>4</sub> until acidic and extracted with Et<sub>2</sub>O (x 3). The combined organic extracts were dried (MgSO<sub>4</sub>), filtered and concentrated *in vacuo*. Recrystallisation from Et<sub>2</sub>O gave (*E*)-3-phenylbut-2-enoic acid **70** as a white solid (1.39 g, 70%); mp 94-

96 °C; {lit.<sup>46</sup> mp 95-97 °C};  $\delta_{\text{H}}$  (500 MHz,  $\text{CDCl}_3$ ) 2.64 (3H, d,  $J$  1.2,  $\text{CH}_3$ ), 6.21 (1H, q,  $J$  1.2, =CH), 7.41-7.44 (3H, m, ArH), 7.51-7.54 (2H, m, ArH). Data are in accordance with the literature.<sup>47</sup>

### **(E)-ethyl 3,4-diphenylbut-2-enoate 71**

Following a literature procedure,<sup>45</sup> to a suspension of 60% NaH in mineral oil (2.04 g, 51.0 mmol) in THF (50 mL) at 0 °C was added ethyl 2-(diethoxyphosphoryl)acetate (10.1 mL, 51.0 mmol) dropwise over 30 minutes and the reaction mixture was stirred for 30 minutes at rt. A solution of 1,2-diphenylethanone (10 g, 51.0 mmol) in THF (20 mL) was added dropwise and the reaction mixture was allowed to stir at rt for 4 h. The reaction mixture was diluted with water and extracted with  $\text{Et}_2\text{O}$  (x 3). The combined organic extracts were dried ( $\text{MgSO}_4$ ), filtered and concentrated *in vacuo*. Chromatographic purification (eluent  $\text{Et}_2\text{O}$ :petrol 5:95) gave (E)-ethyl 3,4-diphenylbut-2-enoate **71** as a colourless oil (2.35 g, 17%);  $\delta_{\text{H}}$  (300 MHz,  $\text{CDCl}_3$ ) 1.35 (3H, t,  $J$  7.1,  $\text{CH}_2\text{CH}_3$ ), 4.27 (2H, q,  $J$  7.1,  $\text{CH}_2\text{CH}_3$ ), 4.55 (2H, s,  $\text{CH}_2\text{Ph}$ ), 6.29 (1H, d, =CH), 7.14-7.27 (5H, m, ArH), 7.33-7.36 (3H, m, ArH), 7.42-7.48 (2H, m, ArH). Data are in accordance with the literature.<sup>48</sup>

### **(E)-3,4-diphenylbut-2-enoic acid 72**

Following a literature procedure,<sup>41</sup> a solution of (E)-ethyl 3,4-diphenylbut-2-enoate **71** (2.35 g, 8.84 mmol) in 0.5 M KOH (26.8 mL, 13.3 mmol) was heated at reflux for 16 h. Once cooled to rt the reaction mixture was extracted with  $\text{Et}_2\text{O}$  (x 3). The reaction mixture was treated with 1M  $\text{H}_2\text{SO}_4$  until acidic and extracted with  $\text{Et}_2\text{O}$  (x 3). The combined organic extracts were dried ( $\text{MgSO}_4$ ), filtered and concentrated *in vacuo*. Chromatographic purification (eluent  $\text{Et}_2\text{O}$ :petrol 25:75) gave (E)-3,4-diphenylbut-2-enoic acid **72** as a white solid (210 mg, 10%); mp 122-124 °C; {lit.<sup>49</sup> mp 138-139 °C};  $\delta_{\text{H}}$  (300 MHz,  $\text{CDCl}_3$ ) 4.59 (2H, s,  $\text{CH}_2\text{Ph}$ ), 6.34 (1H, s, =CH), 7.18-7.29 (5H, m, ArH), 7.34-7.39 (3H, m, ArH), 7.46-7.49 (2H, m, ArH). Data are in accordance with the literature.<sup>49</sup>

**General procedure A:** *Isothiourea catalysed intermolecular reactions.*

To a solution of acid (1-2 equiv.) in CH<sub>2</sub>Cl<sub>2</sub> (~1 mL per 0.2 mmol of acid) were added *i*Pr<sub>2</sub>NEt (1.5 equiv. based upon acid) and activating agent (1.5 equiv. based upon acid) at rt. The reaction mixture was allowed to stir at rt for 10 minutes. The requisite isothioureia (1-10 mol%), Michael acceptor/ketone/imine (1 equiv.) and *i*Pr<sub>2</sub>NEt (2.5 equiv.) were then added at the required temperature. The reaction mixture was stirred at the required temperature until complete by TLC. The reaction mixture was subsequently quenched by addition of HCl (1 M in H<sub>2</sub>O). The reaction mixture was poured into H<sub>2</sub>O and extracted with CH<sub>2</sub>Cl<sub>2</sub> (x 3). The combined organics were dried (MgSO<sub>4</sub>), filtered and concentrated *in vacuo* to give the crude reaction mixture.

**(3*S*,4*S*)-4-phenyl-3-[(*E*)-2-phenylethynyl]-4-(trifluoromethyl)oxetan-2-one **21** and (3*S*,4*R*)-4-phenyl-3-[(*E*)-2-phenylethynyl]-4-(trifluoromethyl)oxetan-2-one **73****

Following general procedure A, (*E*)-4-phenylbut-3-enoic acid **16** (259 mg, 1.60 mmol), *i*Pr<sub>2</sub>NEt (0.42 mL, 2.40 mmol) and pivaloyl chloride (296 μL, 2.40 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL), DHPB **17** (15.2 mg, 0.08 mmol, 10 mol%), 2,2,2-trifluoro-1-phenylethan-1-one **18** (109 μL, 0.80 mmol) and *i*Pr<sub>2</sub>NEt (0.35 mL, 2.00 mmol) for 1.5 h at rt gave crude lactones **21** and **73** (60:40 dr). Chromatographic purification (eluent Et<sub>2</sub>O:petrol 2.5:97.5) gave lactone **21** (>98:2 dr) as a white solid (110 mg, 43%) and lactone **73** (>98:2 dr) as a white solid (73.4 mg, 29%).

Following general procedure A, (*E*)-4-phenylbut-3-enoic acid **16** (259 mg, 1.60 mmol), *i*Pr<sub>2</sub>NEt (0.42 mL, 2.40 mmol) and pivaloyl chloride (296 μL, 2.40 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL), HBTM-2.1 (2*S*,3*R*)-**23** (24.6 mg, 0.08 mmol, 10 mol%), 2,2,2-trifluoro-1-phenylethan-1-one **18** (109 μL, 0.80 mmol) and *i*Pr<sub>2</sub>NEt (0.35 mL, 2.00 mmol) for 1.5 h at -78 °C gave crude lactones (3*S*,4*S*)-**21** and (3*R*,4*R*)-**73** (65:35 dr). Chromatographic purification (eluent Et<sub>2</sub>O:petrol 2.5:97.5) gave lactone (3*S*,4*S*)-**21** (>98:2 dr) as a white solid (98.3 mg, 39%) and lactone (3*R*,4*R*)-**73** (>98:2 dr) as a white solid (52.6 mg, 21 %):

Data for lactone (3*S*,4*S*)-**21**: mp 66-67 °C; [ $\alpha$ ]<sub>D</sub><sup>20</sup>-14.8 (*c* 0.5, CH<sub>2</sub>Cl<sub>2</sub>); Chiral HPLC Chiralcel OD-H (0.5% IPA:hexane, flow rate 1 mL min<sup>-1</sup>, 211 nm, 30 °C) t<sub>R</sub>(3*R*,4*R*): 9.6 min, t<sub>R</sub>(3*S*,4*S*): 12.6 min, 79% *ee*;

$\nu_{\max}$  (ATR)/ $\text{cm}^{-1}$  3080, 3030 (C-H), 1847 (C=O), 1698;  $\delta_{\text{H}}$  (400 MHz,  $\text{CDCl}_3$ ) 4.95-4.98 (1H, m, C(3)H), 5.64 (1H, dd,  $J$  15.7, 9.4, PhCH=CH), 6.71 (1H, d,  $J$  15.7, PhCH=CH), 7.20-7.23 (2H, m, ArH), 7.27-7.31 (3H, m, ArH), 7.46-7.49 (5H, m, ArH);  $\delta_{\text{C}}$  (100 MHz,  $\text{CDCl}_3$ ) 60.9 (C(3)), 79.5 (q,  $J$  32.8, C(4)), 116.1 (PhCH=CH), 123.6 (q,  $J$  280,  $\text{CF}_3$ ), 126.9 (ArC), 127.3 (ArC), 128.8 (ArC), 128.8 (ArC), 128.9 (4ry ArC), 129.0 (ArC), 130.1 (ArC), 135.3 (C(4)ArC(1)), 138.4 (PhCH=CH), 165.9 (C(2)=O);  $\delta_{\text{F}}$  (376 MHz,  $\text{CDCl}_3$ ) -78.7 ( $\text{CF}_3$ );  $m/z$  (APCI<sup>+</sup>) 319 ([M+H]<sup>+</sup>, 100%); HRMS (APCI<sup>+</sup>)  $\text{C}_{18}\text{H}_{14}\text{F}_3\text{O}_2^+$  ([M+H]<sup>+</sup>) requires 319.0940; found 319.0940 (-0.1 ppm).

Data for lactone (3*S*,4*R*)-**73**: mp 110-112 °C;  $[\alpha]_{\text{D}}^{20}$ -93.0 ( $c$  0.5,  $\text{CH}_2\text{Cl}_2$ ); Chiral HPLC Chiralcel OD-H (2% IPA:hexane, flow rate 1 mL min<sup>-1</sup>, 211 nm, 30 °C)  $t_{\text{R}}$ (3*R*,4*S*): 13.1 min,  $t_{\text{R}}$ (3*S*,4*R*): 14.9 min, 77% *ee*;  $\nu_{\max}$  (ATR)/ $\text{cm}^{-1}$  3080, 2944 (C-H), 1834 (C=O), 1692;  $\delta_{\text{H}}$  (400 MHz,  $\text{CDCl}_3$ ) 4.77 (1H, d,  $J$  8.7, C(3)H), 6.38-6.47 (1H, m, PhCH=CH), 6.83-6.88 (1H, m, PhCH=CH), 7.34-7.50 (9H, m, ArH);  $\delta_{\text{C}}$  (100 MHz,  $\text{CDCl}_3$ ) 64.9 (C(3)), 79.6 (q,  $J$  30.1, C(4)), 115.1 (PhCH=CH), 123.3 (q,  $J$  281,  $\text{CF}_3$ ), 126.3 (ArC), 127.1 (ArC), 128.9 (ArC), 128.9 (ArC), 129.1 (ArC), 130.2 (ArC), 132.9 (4ry ArC), 135.4 (C(4)ArC(1)), 139.0 (PhCH=CH), 165.9 (C(2)=O);  $\delta_{\text{F}}$  (376 MHz,  $\text{CDCl}_3$ ) -74.2 ( $\text{CF}_3$ );  $m/z$  (APCI<sup>+</sup>) 319 ([M+H]<sup>+</sup>, 100%); HRMS (APCI<sup>+</sup>)  $\text{C}_{18}\text{H}_{14}\text{F}_3\text{O}_2^+$  ([M+H]<sup>+</sup>) requires 319.0940; found 319.0941 (+0.2 ppm).

### **(3*S*,4*R*)-1-[(4-methylbenzene)sulfonyl]-4-phenyl-3-[(*E*)-2-phenylethenyl]azetid-2-one **22****

Following general procedure A, (*E*)-4-phenylbut-3-enoic acid **16** (259 mg, 1.60 mmol), *i*Pr<sub>2</sub>NEt (0.42 mL, 2.40 mmol) and pivaloyl chloride (296  $\mu\text{L}$ , 2.40 mmol) in  $\text{CH}_2\text{Cl}_2$  (10 mL), DHPB **17** (15.2 mg, 0.08 mmol, 10 mol%), imine **19** (207 mg, 0.80 mmol) (109  $\mu\text{L}$ , 0.80 mmol) and *i*Pr<sub>2</sub>NEt (0.35 mL, 2.00 mmol) for 1.5 h at rt gave crude lactam **22** (83:17 dr). Chromatographic purification (eluent Et<sub>2</sub>O:petrol 20:80) gave lactam **22** (>98:2 dr) as a white solid (219 mg, 68%).

Following general procedure A, (*E*)-4-phenylbut-3-enoic acid **16** (260 mg, 1.60 mmol), *i*Pr<sub>2</sub>NEt (420  $\mu\text{L}$ , 2.40 mmol) and pivaloyl chloride (296  $\mu\text{L}$ , 2.40 mmol) in  $\text{CH}_2\text{Cl}_2$  (10 mL), HBTM-2.1 (2*S*,3*R*)-**23** (24.6 mg, 0.08 mmol, 10 mol%), imine **19** (207 mg, 0.80 mmol) and *i*Pr<sub>2</sub>NEt (348  $\mu\text{L}$ , 2.00 mmol) for 1.5 h at rt

gave crude lactam (3*S*,4*R*)-**22** (85:15 dr). Chromatographic purification (eluent Et<sub>2</sub>O:petrol 20:80) gave lactam (3*S*,4*R*)-**22** (>98:2 dr) as a white solid (125 mg, 39%); mp 137-139 °C;  $[\alpha]_D^{20} +9.8$  (*c* 0.5, CH<sub>2</sub>Cl<sub>2</sub>); Chiral HPLC Chiralpak AD-H (10% IPA:hexane, flow rate 1 mL min<sup>-1</sup>, 211 nm, 30 °C) *t<sub>R</sub>*(3*S*,4*R*): 24.4 min, *t<sub>R</sub>*(3*R*,4*S*): 40.9 min, 72% *ee*;  $\nu_{\max}$  (ATR)/cm<sup>-1</sup> 3024, 2924 (C-H), 1790 (C=O), 1450, 1359 (S=O), 1165 (S=O); Data for major diastereoisomer:  $\delta_H$  (300 MHz, CDCl<sub>3</sub>) 2.44 (3H, s, CH<sub>3</sub>), 3.91 (1H, ddd, *J* 8.0, 3.3, 1.1 Hz, C(3)*H*), 4.90 (1H, d, *J* 3.3 Hz, C(4)*H*), 6.16 (1H, dd, *J* 15.9, 8.0 Hz, PhCH=CH), 6.53 (1H, dd, *J* 15.9, 1.1 Hz, PhCH=CH), 7.24-7.36 (12H, m, Ar*H*), 7.65-7.69 (2H, m, SO<sub>2</sub>Ar(2,6)*H*);  $\delta_C$  (100 MHz, CDCl<sub>3</sub>) 21.8 (CH<sub>3</sub>), 62.9 (C(3)), 64.3 (C(4)), 119.3 (HC=CHPh), 126.6 (*ArC*), 126.8 (*ArC*), 127.7 (*ArC*), 128.4 (*ArC*), 128.8 (*ArC*), 129.1 (*ArC*), 129.1 (*ArC*), 130.0 (*ArC*), 135.8 (HC=CHPh), 135.8 (4ry *ArC*), 135.8 (4ry *ArC*), 135.8 (4ry *ArC*), 145.4 (C(4)*ArC*(1)), 165.2 (C(2)=O); *m/z* (NSI) 404 ([M+H]<sup>+</sup>, 65%); HRMS (NSI) C<sub>24</sub>H<sub>22</sub>NO<sub>3</sub>S<sup>+</sup> ([M+H]<sup>+</sup>) requires 404.1315; found 404.1313 (-0.5 ppm).

#### **(3*S*,4*S*)-1-[(4-methylbenzene)sulfonyl]-4-phenyl-3-[(*E*)-2-phenylethenyl]azetididin-2-one **74****

Following general procedure A, (*E*)-4-phenylbut-3-enoic acid **16** (260 mg, 1.60 mmol), *i*Pr<sub>2</sub>NEt (420  $\mu$ L, 2.40 mmol) and pivaloyl chloride (296  $\mu$ L, 2.40 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL), HBTM-2.1 (2*S*,3*R*)-**23** (24.6 mg, 0.08 mmol, 10 mol%), imine **19** (207 mg, 0.80 mmol) and *i*Pr<sub>2</sub>NEt (348  $\mu$ L, 2.00 mmol) for 2.5 h at -78 °C gave crude lactam (3*S*,4*S*)-**74** (83:17 dr). Chromatographic purification (eluent Et<sub>2</sub>O:petrol 20:80) gave lactam (3*S*,4*S*)-**74** (>98:2 dr) as a white solid (136 mg, 42%); mp 127-129 °C;  $[\alpha]_D^{20} -6.4$  (*c* 0.5, CH<sub>2</sub>Cl<sub>2</sub>); Chiral HPLC Chiralpak AD-H (10% IPA:hexane, flow rate 1 mL min<sup>-1</sup>, 211 nm, 30 °C) *t<sub>R</sub>*(3*S*,4*S*): 23.0 min, *t<sub>R</sub>*(3*R*,4*R*): 46.8 min, 16% *ee*;  $\nu_{\max}$  (ATR)/cm<sup>-1</sup> 3024, 2924 (C-H), 1790 (C=O), 1450, 1359 (S=O), 1165 (S=O); Data for major diastereoisomer:  $\delta_H$  (500 MHz, CDCl<sub>3</sub>) 2.48 (3H, s, CH<sub>3</sub>), 4.40-4.42 (1H, m, C(3)*H*), 5.38 (1H, d, *J* 6.7 Hz, C(4)*H*), 5.49 (1H, dd, *J* 15.9, 7.3 Hz, PhCH=CH), 6.61 (1H, d, *J* 15.8 Hz, PhCH=CH), 7.06-7.07 (2H, m, Ar*H*), 7.16-7.24 (5H, m, Ar*H*), 7.28-7.34 (5H, m, Ar-*H*), 7.80 (2H, d, *J* 8.4 Hz, SO<sub>2</sub>Ar(2,6)*H*);  $\delta_C$  (100 MHz, CDCl<sub>3</sub>) 21.9 (CH<sub>3</sub>), 58.1 (C(4)), 61.8 (C(3)), 118.4 (HC=CHPh), 126.5 (C(4)*ArC*(2,6)), 127.5 (*ArC*), 127.8 (*ArC*), 128.2 (*ArC*), 128.6 (*ArC*), 128.6 (*ArC*),

128.9 (*ArC*), 130.0 (*ArC*), 133.7 (4ry *ArC*), 135.8 (4ry *ArC*), 135.9 (HC=CHPh), 136.1 (4ry *ArC*), 145.5 (C(4)*ArC*(1)), 165.0 (C(2)=O); *m/z* (NSI) 404 ([M+H]<sup>+</sup>, 70%); HRMS (NSI) C<sub>24</sub>H<sub>22</sub>NO<sub>3</sub>S<sup>+</sup> ([M+H]<sup>+</sup>) requires 404.1314; found 404.1313 (-0.2 ppm).

**(3*S*,4*R*)-4-(4-bromophenyl)-1-[(4-methylbenzene)sulfonyl]-3-[(1*E*)-prop-1-en-1-yl]azetidin-2-one 26**  
**and (3*S*,4*S*)-4-(4-bromophenyl)-1-[(4-methylbenzene)sulfonyl]-3-[(1*E*)-prop-1-en-1-yl]azetidin-2-one**  
**27**

Following general procedure A, (*E*)-pent-3-enoic acid **24** (162 μL, 1.60 mmol), *i*Pr<sub>2</sub>NEt (420 μL, 2.40 mmol) and pivaloyl chloride (296 μL, 2.40 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL), HBTM-2.1 (2*S*,3*R*)-**23** (24.6 mg, 0.08 mmol, 10 mol%), imine **25** (270 mg, 0.80 mmol) and *i*Pr<sub>2</sub>NEt (348 μL, 2.00 mmol) for 1.5 h at rt gave crude lactams (3*S*,4*R*)-**26** and (3*S*,4*S*)-**27** (68:32 dr). Chromatographic purification (eluent Et<sub>2</sub>O:petrol 20:80) gave lactam (3*S*,4*R*)-**26** (>98:2 dr) as a colourless oil (177 mg, 53%) and lactam (3*S*,4*S*)-**27** (>98:2 dr) as a white solid (91 mg, 27%):

Data for lactam (3*S*,4*R*)-**26**: Chiral HPLC Chiralpak AD-H (10% IPA:hexane, flow rate 1 mL min<sup>-1</sup>, 220 nm, 30 °C) *t*<sub>R</sub>(3*S*,4*R*): 18.6 min, *t*<sub>R</sub>(3*R*,4*S*): 47.0 min, 79% *ee*; *v*<sub>max</sub> (ATR)/cm<sup>-1</sup> 3032, 2965 (C-H), 1794 (C=O), 1595, 1366 (S=O), 1169 (S=O); δ<sub>H</sub> (400 MHz, CDCl<sub>3</sub>) 1.68 (3H, ddd, *J* 6.5, 1.6, 0.8 Hz, CH<sub>3</sub>CH=CH), 2.44 (3H, s, ArCH<sub>3</sub>), 3.64 (1H, ddt, *J* 8.0, 3.3, 0.9 Hz, C(3)*H*), 4.70 (1H, d, *J* 3.3 Hz, C(4)*H*), 5.38-5.45 (1H, m, CH<sub>3</sub>CH=CH), 5.62-5.69 (1H, m, CH<sub>3</sub>CH=CH), 7.07-7.11 (2H, m, Ar*H*), 7.26-7.29 (2H, m, SO<sub>2</sub>Ar(3,5)*H*), 7.40-7.43 (2H, m, Ar*H*), 7.64-7.67 (2H, m, SO<sub>2</sub>Ar(2,6)*H*); δ<sub>C</sub> (125 MHz, CDCl<sub>3</sub>) 18.2 (CH<sub>3</sub>CH=CH), 21.8 (ArCH<sub>3</sub>), 62.8 (C(3)), 63.4 (C(4)), 121.0 (CH<sub>3</sub>CH=CH), 123.0 (C(4)*ArC*(4)), 127.6 (*ArC*), 128.2 (*ArC*), 130.0 (*ArC*), 132.1 (*ArC*), 133.1 (CH<sub>3</sub>CH=CH), 135.1 (4ry *ArC*), 135.5 (4ry *ArC*), 145.5 (C(4)*ArC*(1)), 165.4 (C(2)=O); *m/z* (APCI) 420 ([M+H]<sup>+</sup>, 98%); HRMS (APCI) C<sub>19</sub>H<sub>18</sub>BrNO<sub>3</sub>S<sup>+</sup> ([M+H]<sup>+</sup>) requires 420.0264; found 420.0266 (+0.6 ppm).

Data for lactam (3*S*,4*S*)-**27**: mp 92-94 °C; Chiral HPLC Chiralpak AD-H (10% IPA:hexane, flow rate 1 mL min<sup>-1</sup>, 211 nm, 30 °C) *t*<sub>R</sub>(3*S*,4*S*): 20.9 min, *t*<sub>R</sub>(3*R*,4*R*): 23.0 min, 72% *ee*; *v*<sub>max</sub> (ATR)/cm<sup>-1</sup> 2941, 2926,

(C-H), 1786 (C=O), 1487, 1368 (S=O), 1125 (S=O);  $\delta_{\text{H}}$  (400 MHz,  $\text{CDCl}_3$ ) 1.51 (3H, ddd,  $J$  6.6, 1.7, 1.0 Hz,  $\text{CH}_3\text{CH}=\text{CH}$ ), 2.46 (3H, s,  $\text{ArCH}_3$ ), 4.16 (1H, ddt,  $J$  7.8, 6.7, 1.1,  $\text{C}(3)\text{H}$ ), 4.78 (1H, ddq,  $J$  15.3, 7.7, 1.7 Hz,  $\text{CH}_3\text{CH}=\text{CH}$ ), 5.17 (1H, d,  $J$  6.7 Hz,  $\text{C}(4)\text{H}$ ), 5.69 (1H, dqd,  $J$  15.3, 6.6, 1.3 Hz,  $\text{CH}_3\text{CH}=\text{CH}$ ), 6.97-7.00 (2H, m,  $\text{ArH}$ ), 7.31-7.33 (2H, m,  $\text{SO}_2\text{Ar}(3,5)\text{H}$ ), 7.40-7.42 (2H, m,  $\text{ArH}$ ), 7.75-7.77 (2H, m,  $\text{SO}_2\text{Ar}(2,6)\text{H}$ );  $\delta_{\text{C}}$  (125 MHz,  $\text{CDCl}_3$ ) 18.2 ( $\text{CH}_3\text{CH}=\text{CH}$ ), 21.9 ( $\text{ArCH}_3$ ), 58.3 ( $\text{C}(3)$ ), 61.1 ( $\text{C}(4)$ ), 119.4 ( $\text{CH}_3\text{CH}=\text{CH}$ ), 122.7 ( $\text{C}(4)\text{ArC}(4)$ ), 127.7 ( $\text{ArC}$ ), 129.1 ( $\text{ArC}$ ), 130.1 ( $\text{ArC}$ ), 131.7 ( $\text{ArC}$ ), 133.2 (4ry  $\text{ArC}$ ), 133.9 ( $\text{CH}_3\text{CH}=\text{CH}$ ), 135.6 (4ry  $\text{ArC}$ ), 145.7 ( $\text{C}(4)\text{ArC}(1)$ ), 165.4 ( $\text{C}(2)=\text{O}$ );  $m/z$  (NSI) 420 ( $[\text{M}+\text{H}]^+$ , 100%); HRMS (NSI)  $\text{C}_{19}\text{H}_{18}\text{BrNO}_3\text{S}^+$  ( $[\text{M}+\text{H}]^+$ ) requires 420.0264; found 420.0263 (-0.1 ppm).

Reaction carried out for 1.5 h at  $-78\text{ }^\circ\text{C}$  gave crude lactams (3*S*,4*R*)-**26**:(3*S*,4*S*)-**27** (71:29 dr). Chromatographic purification (eluent  $\text{Et}_2\text{O}$ :petrol 20:80) gave lactam (3*S*,4*R*)-**26** (>98:2 dr) as a colourless oil (179 mg, 53%) with identical spectroscopic properties as before in 97% *ee*;  $[\alpha]_{\text{D}}^{20}$  0.6 (*c* 0.5,  $\text{CH}_2\text{Cl}_2$ ) and lactam (3*S*,4*S*)-**27** (>98:2 dr) as a white solid (35.6 mg, 11%) with identical spectroscopic properties as before in >99% *ee*;  $[\alpha]_{\text{D}}^{20}$  -14.6 (*c* 0.5,  $\text{CH}_2\text{Cl}_2$ ).

### **(3*S*,4*R*)-4-(4-methoxyphenyl)-1-[(4-methylbenzene)sulfonyl]-3-[(1*E*)-prop-1-en-1-yl]azetidin-2-one** **28**

Following general procedure A, (*E*)-pent-3-enoic acid **24** (162  $\mu\text{L}$ , 1.60 mmol),  $i\text{Pr}_2\text{NEt}$  (420  $\mu\text{L}$ , 2.40 mmol) and pivaloyl chloride (296  $\mu\text{L}$ , 2.40 mmol) in  $\text{CH}_2\text{Cl}_2$  (10 mL), HBTM-2.1 (2*S*,3*R*)-**23** (24.6 mg, 0.08 mmol, 10 mol%), imine **53** (231 mg, 0.80 mmol) and  $i\text{Pr}_2\text{NEt}$  (348  $\mu\text{L}$ , 2.00 mmol) for 1.5 h at rt gave crude lactam (3*S*,4*R*)-**28** (80:20 dr). Chromatographic purification (eluent  $\text{Et}_2\text{O}$ :petrol 30:70) gave lactam (3*S*,4*R*)-**28** (96:4 dr) as a yellow oil (220 mg, 74%);  $[\alpha]_{\text{D}}^{20}$  -11.2 (*c* 0.5,  $\text{CH}_2\text{Cl}_2$ ); Chiral HPLC Chiralpak AD-H (10% IPA:hexane, flow rate 1 mL  $\text{min}^{-1}$ , 211 nm, 30  $^\circ\text{C}$ )  $t_{\text{R}}$ (3*S*,4*R*): 17.6 min,  $t_{\text{R}}$ (3*R*,4*S*): 53.0 min, 86% *ee*;  $\nu_{\text{max}}$  (ATR)/ $\text{cm}^{-1}$  2966 (C-H), 1790 (C=O), 1612, 1516, 1364 (S=O), 1167 (S=O); Data for major diastereomer:  $\delta_{\text{H}}$  (500 MHz,  $\text{CDCl}_3$ ) 1.68 (3H, ddd,  $J$  6.5, 1.6, 0.8 Hz,  $\text{CH}_3\text{CH}=\text{CH}$ ), 2.42 (3H, s,  $\text{ArCH}_3$ ), 3.67 (1H, ddt,  $J$  8.0, 3.3, 0.9 Hz,  $\text{C}(3)\text{H}$ ), 3.80 (3H, s,  $\text{OCH}_3$ ), 4.73 (1H, d,  $J$  3.3 Hz,  $\text{C}(4)\text{H}$ ), 5.43



(1H, ddq, *J* 15.3, 8.0, 1.6 Hz, CH<sub>3</sub>CH=CH), 5.63-5.70 (1H, m, CH<sub>3</sub>CH=CH), 6.80-6.81 (2H, m, C(4)Ar(3,5)*H*), 7.12-7.14 (2H, m, C(4)Ar(2,6)*H*), 7.24 (2H, d, *J* 8.6 Hz, SO<sub>2</sub>Ar(3,5)*H*), 7.60-7.61 (2H, m, SO<sub>2</sub>Ar(2,6)*H*); δ<sub>C</sub> (125 MHz, CDCl<sub>3</sub>) 18.2 (CH<sub>3</sub>CH=CH), 21.8 (ArCH<sub>3</sub>), 55.5 (OCH<sub>3</sub>), 62.6 (C(3)), 64.0 (C(4)), 114.3 (C(4)ArC(3,5)), 121.4 (CH<sub>3</sub>CH=CH), 127.6 (SO<sub>2</sub>ArC(2,6)), 127.8 (C(4)ArC(1)), 128.2 (C(4)ArC(2,6)), 129.8 (SO<sub>2</sub>ArC(3,5)), 132.6 (CH<sub>3</sub>CH=CH), 135.9 (SO<sub>2</sub>ArC(1)), 145.1 (SO<sub>2</sub>ArC(4)), 160.2 (C(4)ArC(4)), 165.9 (C(2)=O); *m/z* (ESI) 394 ([M+Na]<sup>+</sup>, 80%); HRMS (ESI) C<sub>20</sub>H<sub>21</sub>NNaO<sub>4</sub>S<sup>+</sup> ([M+Na]<sup>+</sup>) requires 394.1089; found 394.1075 (-2.2 ppm).

**(3*S*,4*R*)-1-[(4-methylbenzene)sulfonyl]-3-[(1*E*)-prop-1-en-1-yl]-4-[4-(trifluoromethyl)phenyl]azetidin-2-one 29**

Following general procedure A, (*E*)-pent-3-enoic acid **24** (162 μL, 1.60 mmol), *i*Pr<sub>2</sub>NEt (420 μL, 2.40 mmol) and pivaloyl chloride (296 μL, 2.40 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL), HBTM-2.1 (2*S*,3*R*)-**23** (24.6 mg, 0.08 mmol, 10 mol%), imine **54** (262 mg, 0.80 mmol) and *i*Pr<sub>2</sub>NEt (348 μL, 2.00 mmol) for 1.5 h at rt gave crude lactam (3*S*,4*R*)-**29** (87:13 dr). Chromatographic purification (eluent Et<sub>2</sub>O:petrol 20:80) gave lactam (3*S*,4*R*)-**29** (>98:2 dr) as a colourless oil (151 mg, 46%); [α]<sub>D</sub><sup>20</sup>+1.0 (*c* 0.5, CH<sub>2</sub>Cl<sub>2</sub>); Chiral HPLC Chiralpak AD-H (10% IPA:hexane, flow rate 1 mL min<sup>-1</sup>, 211 nm, 30 °C) t<sub>R</sub>(3*S*,4*R*): 20.3 min, t<sub>R</sub>(3*R*,4*S*): 48.4 min, 44% *ee*; ν<sub>max</sub> (ATR)/cm<sup>-1</sup> 2970 (C-H), 1796 (C=O), 1597, 1323 (S=O), 1165 (S=O); Data for major diastereomer: δ<sub>H</sub> (400 MHz, CDCl<sub>3</sub>) 1.69 (3H, ddd, *J* 6.5, 1.6, 0.8 Hz, CH<sub>3</sub>CH=CH), 2.44 (3H, s, ArCH<sub>3</sub>), 3.67 (1H, ddt, *J* 8.0, 3.3, 0.9 Hz, C(3)*H*), 4.79 (1H, d, *J* 3.3 Hz, C(4)*H*), 5.39-5.46 (1H, m, CH<sub>3</sub>CH=CH), 5.64-5.73 (1H, m, CH<sub>3</sub>CH=CH), 7.25-7.28 (2H, m, SO<sub>2</sub>Ar(3,5)*H*), 7.35 (2H, d, *J* 8.3 Hz, C(4)Ar(3,5)*H*), 7.55 (2H, d, *J* 8.1 Hz, C(4)Ar(2,6)*H*), 7.65-7.68 (2H, m, SO<sub>2</sub>Ar(2,6)*H*); δ<sub>C</sub> (125 MHz, CDCl<sub>3</sub>) 18.2 (CH<sub>3</sub>CH=CH), 21.8 (ArCH<sub>3</sub>), 63.0 (C(3) or C(4)), 63.2 (C(3) or C(4)), 120.8 (CH<sub>3</sub>CH=CH), 123.9 (q, *J* 271 Hz, CF<sub>3</sub>), 125.9 (q, *J* 3.5 Hz, C(4)ArC(3,5)), 126.9 (C(4)ArC(2,6)), 127.6 (SO<sub>2</sub>ArC(2,6)), 130.0 (SO<sub>2</sub>ArC(3,5)), 131.2 (q, *J* 32.5 Hz, C(4)ArC(4)), 133.4 (CH<sub>3</sub>CH=CH), 135.4 (SO<sub>2</sub>ArC(1)), 140.2 (C(4)ArC(1)), 145.7 (SO<sub>2</sub>ArC(4)), 165.2 (C(2)=O); δ<sub>F</sub> (376 MHz, CDCl<sub>3</sub>) -63.3 (CF<sub>3</sub>); *m/z* (NSI) 410 ([M+H]<sup>+</sup>, 15%); HRMS (NSI) C<sub>20</sub>H<sub>19</sub>F<sub>3</sub>NO<sub>3</sub>S<sup>+</sup> ([M+H]<sup>+</sup>) requires 410.1032; found 410.1030 (-0.5 ppm)

**(3*S*,3*R*)-4-(furan-2-yl)-1-[(4-methylbenzene)sulfonyl]-3-[(1*E*)-prop-1-en-1-yl]azetidin-2-one 30**

Following general procedure A, (E)-pent-3-enoic acid **24** (162  $\mu$ L, 1.60 mmol), *i*Pr<sub>2</sub>NEt (420  $\mu$ L, 2.40 mmol) and pivaloyl chloride (296  $\mu$ L, 2.40 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL), HBTM-2.1 (2*S*,3*R*)-**23** (24.6 mg, 0.08 mmol, 10 mol%), imine **55** (199 mg, 0.80 mmol) and *i*Pr<sub>2</sub>NEt (348  $\mu$ L, 2.00 mmol) for 1.5 h at rt gave crude lactam (3*S*,4*R*)-**30** (73:27 dr). Chromatographic purification (eluent Et<sub>2</sub>O:petrol 20:80) gave lactam (3*S*,4*R*)-**30** (95:5 dr) as a white solid (171 mg, 65%); mp 137-139 °C; Chiral HPLC Chiralpak AD-H (10% IPA:hexane, flow rate 1 mL min<sup>-1</sup>, 211 nm, 30 °C) t<sub>R</sub>(3*S*,4*R*): 11.6 min, t<sub>R</sub>(3*R*,4*S*): 13.4 min, 45% *ee*;  $\nu_{\max}$  (ATR)/cm<sup>-1</sup> 2976 (C-H), 1788 (C=O), 1595, 1362 (S=O), 1165 (S=O); Data for major diastereoisomer:  $\delta_{\text{H}}$  (400 MHz, CDCl<sub>3</sub>) 1.71 (3H, ddd, *J* 6.5, 1.6, 0.9 Hz, CH<sub>3</sub>CH=CH), 2.42 (3H, s, ArCH<sub>3</sub>), 4.00-4.03 (1H, m, C(3)*H*), 4.86-4.87 (1H, m, C(4)*H*), 5.45-5.52 (1H, m, CH<sub>3</sub>CH=CH), 5.71-5.80 (1H, m, CH<sub>3</sub>CH=CH), 6.35 (1H, dd, *J* 3.3, 1.9 Hz, C(4)ArC(4)*H*), 6.50 (1H, dd, *J* 3.3, 0.7 Hz, C(4)ArC(3)*H*), 7.20 (1H, dt, *J* 1.0, 0.5 Hz, C(4)ArC(5)*H*), 7.22-7.24 (2H, m, SO<sub>2</sub>Ar(3,5)*H*), 7.52-7.55 (2H, m, SO<sub>2</sub>Ar(2,6)*H*);  $\delta_{\text{C}}$  (125 MHz, CDCl<sub>3</sub>) 18.2 (CH<sub>3</sub>CH=CH), 21.8 (ArCH<sub>3</sub>), 56.7 (C(3)), 58.7 (C(4)), 110.9 (C(4)ArC), 112.0 (C(4)ArC), 121.1 (CH<sub>3</sub>CH=CH), 127.4 (SO<sub>2</sub>ArC(2,6)), 129.8 (SO<sub>2</sub>ArC(3,5)), 133.0 (CH<sub>3</sub>CH=CH), 135.7 (C(4)ArC(1)), 143.5 (C(4)ArC(5)), 145.0 (SO<sub>2</sub>ArC(1)), 147.6 (SO<sub>2</sub>ArC(4)), 164.9 (C(2)=O); *m/z* (APCI) 332 ([M+H]<sup>+</sup>, 100%); HRMS (APCI) C<sub>17</sub>H<sub>18</sub>NO<sub>4</sub>S<sup>+</sup> ([M+H]<sup>+</sup>) requires 332.0951; found 332.0954 (+0.9 ppm).

Reaction carried out for 1.5 h at -78 °C gave crude lactam (3*S*,4*R*)-**30** (63:37 dr). Chromatographic purification (eluent Et<sub>2</sub>O:petrol 20:80) gave lactam (3*S*,4*R*)-**30** (95:5 dr) as a white solid (126 mg, 48%) with identical spectroscopic properties as before in 95% *ee*; [ $\alpha$ ]<sub>D</sub><sup>20</sup> -6.4 (*c* 0.5, CH<sub>2</sub>Cl<sub>2</sub>).

**(3*S*,4*R*)-1-[(4-methylbenzene)sulfonyl]-4-(naphthalen-2-yl)-3-[(1*E*)-prop-1-en-1-yl]azetidin-2-one 31**  
**and (3*S*,4*S*)-1-[(4-methylbenzene)sulfonyl]-4-(naphthalen-2-yl)-3-[(1*E*)-prop-1-en-1-yl]azetidin-2-one 75**

Following general procedure A, (*E*)-pent-3-enoic acid **24** (162  $\mu$ L, 1.60 mmol), *i*Pr<sub>2</sub>NEt (420  $\mu$ L, 2.40 mmol) and pivaloyl chloride (296  $\mu$ L, 2.40 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL), HBTM-2.1 (2*S*,3*R*)-**23** (24.6 mg, 0.08 mmol, 10 mol%), imine **56** (247 mg, 0.80 mmol) and *i*Pr<sub>2</sub>NEt (348  $\mu$ L, 2.00 mmol) for 1.5 h at rt gave crude lactams (3*S*,4*R*)-**31** and (3*S*,4*S*)-**75** (67:33 dr). Chromatographic purification (eluent Et<sub>2</sub>O:petrol 20:80) gave lactam (3*S*,4*R*)-**31** (>98:2 dr) as a colourless oil (188 mg, 60%) and lactam (3*S*,4*S*)-**75** (94:6 dr) as a colourless oil (96 mg, 31%):

Data for lactam (3*S*,4*R*)-**31**: Chiral HPLC Chiralpak AD-H (10% IPA:hexane, flow rate 1 mL min<sup>-1</sup>, 211 nm, 30 °C) *t*<sub>R</sub>(3*S*,4*R*): 17.1 min, *t*<sub>R</sub>(3*R*,4*S*): 37.0 min, 81% *ee*;  $\nu_{\max}$  (ATR)/cm<sup>-1</sup> 2972 (C-H), 1792 (C=O), 1699, 1364 (S=O), 1167 (S=O);  $\delta_{\text{H}}$  (500 MHz, CDCl<sub>3</sub>) 1.71 (3H, ddd, *J* 6.5, 1.5, 0.7 Hz, CH<sub>3</sub>CH=CH), 2.38 (3H, s, ArCH<sub>3</sub>), 3.77 (1H, ddd, *J* 7.9, 2.4, 0.8 Hz, C(3)*H*), 4.95 (1H, d, *J* 3.3 Hz, C(4)*H*), 5.48-5.53 (1H, m, CH<sub>3</sub>CH=CH), 5.68-5.72 (1H, m, CH<sub>3</sub>CH=CH), 7.14-7.16 (2H, m, SO<sub>2</sub>Ar(3,5)*H*), 7.23 (1H, dd, *J* 8.5, 1.8 Hz, C(4)Ar*H*), 7.49-7.53 (2H, m, Ar*H*), 7.60-7.63 (2H, m, SO<sub>2</sub>Ar(2,6)*H*), 7.70-7.72 (1H, m, C(4)Ar(1)*H*), 7.74 (1H, d, *J* 8.5, C(4)Ar*H*), 7.81-7.84 (1H, m, C(4)Ar*H*);  $\delta_{\text{C}}$  (125 MHz, CDCl<sub>3</sub>) 18.2 (CH<sub>3</sub>CH=CH), 21.7 (ArCH<sub>3</sub>), 62.9 (C(3)), 64.4 (C(4)), 121.3 (CH<sub>3</sub>CH=CH), 123.3 (ArC), 126.6 (ArC), 126.7 (ArC), 126.8 (ArC), 127.6 (SO<sub>2</sub>ArC(2,6)), 127.8 (ArC), 128.1 (ArC), 129.0 (ArC), 129.8 (SO<sub>2</sub>ArC(3.5)), 132.9 (CH<sub>3</sub>CH=CH), 133.0 (4ry ArC), 133.1 (4ry ArC), 133.5 (4ry ArC), 135.7 (4ry ArC), 145.4 (C(4)ArC(1)), 165.7 (C(2)=O); *m/z* (APCI) 392 ([M+H]<sup>+</sup>, 26%); HRMS (APCI) C<sub>23</sub>H<sub>22</sub>NO<sub>3</sub>S<sup>+</sup> ([M+H]<sup>+</sup>) requires 392.1315; found 392.1318 (+0.8 ppm).

Data for lactam (3*S*,4*S*)-**75**: Chiral HPLC Chiralcel OD-H (10% IPA:hexane, flow rate 1 mL min<sup>-1</sup>, 211 nm, 30 °C) *t*<sub>R</sub>(3*S*,4*S*): 19.2 min, *t*<sub>R</sub>(3*R*,4*R*): 25.0 min, 81% *ee*;  $\nu_{\max}$  (ATR)/cm<sup>-1</sup> 2972 (C-H), 1790 (C=O), 1597, 1364 (S=O), 1169 (S=O);  $\delta_{\text{H}}$  (400 MHz, CDCl<sub>3</sub>) 1.43 (3H, ddd, *J* 6.6, 1.7, 1.0 Hz, CH<sub>3</sub>CH=CH), 2.43 (3H, s, ArCH<sub>3</sub>), 4.26 (1H, ddq, *J* 7.8, 6.8, 1.0, C(3)*H*), 4.84 (1H, ddq, *J* 15.3, 7.8, 1.7 Hz, CH<sub>3</sub>CH=CH), 5.42 (1H, d, *J* 6.7 Hz, C(4)*H*), 5.66-5.75 (1H, m, CH<sub>3</sub>CH=CH), 7.13 (1H, dd, *J* 8.5, 1.9 Hz, C(4)Ar*H*), 7.24-7.27 (2H, m, SO<sub>2</sub>Ar(3,5)*H*), 7.48-7.52 (2H, m, Ar*H*), 7.55 (1H, dd, *J* 1.2, 0.5, C(4)Ar(1)*H*), 7.66-7.68 (1H, m, C(4)Ar*H*), 7.72-7.77 (3H, m, Ar*H*), 7.81-7.84 (1H, m, C(4)Ar*H*);  $\delta_{\text{C}}$  (100

MHz, CDCl<sub>3</sub>) 18.1 (CH<sub>3</sub>CH=CH), 21.8 (ArCH<sub>3</sub>), 58.6 (C(3)), 62.0 (C(4)), 119.7 (CH<sub>3</sub>CH=CH), 124.8 (ArC), 126.6 (ArC), 126.6 (ArC), 127.1 (ArC), 127.8 (ArC), 127.8 (SO<sub>2</sub>ArC(2,6)), 128.1 (ArC), 128.3 (ArC), 130.0 (SO<sub>2</sub>ArC(3,5)), 131.5 (4ry ArC), 133.0 (4ry ArC), 133.4 (4ry ArC), 133.6 (CH<sub>3</sub>CH=CH), 135.9 (4ry ArC), 145.4 (C(4)ArC(1)), 165.7 (C(2)=O); *m/z* (APCI) 392 ([M+H]<sup>+</sup>, 83%); HRMS (APCI) C<sub>23</sub>H<sub>22</sub>NO<sub>3</sub>S<sup>+</sup> ([M+H]<sup>+</sup>) requires 392.1315; found 392.1316 (+0.3 ppm).

Reaction carried out for 1.5 h at -78 °C gave crude lactams (3*S*,4*R*)-**31**:(3*S*,4*S*)-**75** (76:24 dr). Chromatographic purification (eluent Et<sub>2</sub>O:petrol 20:80) gave lactam (3*S*,4*R*)-**31** (>98:2 dr) as a colourless oil (201 mg, 64%) with identical spectroscopic properties as before in 97% *ee*; [ $\alpha$ ]<sub>D</sub><sup>20</sup>-10.6 (*c* 0.5, CH<sub>2</sub>Cl<sub>2</sub>) and lactam (3*S*,4*S*)-**75** (95:5 dr) as a colourless oil (69.0 mg, 22%) with identical spectroscopic properties as before in 99% *ee*; [ $\alpha$ ]<sub>D</sub><sup>20</sup>+0.6 (*c* 0.5, CH<sub>2</sub>Cl<sub>2</sub>).

**(3*S*,4*R*)-3-[(1*E*)-but-1-en-1-yl]-1-[(4-methylbenzene)sulfonyl]-4-phenylazetid-2-one **32** and (3*S*,4*S*)-3-[(1*E*)-but-1-en-1-yl]-1-[(4-methylbenzene)sulfonyl]-4-phenylazetid-2-one **76****

Following general procedure A, (*E*)-hex-3-enoic acid **81** (190  $\mu$ L, 1.60 mmol), *i*Pr<sub>2</sub>NEt (420  $\mu$ L, 2.40 mmol) and pivaloyl chloride (296  $\mu$ L, 2.40 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL), HBTM-2.1 (2*S*,3*R*)-**23** (24.6 mg, 0.08 mmol, 10 mol%), imine **19** (207 mg, 0.80 mmol) and *i*Pr<sub>2</sub>NEt (348  $\mu$ L, 2.00 mmol) for 1.5 h at rt gave crude lactams (3*S*,4*R*)-**32** and (3*S*,4*S*)-**76** (84:16 dr). Chromatographic purification (eluent Et<sub>2</sub>O:petrol 20:80) gave lactam (3*S*,4*R*)-**32** (>98:2 dr) as a colourless oil (158 mg, 55%) and lactam (3*S*,4*S*)-**76** (98:2 dr) as a white solid (22 mg, 8%):

Data for lactam (3*S*,4*R*)-**32**: Chiral HPLC Chiralpak AD-H (10% IPA:hexane, flow rate 1 mL min<sup>-1</sup>, 211 nm, 30 °C) *t*<sub>R</sub>(3*S*,4*R*): 11.5 min, *t*<sub>R</sub>(3*R*,4*S*): 17.8 min, 81% *ee*;  $\nu_{\max}$  (ATR)/cm<sup>-1</sup> 2967 (C-H), 1794 (C=O), 1699, 1366 (S=O), 1169 (S=O); Data for major diastereomer:  $\delta_{\text{H}}$  (500 MHz, CDCl<sub>3</sub>) 0.95 (3H, t, *J* 7.5 Hz, CH<sub>2</sub>CH<sub>3</sub>), 2.00-2.07 (2H, m, CH<sub>2</sub>CH<sub>3</sub>), 2.42 (3H, s, ArCH<sub>3</sub>), 3.70 (1H, ddt, *J* 7.8, 2.4, 0.9 Hz, C(3)*H*), 4.77 (1H, d, *J* 3.3 Hz, C(4)*H*), 5.42 (1H, ddt, *J* 15.4, 7.8, 1.6 Hz, EtCH=CH), 5.70 (1H, dtd, *J* 15.4, 6.3, 1.1 Hz, EtCH=CH), 7.21-7.25 (4H, m, Ar*H*), 7.27-7.34 (3H, m, Ar*H*), 7.62-7.64 (2H, m, SO<sub>2</sub>Ar(2,6)*H*);

$\delta_C$  (125 MHz,  $CDCl_3$ ) 13.1 ( $CH_2CH_3$ ), 21.8 ( $ArCH_3$ ), 25.6 ( $CH_2CH_3$ ), 62.6 ( $C(3)$  or  $C(4)$ ), 64.2 ( $C(3)$  or  $C(4)$ ), 119.1 ( $EtCH=CH$ ), 126.7 ( $C(4)ArC(2,6)$ ), 127.6 ( $SO_2ArC(2,6)$ ), 128.9 ( $C(4)ArC(3,5)$ ), 129.0 ( $C(4)ArC(4)$ ), 129.9 ( $SO_2ArC(3,5)$ ), 135.7 (4ry  $ArC$ ), 136.0 (4ry  $ArC$ ), 139.3 ( $EtCH=CH$ ), 145.2 ( $C(4)ArC(1)$ ), 165.8 ( $C(2)=O$ );  $m/z$  (NSI) 356 ( $[M+H]^+$ , 37%); HRMS (NSI)  $C_{20}H_{22}NO_3S^+$  ( $[M+H]^+$ ) requires 356.1315; found 356.1316 (+0.3 ppm).

Data for lactam (3*S*,4*S*)-**76**: mp 85-87 °C; Chiral HPLC Chiralpak AD-H (10% IPA:hexane, flow rate 1 mL min<sup>-1</sup>, 211 nm, 30 °C)  $t_R(3S,4S)$ : 14.9 min,  $t_R(3R,4R)$ : 27.9 min, 74% *ee*;  $v_{max}$  (ATR)/cm<sup>-1</sup> 2967 (C-H), 1788 (C=O), 1456, 1368 (S=O), 1171 (S=O); Data for major diastereomer:  $\delta_H$  (500 MHz,  $CDCl_3$ ) 0.72 (3H, t, *J* 7.4 Hz,  $CH_3CH_2$ ), 1.78-1.84 (2H, m,  $CH_3CH_2$ ), 2.45 (3H, s,  $ArCH_3$ ), 4.16 (1H, ddd, *J* 7.6, 6.7, 1.0,  $C(3)H$ ), 4.76 (1H, ddt, *J* 15.5, 7.6, 1.6 Hz,  $EtCH=CH$ ), 5.24 (1H, d, *J* 6.7 Hz,  $C(4)H$ ), 5.69 (1H, dtd, *J* 15.5, 6.4, 1.2 Hz,  $EtCH=CH$ ), 7.08-7.11 (2H, m,  $ArH$ ), 7.25-7.31 (5H, m,  $ArH$ ), 7.76-7.78 (2H, m,  $SO_2Ar(2,6)H$ );  $\delta_C$  (100 MHz,  $CDCl_3$ ) 13.1 ( $CH_3CH_2$ ), 21.8 ( $ArCH_3$ ), 25.6 ( $CH_3CH_2$ ), 58.2 ( $C(3)$ ), 61.8 ( $C(4)$ ), 117.7 ( $EtCH=CH$ ), 127.5 ( $C(4)ArC(2,6)$ ), 127.8 ( $SO_2ArC(2,6)$ ), 128.4 ( $C(4)ArC(3,5)$ ), 128.6 ( $C(4)ArC(4)$ ), 130.0 ( $SO_2ArC(3,5)$ ), 134.0 (4ry  $ArC$ ), 135.8 (4ry  $ArC$ ), 140.0 ( $EtCH=CH$ ), 145.4 ( $C(4)ArC(1)$ ), 165.7 ( $C(2)=O$ );  $m/z$  (NSI) 356 ( $[M+H]^+$ , 39%); HRMS (NSI)  $C_{20}H_{22}NO_3S^+$  ( $[M+H]^+$ ) requires 356.1315; found 356.1316 (+0.3 ppm)

Reaction carried out for 1.5 h at -78 °C gave crude lactams (3*S*,4*R*)-**32**:(3*S*,4*S*)-**76** (82:18 dr). Chromatographic purification (eluent  $Et_2O$ :petrol 20:80) gave lactam (3*S*,4*R*)-**32** (>98:2 dr) as a colourless oil (189 mg, 67%) with identical spectroscopic properties as before in 98% *ee*;  $[\alpha]_D^{20} +2.4$  (*c* 0.5,  $CH_2Cl_2$ ) and lactam (3*S*,4*S*)-**76** (98:2 dr) as a white solid (47.0 mg, 16%) with identical spectroscopic properties as before in >99% *ee*;  $[\alpha]_D^{20} -9.3$  (*c* 0.5,  $CH_2Cl_2$ ).

### **(3*S*,4*R*)-1-[(4-methylbenzene)sulfonyl]-3-[(1*E*)-3-methylbut-1-en-1-yl]-4-phenylazetid-2-one 33**

Following general procedure A, (*E*)-5-methylhex-3-enoic acid **65** (205 mg, 1.60 mmol), *i*Pr<sub>2</sub>NEt (420  $\mu$ L, 2.40 mmol) and pivaloyl chloride (296  $\mu$ L, 2.40 mmol) in  $CH_2Cl_2$  (10 mL), HBTM-2.1 (2*S*,3*R*)-**23** (24.6

mg, 0.08 mmol, 10 mol%), imine **19** (207 mg, 0.80 mmol) and *i*Pr<sub>2</sub>NEt (348 μL, 2.00 mmol) for 1.5 h at rt gave crude lactam (3*S*,4*R*)-**33** (73:27 dr). Chromatographic purification (eluent Et<sub>2</sub>O:petrol 15:85) gave lactam (3*S*,4*R*)-**33** (>98:2 dr) as a colourless solid (155 mg, 53%); Chiral HPLC Chiralpak AD-H (10% IPA:hexane, flow rate 1 mL min<sup>-1</sup>, 220 nm, 30 °C) *t*<sub>R</sub>(3*S*,4*R*): 9.9 min, *t*<sub>R</sub>(3*R*,4*S*): 14.4 min, 82% *ee*; *v*<sub>max</sub> (ATR)/cm<sup>-1</sup> 2961 (C-H), 1794 (C=O), 1597, 1435, 1366 (S=O), 1169 (S=O); Data for major diastereomer: δ<sub>H</sub> (500 MHz, CDCl<sub>3</sub>) 0.95 (6H, d, *J* 6.8 Hz, CH(CH<sub>3</sub>)<sub>2</sub>), 2.23-2.30 (1H, m, CH(CH<sub>3</sub>)<sub>2</sub>), 2.42 (3H, s, ArCH<sub>3</sub>), 3.68-3.70 (1H, m, C(3)*H*), 4.77 (1H, d, *J* 3.3 Hz, C(4)*H*), 5.38 (1H, ddd, *J* 15.5, 7.7, 1.4 Hz, *i*PrCH=CH), 5.62 (1H, ddd, *J* 15.5, 6.5, 1.1 Hz, *i*PrCH=CH), 7.21-7.25 (4H, m, Ar*H*), 7.27-7.34 (3H, m, Ar*H*), 7.62-7.64 (2H, m, SO<sub>2</sub>Ar(2,6)*H*); δ<sub>C</sub> (125 MHz, CDCl<sub>3</sub>) 21.8 (ArCH<sub>3</sub>), 22.0 (CH(CH<sub>3</sub>)<sub>2</sub>), 31.2 (CH(CH<sub>3</sub>)<sub>2</sub>), 62.5 (C(3)), 64.3 (C(4)), 117.3 (*i*PrCH=CH), 126.7 (C(4)ArC(2,6)), 127.6 (SO<sub>2</sub>ArC(2,6)), 128.9 (C(4)ArC(3,5)), 129.0 (C(4)ArC(4)), 129.8 (SO<sub>2</sub>ArC(3,5)), 135.7 (4ry ArC), 136.0 (4ry ArC), 144.4 (*i*PrCH=CH), 145.2 (C(4)ArC(1)), 165.8 (C(2)=O); *m/z* (NSI) 370 ([M+H]<sup>+</sup>, 32%); HRMS (NSI) C<sub>21</sub>H<sub>24</sub>NO<sub>3</sub>S<sup>+</sup> ([M+H]<sup>+</sup>) requires 370.1471; found 370.1472 (+0.2 ppm).

Reaction carried out for 1.5 h at -78 °C gave crude lactam (3*S*,4*R*)-**33** (79:21 dr). Chromatographic purification (eluent Et<sub>2</sub>O:petrol 15:85) gave lactam (3*S*,4*R*)-**33** (>98:2 dr) as a colourless oil (185 mg, 63%) with identical spectroscopic properties as before in 97% *ee*; [*α*]<sub>D</sub><sup>20</sup>+1.6 (*c* 0.5, CH<sub>2</sub>Cl<sub>2</sub>).

**(3*S*,4*R*)-1-[(4-methylbenzene)sulfonyl]-4-phenyl-3-[(1*E*)-3-phenylprop-1-en-1-yl]azetid-2-one 34**  
**and (3*S*,4*S*)-1-[(4-methylbenzene)sulfonyl]-4-phenyl-3-[(1*E*)-3-phenylprop-1-en-1-yl]azetid-2-one**  
**77**

Following general procedure A, (*E*)-5-phenylpent-3-enoic acid **66** (282 mg, 1.60 mmol), *i*Pr<sub>2</sub>NEt (420 μL, 2.40 mmol) and pivaloyl chloride (296 μL, 2.40 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL), HBTM-2.1 (2*S*,3*R*)-**23** (24.6 mg, 0.08 mmol, 10 mol%), imine **19** (207 mg, 0.80 mmol) and *i*Pr<sub>2</sub>NEt (348 μL, 2.00 mmol) for 1.5 h at rt gave crude lactams (3*S*,4*R*)-**34** and (3*S*,4*S*)-**77** (72:28 dr). Chromatographic purification (eluent

Et<sub>2</sub>O:petrol 25:75) gave lactam (3*S*,4*R*)-**34** (>98:2 dr) as a colourless oil (197 mg, 59%) and lactam (3*S*,4*S*)-**77** (95:5 dr) as a colourless oil (61 mg, 18%):

Data for lactam (3*S*,4*R*)-**34**: Chiral HPLC Chiralpak AD-H (10% IPA:hexane, flow rate 1 mL min<sup>-1</sup>, 211 nm, 30 °C) t<sub>R</sub>(3*S*,4*R*): 18.4 min, t<sub>R</sub>(3*R*,4*S*): 25.3 min, 62% *ee*; ν<sub>max</sub> (ATR)/cm<sup>-1</sup> 3028 (C-H), 1792 (C=O), 1597, 1364 (S=O), 1169 (S=O); Data for major diastereoisomer: δ<sub>H</sub> (500 MHz, CDCl<sub>3</sub>) 2.42 (3H, s, ArCH<sub>3</sub>), 3.37 (2H, d, *J* 6.7 Hz, PhCH<sub>2</sub>), 3.76 (1H, ddd, *J* 7.7, 3.3, 0.9 Hz, C(3)*H*), 4.81 (1H, d, *J* 3.3 Hz, C(4)*H*), 5.51 (1H, ddt, *J* 15.4, 7.7, 1.5 Hz, BnCH=CH), 5.84 (1H, dtd, *J* 15.3, 6.7, 1.2 Hz, BnCH=CH), 7.12-7.14 (2H, m, Ar*H*), 7.20-7.23 (5H, m, Ar*H*), 7.28-7.35 (5H, m, Ar*H*), 7.62-7.64 (2H, m, SO<sub>2</sub>(2,6)*H*); δ<sub>C</sub> (125 MHz, CDCl<sub>3</sub>) 21.8 (ArCH<sub>3</sub>), 38.9 (PhCH<sub>2</sub>CH=CH), 62.3 (C(3)), 64.1 (C(4)), 121.4 (BnCH=CH), 126.4 (*ArC*), 126.7 (*ArC*), 127.5 (*ArC*), 128.6 (*ArC*), 128.6 (*ArC*), 128.9 (*ArC*), 129.1 (C(4)*ArC*(4)), 129.8 (SO<sub>2</sub>*ArC*(3,5)), 135.7 (4ry *ArC*), 135.8 (4ry *ArC*), 136.1 (BnCH=CH), 139.0 (SO<sub>2</sub>*ArC*(1)), 145.2 (C(4)*ArC*(1)), 165.4 (C(2)=O); *m/z* (NSI) 418 ([M+H]<sup>+</sup>, 20%); HRMS (NSI) C<sub>25</sub>H<sub>24</sub>NO<sub>3</sub>S<sup>+</sup> ([M+H]<sup>+</sup>) requires 418.1471; found 418.1467 (-1.1 ppm).

Data for lactam (3*S*,4*S*)-**77**: Chiral HPLC Chiralpak AD-H (10% IPA:hexane, flow rate 1 mL min<sup>-1</sup>, 211 nm, 30 °C) t<sub>R</sub>(3*S*,4*S*): 14.4 min, t<sub>R</sub>(3*R*,4*R*): 26.7 min, 39% *ee*; ν<sub>max</sub> (ATR)/cm<sup>-1</sup> 3028, 2924 (C-H), 1788 (C=O), 1595, 1359 (S=O), 1167 (S=O); Data for minor diastereoisomer: δ<sub>H</sub> (500 MHz, CDCl<sub>3</sub>) 2.45 (3H, s, ArCH<sub>3</sub>), 3.12 (2H, d, *J* 6.7 Hz, PhCH<sub>2</sub>), 4.18-4.21 (1H, m, C(3)*H*), 4.85 (1H, ddt, *J* 15.4, 7.7, 1.5 Hz, BnCH=CH), 5.26 (1H, d, *J* 6.7 Hz, C(4)*H*), 5.78 (1H, dtd, *J* 15.4, 6.8, 1.2, BnCH=CH), 6.76-6.79 (2H, m, Ar*H*), 7.08-7.23 (5H, m, Ar*H*), 7.27-7.35 (5H, m, Ar*H*), 7.77-7.79 (2H, m, SO<sub>2</sub>(2,6)*H*); δ<sub>C</sub> (125 MHz, CDCl<sub>3</sub>) 21.9 (ArCH<sub>3</sub>), 38.9 (PhCH<sub>2</sub>), 58.1 (C(3)), 61.8 (C(4)), 120.4 (BnCH=CH), 126.2 (*ArC*), 127.4 (*ArC*), 127.8 (*ArC*), 128.4 (*ArC*), 128.6 (*ArC*), 128.7 (*ArC*), 128.7 (*ArC*), 130.0 (SO<sub>2</sub>*ArC*(3,5)), 134.0 (4ry *ArC*), 135.7 (4ry *ArC*), 136.8 (BnCH=CH), 138.9 (SO<sub>2</sub>*ArC*(1)), 145.5 (C(4)*ArC*(1)), 165.4 (C(2)=O); *m/z* (NSI) 418 ([M+H]<sup>+</sup>, 28%); HRMS (NSI) C<sub>25</sub>H<sub>24</sub>NO<sub>3</sub>S<sup>+</sup> ([M+H]<sup>+</sup>) requires 418.1471; found 418.1459 (-3.0 ppm)

Reaction carried out for 1.5 h at  $-78\text{ }^{\circ}\text{C}$  gave crude lactams (3*S*,4*R*)-**34**:(3*S*,4*S*)-**77** (72:28 dr). Chromatographic purification (eluent Et<sub>2</sub>O:petrol 25:75) gave lactam (3*S*,4*R*)-**34** (>98:2 dr) as a colourless oil (189 mg, 57%) with identical spectroscopic properties as before in 95% *ee*;  $[\alpha]_D^{20} +0.8$  (*c* 0.5, CH<sub>2</sub>Cl<sub>2</sub>) and lactam (3*S*,4*S*)-**77** (95:5 dr) as a colourless oil (53.0 mg, 16%) with identical spectroscopic properties as before in 97% *ee*;  $[\alpha]_D^{20} -6.8$  (*c* 0.5, CH<sub>2</sub>Cl<sub>2</sub>).

**(3*S*,4*R*)-1-[(4-methylbenzene)sulfonyl]-4-phenyl-3-[(1*Z*)-prop-1-en-1-yl]azetid-2-one 35 and (3*S*,4*S*)-1-[(4-methylbenzene)sulfonyl]-4-phenyl-3-[(1*Z*)-prop-1-en-1-yl]azetid-2-one 78**

Following general procedure A, (*Z*)-pent-3-enoic acid **68** (160 mg, 1.60 mmol), *i*Pr<sub>2</sub>NEt (420 μL, 2.40 mmol) and pivaloyl chloride (296 μL, 2.40 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL), HBTM-2.1 (2*S*,3*R*)-**23** (24.6 mg, 0.08 mmol, 10 mol%), imine **19** (207 mg, 0.80 mmol) and *i*Pr<sub>2</sub>NEt (348 μL, 2.00 mmol) for 1.5 h at rt gave crude lactams (3*S*,4*R*)-**35** and (3*S*,4*S*)-**78** (48:52 dr). Chromatographic purification (eluent Et<sub>2</sub>O:petrol 20:80) gave lactam (3*S*,4*R*)-**35** (92:8 dr) as a colourless oil (89 mg, 33%) and lactam (3*S*,4*S*)-**78** (88:12 dr) as a white solid (97 mg, 36%):

Data for lactam (3*S*,4*R*)-**35**: Chiral HPLC Chiralpak AD-H (10% IPA:hexane, flow rate 1 mL min<sup>-1</sup>, 211 nm, 30 °C) *t*<sub>R</sub>(3*R*,4*S*): 14.5 min, *t*<sub>R</sub>(3*S*,4*R*): 16.0 min, 92% *ee*;  $\nu_{\text{max}}$  (ATR)/cm<sup>-1</sup> 3030, 2967 (C-H), 1788 (C=O), 1456, 1362 (S=O), 1167 (S=O); Data for major diastereoisomer:  $\delta_{\text{H}}$  (500 MHz, CDCl<sub>3</sub>) 1.51 (3H, dd, *J* 6.9, 1.8 Hz, CH<sub>3</sub>CH=CH), 2.43 (3H, s, ArCH<sub>3</sub>), 4.00-4.02 (1H, m, C(3)*H*), 4.75 (1H, d, *J* 3.2 Hz, C(4)*H*), 5.44 (1H, ddq, *J* 10.6, 8.8, 1.8 Hz, CH<sub>3</sub>CH=CH), 5.78 (1H, dqd, *J* 10.7, 6.9, 1.4 Hz, CH<sub>3</sub>CH=CH), 7.23-7.25 (4H, m, Ar*H*), 7.28-7.35 (3H, m, Ar*H*), 7.62-7.65 (2H, m, SO<sub>2</sub>Ar(2,6)*H*);  $\delta_{\text{C}}$  (125 MHz, CDCl<sub>3</sub>) 14.0 (CH<sub>3</sub>CH=CH), 21.8 (ArCH<sub>3</sub>), 58.2 (C(3)), 64.4 (C(4)), 120.5 (CH<sub>3</sub>CH=CH), 126.7 (C(4)ArC(3,5)), 127.6 (SO<sub>2</sub>ArC(3,5)), 128.9 (SO<sub>2</sub>ArC(2,6)), 129.1 (C(4)ArC(4)), 129.9 (C(4)ArC(2,6)), 132.1 (CH<sub>3</sub>CH=CH), 135.7 (4ry ArC), 136.0 (4ry ArC), 145.3 (C(4)ArC(1)), 165.9 (C(2)=O); *m/z* (NSI) 342 ([M+H]<sup>+</sup>, 42%); HRMS (NSI) C<sub>19</sub>H<sub>20</sub>NO<sub>3</sub>S<sup>+</sup> ([M+H]<sup>+</sup>) requires 342.1158; found 342.1159 (+0.2 ppm)



Data for lactam (3*S*,4*S*)-**78**: mp 83-85 °C: Chiral HPLC Chiralcel OD-H (10% IPA:hexane, flow rate 1 mL min<sup>-1</sup>, 211 nm, 30 °C) t<sub>R</sub>(3*S*,4*S*): 12.0 min, t<sub>R</sub>(3*R*,4*R*): 15.8 min, 98% *ee*; ν<sub>max</sub> (ATR)/cm<sup>-1</sup> 3032, 2922 (C-H), 1788 (C=O), 1458, 1354 (S=O), 1165 (S=O); Data for minor diastereoisomer: δ<sub>H</sub> (500 MHz, CDCl<sub>3</sub>) 1.55-1.57 (3H, m, CH<sub>3</sub>CH=CH), 2.46 (3H, s, ArCH<sub>3</sub>), 4.47-4.50 (1H, m, C(3)*H*), 4.89-4.94 (1H, m, CH<sub>3</sub>CH=CH), 5.31 (1H, d, *J* 6.8 Hz, C(4)*H*), 5.54 (1H, dqd, *J* 10.8, 6.9, 1.5 Hz, CH<sub>3</sub>CH=CH), 7.09-7.11 (2H, m, Ar*H*), 7.23-7.34 (5H, m, Ar*H*), 7.76-7.78 (2H, m, SO<sub>2</sub>Ar(2,6)*H*); δ<sub>C</sub> (125 MHz, CDCl<sub>3</sub>) 13.9 (CH<sub>3</sub>CH=CH), 21.9 (ArCH<sub>3</sub>), 53.7 (C(3)), 61.8 (C(4)), 118.6 (CH<sub>3</sub>CH=CH), 127.4 (C(4)ArC(3,5)), 127.8 (SO<sub>2</sub>ArC(3,5)), 128.5 (SO<sub>2</sub>ArC(2,6)), 128.7 (C(4)ArC(4)), 130.0 (C(4)ArC(2,6)), 132.1 (CH<sub>3</sub>CH=CH), 134.0 (4ry ArC), 135.7 (4ry ArC), 145.4 (C(4)ArC(1)), 165.9 (C(2)=O); *m/z* (NSI) 342 ([M+H]<sup>+</sup>, 30%); HRMS (NSI) C<sub>19</sub>H<sub>20</sub>NO<sub>3</sub>S<sup>+</sup> ([M+H]<sup>+</sup>) requires 342.1158; found 342.1160 (+0.5 ppm)

Reaction carried out for 1.5 h at -78 °C gave crude lactams (3*S*,4*R*)-**35**:(3*S*,4*S*)-**78** (43:57 dr). Chromatographic purification (eluent Et<sub>2</sub>O:petrol 20:80) gave lactam (3*S*,4*R*)-**35** (92:8 dr) as a colourless oil (58 mg, 21%) with identical spectroscopic properties as before in 99% *ee*; [α]<sub>D</sub><sup>20</sup>+4.2 (*c* 0.5, CH<sub>2</sub>Cl<sub>2</sub>) and lactam (3*S*,4*S*)-**78** (88:12 dr) as a white solid (99.0 mg, 36%) with identical spectroscopic properties as before in 99% *ee*; [α]<sub>D</sub><sup>20</sup>-14.2 (*c* 0.5, CH<sub>2</sub>Cl<sub>2</sub>).

### **(3*S*,4*R*)-4-phenyl-3-((*E*)-prop-1-en-1-yl)-6-(trifluoromethyl)-3,4-dihydro-2H-pyran-2-one 36**

Following general procedure A, (*E*)-pent-3-enoic acid **24** (40.6 μL, 0.40 mmol), *i*Pr<sub>2</sub>NEt (104 μL, 0.60 mmol) and pivaloyl chloride (74.0 μL, 0.60 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2 mL), HBTM-2.1 (2*S*,3*R*)-**23** (6.16 mg, 0.02 mmol, 5 mol%), (*E*)-1,1,1-trifluoro-4-phenyl-3-buten-2-one **57** (80.0 mg, 0.40 mmol) and *i*Pr<sub>2</sub>NEt (174 μL, 1.0 mmol) for 5 minutes at rt gave crude lactone (3*S*,4*R*)-**36** (88:12 dr). Chromatographic purification (eluent Et<sub>2</sub>O:petrol 4:96) gave lactone (3*S*,4*R*)-**36** (88:12 dr) as a colourless oil (89.8 mg, 80%); [α]<sub>D</sub><sup>20</sup>-212.4 (*c* 0.5, CH<sub>2</sub>Cl<sub>2</sub>); Chiral HPLC Chiralcel OD-H (1% IPA:hexane, flow rate 1 mL min<sup>-1</sup>, 211 nm, 30 °C) major diastereoisomer: t<sub>R</sub>(3*S*,4*R*): 9.7 min, t<sub>R</sub>(3*R*,4*S*): 13.2 min, 96% *ee*; minor diastereoisomer t<sub>R</sub>: 10.7 min, t<sub>R</sub>: 14.8 min, 15% *ee*; ν<sub>max</sub> (ATR)/cm<sup>-1</sup> 3060, 3027 (C-H), 1784 (C=O),

1699; Data for major diastereoisomer:  $\delta_{\text{H}}$  (500 MHz,  $\text{CDCl}_3$ ) 1.68 (3H, t,  $J$ , 5.9,  $\text{CH}_3$ ), 3.43 (1H, t,  $J$  6.9, C(3) $H$ ), 3.70-3.75 (1H, m, C(4) $H$ ), 5.44-5.56 (2H, m, C(3) $\text{CH}=\text{CHCH}_3$  and C(3) $\text{CH}=\text{CHCH}_3$ ), 6.09 (1H, d,  $J$  4.5, C(5) $H$ ), 7.11 (2H, d,  $J$  7.8, C(4)Ar(2,6) $H$ ), 7.31-7.40 (3H, m, C(4)Ar(3,5) $H$  and C(4)Ar(4) $H$ );  $\delta_{\text{C}}$  (75 MHz,  $\text{CDCl}_3$ ) 18.1 ( $\text{CH}_3$ ), 43.2 (C(4)), 49.9 (C(3)), 109.7 (q,  $J$  3.5, C(5)), 118.5 (q,  $J$  270,  $\text{CF}_3$ ), 123.8 (C(3) $\text{CH}=\text{CHCH}_3$ ), 127.4 (ArC), 128.1 (ArC), 129.2 (ArC), 132.1 (C(3) $\text{CH}=\text{CHCH}_3$ ), 138.7 (4ry C(4)ArC(1)), 140.8 (q,  $J$  37.9, C(6)), 166.1 (C(2));  $\delta_{\text{F}}$  (376 MHz,  $\text{CDCl}_3$ ) -72.6 ( $\text{CF}_3$ ); Selected data or minor diastereoisomer:  $\delta_{\text{H}}$  (500 MHz,  $\text{CDCl}_3$ ) 3.63 (1H, t,  $J$  7.8, C(3) $H$ ), 3.86-3.88 (1H, m, C(4) $H$ ), 5.13 (1H, dd,  $J$  15.4, 8.6, C(3) $\text{CH}=\text{CHCH}_3$ ), 5.69 (1H, dq,  $J$  14.7, 7.1, C(3) $\text{CH}=\text{CHCH}_3$ ), 6.23 (1H, d,  $J$  5.7, C(5) $H$ ), 7.11 (2H, d,  $J$  7.7, Ar(2,6) $H$ );  $\delta_{\text{C}}$  (75 MHz,  $\text{CDCl}_3$ ) 18.0 ( $\text{CH}_3$ ), 43.0 (C(4)), 47.7 (C(3)), 110.8 (q,  $J$  3.5, C(5)), 122.6 (C(3) $\text{CH}=\text{CHCH}_3$ ), 128.2 (ArC), 128.3 (ArC), 129.1 (ArC), 132.2 (C(3) $\text{CH}=\text{CHCH}_3$ ), 166.6 (C(2));  $\delta_{\text{F}}$  (376 MHz,  $\text{CDCl}_3$ ) -72.7 ( $\text{CF}_3$ );  $m/z$  (NSI<sup>+</sup>) 300 ([M+NH<sub>4</sub>]<sup>+</sup>, 100%); HRMS (NSI<sup>+</sup>) C<sub>15</sub>H<sub>17</sub>F<sub>3</sub>NO<sub>2</sub><sup>+</sup> ([M+NH<sub>4</sub>]<sup>+</sup>) requires 300.1206; found 300.1206 (+0.0 ppm).

### **(3*S*,4*R*)-4-phenyl-3-((*E*)-but-1-en-1-yl)-6-(trifluoromethyl)-3,4-dihydro-2H-pyran-2-one 37**

Following general procedure A, (*E*)-hex-3-enoic acid **81** (47.4  $\mu\text{L}$ , 0.40 mmol), *i*Pr<sub>2</sub>NEt (104  $\mu\text{L}$ , 0.60 mmol) and pivaloyl chloride (74.0  $\mu\text{L}$ , 0.60 mmol) in  $\text{CH}_2\text{Cl}_2$  (2 mL), HBTM-2.1 (2*S*,3*R*)-**23** (6.16 mg, 0.02 mmol, 5 mol%), (*E*)-1,1,1-trifluoro-4-phenyl-3-buten-2-one **57** (80.0 mg, 0.40 mmol) and *i*Pr<sub>2</sub>NEt (174  $\mu\text{L}$ , 1.0 mmol) for 5 minutes at rt gave crude lactone (3*S*,4*R*)-**37** (90:10 dr). Chromatographic purification (eluent Et<sub>2</sub>O:petrol 3:97) gave lactone (3*S*,4*R*)-**37** (93:7 dr) as a colourless oil (98.7 mg, 83%);  $[\alpha]_{\text{D}}^{20}$  -191.0 ( $c$  0.5,  $\text{CH}_2\text{Cl}_2$ ); Chiral HPLC Chiralcel OD-H (1% IPA:hexane, flow rate 1 mL min<sup>-1</sup>, 211 nm, 30 °C) major diastereoisomer:  $t_{\text{R}}$ (3*S*,4*R*): 8.9 min,  $t_{\text{R}}$ (3*R*,4*S*): 12.4 min, 96% *ee*; minor diastereoisomer  $t_{\text{R}}$ : 9.9 min,  $t_{\text{R}}$ : 14.4 min, 12% *ee*;  $\nu_{\text{max}}$  (ATR)/cm<sup>-1</sup> 3065, 2968 (C-H), 1786 (C=O), 1699; Data for major diastereoisomer:  $\delta_{\text{H}}$  (500 MHz,  $\text{CDCl}_3$ ) 0.92 (3H, t,  $J$  7.5,  $\text{CH}_3$ ), 2.00-2.06 (2H, m,  $\text{CH}_2\text{CH}_3$ ), 3.42 (1H, t,  $J$  7.1, C(3) $H$ ), 3.71-3.74 (1H, m, C(4) $H$ ), 5.41-5.45 (1H, m, C(3) $\text{CH}=\text{CHCH}_2\text{CH}_3$  or C(3) $\text{CH}=\text{CHCH}_2\text{CH}_3$ ), 5.49-5.54 (1H, m, C(3) $\text{CH}=\text{CHCH}_2\text{CH}_3$  or C(3) $\text{CH}=\text{CHCH}_2\text{CH}_3$ ), 6.10 (1H, d,  $J$  4.6, C(5) $H$ ), 7.14-7.16 (2H, m, C(4)Ar(2,6) $H$ ), 7.31-7.40 (3H, m, C(4)Ar(3,5) $H$  and C(4)Ar(4) $H$ );  $\delta_{\text{C}}$

(125 MHz, CDCl<sub>3</sub>) 13.2 (CH<sub>3</sub>), 25.6 (CH<sub>2</sub>CH<sub>3</sub>), 43.3 (C(4)), 49.9 (C(3)), 109.7 (q, *J* 3.5, C(5)), 118.5 (q, *J* 270, CF<sub>3</sub>), 121.6 (C(3)CH=CHCH<sub>2</sub>CH<sub>3</sub>), 127.5 (*ArC*), 128.1 (*ArC*), 129.2 (*ArC*), 138.7 (4ry C(4)ArC(1)), 138.8 (C(3)CH=CHCH<sub>2</sub>CH<sub>3</sub>), 140.8 (q, *J* 37.9, C(6)), 166.2 (C(2)); δ<sub>F</sub> (376 MHz, CDCl<sub>3</sub>) -72.6 (CF<sub>3</sub>); Selected data or minor diastereoisomer: δ<sub>H</sub> (500 MHz, CDCl<sub>3</sub>) 3.63 (1H, t, *J* 7.7, C(3)*H*), 3.87-3.90 (1H, m, C(4)*H*), 5.10 (1H, ddt, *J* 15.5, 8.5, 1.6, C(3)CH=CHCH<sub>2</sub>CH<sub>3</sub>), 5.70 (1H, dt, *J* 15.4, 6.4, C(3)CH=CHCH<sub>2</sub>CH<sub>3</sub>), 6.23 (1H, d, *J* 5.7, C(5)*H*), 7.11 (2H, d, *J* 8.0, Ar(2,6)*H*); δ<sub>C</sub> (125 MHz, CDCl<sub>3</sub>) 43.0 (C(4)), 47.6 (C(3)), 110.7 (q, *J* 3.5, C(5)), 120.5 (C(3)CH=CHCH<sub>2</sub>CH<sub>3</sub>), 128.2 (*ArC*), 128.2 (*ArC*), 129.0 (*ArC*), 138.9 (C(3)CH=CHCH<sub>2</sub>CH<sub>3</sub>), 166.6 (C(2)); δ<sub>F</sub> (376 MHz, CDCl<sub>3</sub>) -72.6 (CF<sub>3</sub>); *m/z* (NSI<sup>+</sup>) 297 ([M+H]<sup>+</sup>, 20%); HRMS (NSI<sup>+</sup>) C<sub>16</sub>H<sub>16</sub>F<sub>3</sub>O<sub>2</sub><sup>+</sup> ([M+H]<sup>+</sup>) requires 297.1097; found 297.1101 (+1.4 ppm).

### **(3*S*,4*R*)-4-phenyl-3-((*E*)-styryl)-6-(trifluoromethyl)-3,4-dihydro-2H-pyran-2-one 38**

Following general procedure A, (*E*)-4-phenylbut-3-enoic acid **16** (64.9 mg, 0.40 mmol), *i*Pr<sub>2</sub>NEt (104 μL, 0.60 mmol) and pivaloyl chloride (74.0 μL, 0.60 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2 mL), HBTM-2.1 (2*S*,3*R*)-**23** (6.16 mg, 0.02 mmol, 5 mol%), (*E*)-1,1,1-trifluoro-4-phenyl-3-buten-2-one **57** (80.0 mg, 0.40 mmol) and *i*Pr<sub>2</sub>NEt (174 μL, 1.0 mmol) for 5 minutes at -78 °C gave crude lactone (3*S*,4*R*)-**38** (95:5 dr). Chromatographic purification (eluent Et<sub>2</sub>O:petrol 7.5:92.5) gave lactone (3*S*,4*R*)-**38** (95:5 dr) as a colourless oil (113 mg, 82%); [α]<sub>D</sub><sup>20</sup>-159.6 (*c* 0.5, CH<sub>2</sub>Cl<sub>2</sub>); Chiral HPLC Chiralpak IB (5% IPA:hexane, flow rate 1 mL min<sup>-1</sup>, 211 nm, 30 °C) major diastereoisomer: t<sub>R</sub>(3*R*,4*S*): 12.3 min, t<sub>R</sub>(3*S*,4*R*): 13.9 min, 60% *ee*; minor diastereoisomer t<sub>R</sub>: 8.00 min, t<sub>R</sub>: 10.6 min, 52% *ee*; ν<sub>max</sub> (ATR)/cm<sup>-1</sup> 3063, 3030 (C-H), 1782 (C=O), 1699, 1601; Data for major diastereoisomer: δ<sub>H</sub> (500 MHz, CDCl<sub>3</sub>) 3.65 (1H, t, *J* 7.6, C(3)*H*), 3.85-3.90 (1H, m, C(4)*H*), 6.15-6.20 (2H, m, C(5)*H* and C(3)CH=CHPh), 6.36 (1H, d, *J* 15.9, C(3)CH=CHPh), 7.21 (2H, d, *J* 7.5, Ar*H*), 7.28-7.42 (8H, m, Ar*H*); δ<sub>C</sub> (125 MHz, CDCl<sub>3</sub>) 43.3 (C(4)), 50.0 (C(3)), 109.9 (q, *J* 3.3, C(5)), 118.5 (q, *J* 270, CF<sub>3</sub>), 122.0 (C(3)CH=CHPh), 126.6 (*ArC*), 127.5 (*ArC*), 128.3 (*ArC*), 128.4 (*ArC*), 128.7 (*ArC*), 129.4 (*ArC*), 135.7 (C(3)CH=CHPh), 135.8 (4ry *ArC*),

138.5 (4ry ArC), 141.0 (q,  $J$  38.0, C(6)), 165.6 (C(2));  $\delta_F$  (376 MHz, CDCl<sub>3</sub>) -72.6 (CF<sub>3</sub>); Selected data or minor diastereoisomer:  $\delta_H$  (500 MHz, CDCl<sub>3</sub>) 3.99 (1H, t,  $J$  6.2, C(4)H), 5.84 (1H, dd,  $J$  16.0, 8.6, C(3)CH=CHPh), 6.30 (1H, d,  $J$  5.9, C(5)H), 6.59 (1H, d,  $J$  16.0, C(3)CH=CHPh), 7.16 (2H, d,  $J$  7.6, ArH);  $\delta_C$  (125 MHz, CDCl<sub>3</sub>) 47.9 (C(3)), 110.7 (q,  $J$  3.4, C(5)), 121.4 (C(3)CH=CHPh), 128.2 (ArC), 128.5 (ArC), 129.3 (ArC), 135.4 (C(3)CH=CHPh), 166.2 (C(2));  $\delta_F$  (376 MHz, CDCl<sub>3</sub>) -72.7 (CF<sub>3</sub>);  $m/z$  (NSI<sup>+</sup>) 345 ([M+H]<sup>+</sup>, 15%); HRMS (NSI<sup>+</sup>) C<sub>20</sub>H<sub>16</sub>F<sub>3</sub>O<sub>2</sub><sup>+</sup> ([M+H]<sup>+</sup>) requires 345.1097; found 345.1098 (+0.3 ppm).

**(3*S*,4*R*)-4-(4-bromophenyl)-3-((*E*)-prop-1-en-1-yl)-6-(trifluoromethyl)-3,4-dihydro-2H-pyran-2-one**  
**39**

Following general procedure A, (*E*)-pent-3-enoic acid **24** (40.6  $\mu$ L, 0.40 mmol), *i*Pr<sub>2</sub>NEt (104  $\mu$ L, 0.60 mmol) and pivaloyl chloride (74.0  $\mu$ L, 0.60 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2 mL), HBTM-2.1 (2*S*,3*R*)-**23** (6.16 mg, 0.02 mmol, 5 mol%), (*E*)-1,1,1-trifluoro-4-(4-bromophenyl)-3-buten-2-one **58** (112 mg, 0.40 mmol) and *i*Pr<sub>2</sub>NEt (174  $\mu$ L, 1.0 mmol) for 5 minutes at rt gave crude lactone (3*S*,4*R*)-**39** (80:20 dr). Chromatographic purification (eluent Et<sub>2</sub>O:petrol 3:97) gave lactone (3*S*,4*R*)-**39** (95:5 dr) as a colourless oil (105 mg, 73%);  $[\alpha]_D^{20}$  -201.0 ( $c$  0.5, CH<sub>2</sub>Cl<sub>2</sub>); Chiral HPLC Chiralcel OD-H (1% IPA:hexane, flow rate 1 mL min<sup>-1</sup>, 211 nm, 30 °C) major diastereoisomer:  $t_R$ (3*R*,4*S*): 10.1 min,  $t_R$ (3*S*,4*R*): 11.8 min, 92% *ee*; minor diastereoisomer  $t_R$ : 9.3 min,  $t_R$ : 12.8 min, 90% *ee*;  $\nu_{max}$  (ATR)/cm<sup>-1</sup> 2987 (C-H), 1786 (C=O), 1753, 1660; Data for major diastereoisomer:  $\delta_H$  (500 MHz, CDCl<sub>3</sub>) 1.69 (3H, t,  $J$ , 6.4, CH<sub>3</sub>), 3.37 (1H, t,  $J$  7.4, C(3)H), 3.68-3.71 (1H, m, C(4)H), 5.43 (1H, ddd,  $J$  15.3, 7.5, 1.3, C(3)CH=CHCH<sub>3</sub>), 5.52 (1H, dq,  $J$  15.4, 6.3, C(3)CH=CHCH<sub>3</sub>), 6.03 (1H, d,  $J$  4.4, C(5)H), 7.02-7.04 (2H, m, C(4)Ar(3,5)H), 7.50-7.52 (2H, m, C(4)Ar(2,6)H);  $\delta_C$  (125 MHz, CDCl<sub>3</sub>) 18.1 (CH<sub>3</sub>), 42.7 (C(4)), 49.7 (C(3)), 109.2 (q,  $J$  3.5, C(5)), 118.4 (q,  $J$  270, CF<sub>3</sub>), 122.1 (C(4)ArC(4)), 123.4 (C(3)CH=CHCH<sub>3</sub>), 129.1 (C(4)ArC(3,5)), 132.3 (C(4)ArC(2,6)), 132.6 (C(3)CH=CHCH<sub>3</sub>), 137.7 (4ry C(4)ArC(1)), 141.1 (q,  $J$  38, C(6)), 165.8 (C(2));  $\delta_F$  (376 MHz, CDCl<sub>3</sub>) -72.7 (CF<sub>3</sub>); Selected data or minor diastereoisomer:  $\delta_H$  (500 MHz, CDCl<sub>3</sub>) 3.62 (1H,

t,  $J$  7.8, C(3)*H*), 3.82-3.85 (1H, m, C(4)*H*), 5.09-5.14 (1H, m, C(3)*CH=CHCH*<sub>3</sub>), 5.65-5.72 (1H, m, C(3)*CH=CHCH*<sub>3</sub>), 6.18 (1H, d,  $J$  5.7, C(5)*H*);  $\delta_C$  (75 MHz, CDCl<sub>3</sub>) 18.0 (CH<sub>3</sub>), 44.4 (C(4)), 47.4 (C(3));  $\delta_F$  (376 MHz, CDCl<sub>3</sub>) -72.8 (CF<sub>3</sub>);  $m/z$  (NSI<sup>+</sup>) 378 ([M+NH<sub>4</sub>]<sup>+</sup>, 56%); HRMS (NSI<sup>+</sup>) C<sub>15</sub>H<sub>16</sub><sup>78</sup>BrF<sub>3</sub>NO<sub>2</sub><sup>+</sup> ([M+ NH<sub>4</sub>]<sup>+</sup>) requires 378.0311; found 378.0311 (+0.0 ppm).

**(3*S*,4*R*)-4-(thiophen-2-yl)-3-((*E*)-prop-1-en-1-yl)-6-(trifluoromethyl)-3,4-dihydro-2H-pyran-2-one 40**

Following general procedure A, (*E*)-pent-3-enoic acid **24** (40.6  $\mu$ L, 0.40 mmol), *i*Pr<sub>2</sub>NEt (104  $\mu$ L, 0.60 mmol) and pivaloyl chloride (74.0  $\mu$ L, 0.60 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2 mL), HBTM-2.1 (2*S*,3*R*)-**23** (6.16 mg, 0.02 mmol, 5 mol%), (*E*)-1,1,1-trifluoro-4-(2-thienyl)-3-buten-2-one **59** (82.4 mg, 0.40 mmol) and *i*Pr<sub>2</sub>NEt (174  $\mu$ L, 1.0 mmol) for 5 minutes at rt gave crude lactone (3*S*,4*R*)-**40** (84:16 dr). Chromatographic purification (eluent Et<sub>2</sub>O:petrol 4:96) gave lactone (3*S*,4*R*)-**40** (84:16 dr) as a colourless oil (95.8 mg, 83%);  $[\alpha]_D^{20}$ -187.0 (*c* 0.5, CH<sub>2</sub>Cl<sub>2</sub>); Chiral HPLC Chiralpak AS-H (0.5% IPA:hexane, flow rate 1 mL min<sup>-1</sup>, 211 nm, 30 °C) major diastereoisomer:  $t_R$ (3*S*,4*R*): 14.1 min,  $t_R$ (3*R*,4*S*): 16.1 min, 93% *ee*;  $\nu_{\max}$  (ATR)/cm<sup>-1</sup> 2998 (C-H), 1784 (C=O), 1699, 1674; Data for major diastereoisomer:  $\delta_H$  (300 MHz, CDCl<sub>3</sub>) 1.72-1.74 (3H, m, CH<sub>3</sub>), 3.55 (1H, td,  $J$  6.7, 0.7, C(3)*H*), 4.00-4.04 (1H, m, C(4)*H*), 5.47 (1H, ddq,  $J$  15.4, 8.4, 1.7, C(3)*CH=CHCH*<sub>3</sub>), 5.63-5.75 (1H, m, C(3)*CH=CHCH*<sub>3</sub>), 6.16 (1H, d,  $J$  5.0, C(5)*H*), 6.89-6.90 (1H, m, Ar*H*), 6.98-7.03 (1H, m, Ar*H*), 7.27-7.30 (1H, m, Ar*H*);  $\delta_C$  (125 MHz, CDCl<sub>3</sub>) 18.1 (CH<sub>3</sub>), 38.2 (C(4)), 50.6 (C(3)), 109.2 (q,  $J$  3.5, C(5)), 118.4 (q,  $J$  270, CF<sub>3</sub>), 123.2 (C(3)*CH=CHCH*<sub>3</sub>), 125.4 (ArC), 125.4 (ArC), 127.4 (ArC), 132.4 (C(3)*CH=CHCH*<sub>3</sub>), 140.7 (q,  $J$  37.9, C(6)), 141.2 (C(4)ArC(1)), 165.5 (C(2));  $\delta_F$  (376 MHz, CDCl<sub>3</sub>) -72.4 (CF<sub>3</sub>); Selected data or minor diastereoisomer:  $\delta_H$  (500 MHz, CDCl<sub>3</sub>) 3.64 (1H, t,  $J$  7.5, C(3)*H*), 4.13-4.18 (1H, m, C(4)*H*), 5.35 (1H, ddq,  $J$  15.4, 8.4, 1.7, C(3)*CH=CHCH*<sub>3</sub>), 6.28 (1H, d,  $J$  5.8, C(5)*H*);  $\delta_C$  (75 MHz, CDCl<sub>3</sub>) 18.1 (CH<sub>3</sub>), 38.0 (C(4)), 48.0 (C(3)), 110.7 (q,  $J$  3.5, C(5)), 122.5 (C(3)*CH=CHCH*<sub>3</sub>), 125.7 (ArC), 126.3 (ArC), 127.4 (ArC), 132.7 (C(3)*CH=CHCH*<sub>3</sub>), 166.2 (C(2));  $\delta_F$  (376 MHz, CDCl<sub>3</sub>) -72.6 (CF<sub>3</sub>);  $m/z$  (APCI<sup>+</sup>) 289 ([M+H]<sup>+</sup>, 100%); HRMS (APCI<sup>+</sup>) C<sub>13</sub>H<sub>12</sub>F<sub>3</sub>O<sub>2</sub>S<sup>+</sup> ([M+H]<sup>+</sup>) requires 289.0505; found 289.0507 (+0.8 ppm).

### **(2R)-(E)-methyl 2-(2-benzoyl-1-phenylhydrazinyl)pent-3-enoate 41**

Following general procedure A, (E)-pent-3-enoic acid **24** (40.6  $\mu\text{L}$ , 0.40 mmol), *i*Pr<sub>2</sub>NEt (104  $\mu\text{L}$ , 0.60 mmol) and pivaloyl chloride (74.0  $\mu\text{L}$ , 0.60 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2 mL), HBTM-2.1 (2*S*,3*R*)-**23** (1.23 mg, 0.004 mmol, 1 mol%), (NE)-N-(phenylimino)benzamide **60** (84.0 mg, 0.40 mmol) and *i*Pr<sub>2</sub>NEt (174  $\mu\text{L}$ , 1.00 mmol) for 15 min at rt, followed by addition of MeOH (2 mL) and stirring for 1 h at rt gave, after chromatographic purification (eluent Et<sub>2</sub>O:petrol 40:60) a rotameric mixture (ratio 95:5) of (2*R*)-**41** as a white solid (105 mg, 80%); mp 108-110 °C;  $[\alpha]_D^{20}$ -67.0 (*c* 0.5, CH<sub>2</sub>Cl<sub>2</sub>); Chiral HPLC Chiralpak IB (5% IPA:hexane, flow rate 1 mL min<sup>-1</sup>, 211 nm, 30 °C) *t*<sub>R</sub>(2*S*): 13.2 min, *t*<sub>R</sub>(2*R*): 17.3 min, 96% *ee*;  $\nu_{\text{max}}$  (ATR)/cm<sup>-1</sup> 3350 (N-H), 2949 (C-H), 1721 (C=O), 1698 (C=O), 1597; Data for major rotamer:  $\delta_{\text{H}}$  (500 MHz, CDCl<sub>3</sub>) 1.72 (3H, d, *J* 4.7, CH<sub>3</sub>CH=), 3.78 (3H, s, OCH<sub>3</sub>), 5.25-5.26 (1H, m, C(2)*H*), 5.79-5.89 (2H, m, CH=CHCH<sub>3</sub> and CH=CHCH<sub>3</sub>), 6.94-6.97 (3H, m, NAr(2,6)*H* and NAr(4)*H*), 7.27-7.30 (2H, m, NAr(3,5)*H*), 7.50 (2H, t, *J* 7.6, C(O)Ar(3,5)*H*), 7.58 (1H, t, *J* 7.4, C(O)Ar(4)*H*), 7.86-7.88 (2H, m, C(O)Ar(2,6)*H*), 8.64 (1H, s, NH);  $\delta_{\text{C}}$  (125 MHz, CDCl<sub>3</sub>) 18.2 (CH<sub>3</sub>CH=), 52.4 (OCH<sub>3</sub>), 64.6 (C(2)), 114.7 (NArC(2,6)), 121.5 (NArC(4)), 123.6 (CH=CHCH<sub>3</sub>), 127.2 (C(O)ArC(2,6)), 128.8 (C(O)ArC(3,5)), 129.4 (NArC(3,5)), 132.0 (C(O)ArC(4) or CH=CHCH<sub>3</sub>), 132.3 (C(O)ArC(4) or CH=CHCH<sub>3</sub>), 133.0 (4ry C(O)ArC(1)), 148.1 (NArC(1)), 167.4 (NHC=O), 173.3 (MeOC=O); Selected data for minor rotamer:  $\delta_{\text{H}}$  (500 MHz, CDCl<sub>3</sub>) 1.65 (3H, d, *J* 5.9, CH<sub>3</sub>CH=), 3.67 (3H, s, OCH<sub>3</sub>), 4.97 (1H, d, *J* 7.1, C(2)*H*);  $\delta_{\text{C}}$  (125 MHz, CDCl<sub>3</sub>) 18.1 (CH<sub>3</sub>CH=), 52.3 (OCH<sub>3</sub>), 65.8 (C(2)), 115.0 (NArC(2,6)); *m/z* (NSI<sup>+</sup>) 325 ([M+H]<sup>+</sup>, 100%); HRMS (NSI<sup>+</sup>) C<sub>19</sub>H<sub>21</sub>N<sub>2</sub>O<sub>3</sub><sup>+</sup> ([M+H]<sup>+</sup>) requires 325.1547; found 325.1548 (+0.4 ppm).

### **(2R)-(E)-methyl 2-(2-benzoyl-1-phenylhydrazinyl)hex-3-enoate 42**

Following general procedure A, (E)-hex-3-enoic acid **81** (47.4  $\mu\text{L}$ , 0.40 mmol), *i*Pr<sub>2</sub>NEt (104  $\mu\text{L}$ , 0.60 mmol) and pivaloyl chloride (74.0  $\mu\text{L}$ , 0.60 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2 mL), HBTM-2.1 (2*S*,3*R*)-**23** (1.23 mg, 0.004 mmol, 1 mol%), (NE)-N-(phenylimino)benzamide **60** (84.0 mg, 0.40 mmol) and *i*Pr<sub>2</sub>NEt (174  $\mu\text{L}$ , 1.00 mmol) for 15 min at rt, followed by addition of MeOH (2 mL) and stirring for 1 h at rt gave, after

chromatographic purification (eluent Et<sub>2</sub>O:petrol 40:60) a rotameric mixture (ratio 95:5) of (2*R*)-**42** as a white solid (115 mg, 85%); mp 98-100 °C;  $[\alpha]_D^{20}$ -54.8 (*c* 0.5, CH<sub>2</sub>Cl<sub>2</sub>); Chiral HPLC Chiralpak IB (5% IPA:hexane, flow rate 1 mL min<sup>-1</sup>, 211 nm, 30 °C) *t*<sub>R</sub>(2*S*): 11.3 min, *t*<sub>R</sub>(2*R*): 15.6 min, 99% *ee*; *v*<sub>max</sub> (ATR)/cm<sup>-1</sup> 3352 (N-H), 2990 (C-H), 1721 (C=O), 1688 (C=O), 1597, 1508; Data for major rotamer: δ<sub>H</sub> (500 MHz, CDCl<sub>3</sub>) 0.90 (3H, t, *J* 7.4, CH<sub>3</sub>CH<sub>2</sub>), 2.03-2.09 (2H, m, CH<sub>3</sub>CH<sub>2</sub>) 3.78 (3H, s, OCH<sub>3</sub>), 5.26-5.27 (1H, m, C(2)*H*), 5.77-5.88 (2H, m, CH=CHCH<sub>2</sub>CH<sub>3</sub> and CH=CHCH<sub>2</sub>CH<sub>3</sub>), 6.93-6.97 (3H, m, NAr(2,6)*H* and NAr(4)*H*), 7.26-7.29 (2H, m, NAr(3,5)*H*), 7.47-7.50 (2H, m, C(O)Ar(3,5)*H*), 7.55-7.58 (1H, m, C(O)Ar(4)*H*), 7.85-7.87 (2H, m, C(O)Ar(2,6)*H*), 8.62 (1H, s, NH); δ<sub>C</sub> (125 MHz, CDCl<sub>3</sub>) 13.1 (CH<sub>3</sub>CH<sub>2</sub>), 25.6 (CH<sub>3</sub>CH<sub>2</sub>), 52.4 (OCH<sub>3</sub>), 64.5 (C(2)), 114.7 (NArC(2,6)), 121.6 (NArC(4) or CH=CHCH<sub>2</sub>CH<sub>3</sub>), 121.7 (NArC(4) or CH=CHCH<sub>2</sub>CH<sub>3</sub>), 127.3 (C(O)ArC(2,6)), 128.9 (C(O)ArC(3,5)), 129.4 (NArC(3,5)), 132.1 (C(O)ArC(4)), 133.1 (C(O)ArC(1)), 138.8 (CH=CHCH<sub>2</sub>CH<sub>3</sub>), 148.2 (NArC(1)), 167.4 (NHC=O), 173.4 (MeOC=O); Selected data for minor rotamer: δ<sub>H</sub> (500 MHz, CDCl<sub>3</sub>) 3.67 (3H, s, OCH<sub>3</sub>), 4.99-5.00 (1H, m, C(2)*H*); δ<sub>C</sub> (125 MHz, CDCl<sub>3</sub>) 12.5 (CH<sub>3</sub>CH<sub>2</sub>), 52.3 (OCH<sub>3</sub>), 66.1 (C(2)), 115.1 (NArC(2,6)), 141.1 (CH=CHCH<sub>2</sub>CH<sub>3</sub>), 148.7 (NArC(1)), 167.4 (NHC=O), 173.4 (MeOC=O); *m/z* (NSI<sup>+</sup>) 339 ([M+H]<sup>+</sup>, 100%); HRMS (NSI<sup>+</sup>) C<sub>20</sub>H<sub>23</sub>N<sub>2</sub>O<sub>3</sub><sup>+</sup> ([M+H]<sup>+</sup>) requires 339.1703; found 339.1708 (+1.4 ppm).

### (2*R*)-(E)-methyl 2-(2-benzoyl-1-phenylhydrazinyl)-5-methylhex-3-enoate **43**

Following general procedure A, (*E*)-5-methylhex-3-enoic acid **65** (51.2 mg, 0.40 mmol), *i*Pr<sub>2</sub>NEt (104 μL, 0.60 mmol) and pivaloyl chloride (74.0 μL, 0.60 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2 mL), HBTM-2.1 (2*S*,3*R*)-**23** (1.23 mg, 0.004 mmol, 1 mol%), (NE)-N-(phenylimino)benzamide **60** (84.0 mg, 0.40 mmol) and *i*Pr<sub>2</sub>NEt (174 μL, 1.00 mmol) for 15 min at rt, followed by addition of MeOH (2 mL) and stirring for 1 h at rt gave, after chromatographic purification (eluent Et<sub>2</sub>O:petrol 40:60) a rotameric mixture (ratio 95:5) of (2*R*)-**43** as a white solid (104 mg, 74%); mp 128-130 °C;  $[\alpha]_D^{20}$ -66.6 (*c* 0.5, CH<sub>2</sub>Cl<sub>2</sub>); Chiral HPLC Chiralpak IB (5% IPA:hexane, flow rate 1 mL min<sup>-1</sup>, 211 nm, 30 °C) *t*<sub>R</sub>(2*S*): 14.5 min, *t*<sub>R</sub>(2*R*): 19.0 min, 99% *ee*; *v*<sub>max</sub>

(ATR)/cm<sup>-1</sup> 3326 (N-H), 2988 (C-H), 1719 (C=O Ester), 1678 (C=O Amide), 1597, 1506; Data for major rotamer:  $\delta_{\text{H}}$  (500 MHz, CDCl<sub>3</sub>) 0.89 (3H, t, *J* 6.8, CH(CH<sub>3</sub>)CH<sub>3</sub>), 0.92 (3H, t, *J* 6.8, CH(CH<sub>3</sub>)CH<sub>3</sub>), 2.27-2.34 (1H, m, CH(CH<sub>3</sub>)CH<sub>3</sub>), 3.78 (3H, s, OCH<sub>3</sub>), 5.27-5.28 (1H, m, C(2)*H*), 5.72-5.80 (2H, m, CH=CHCH(CH<sub>3</sub>)CH<sub>3</sub> and CH=CHCH(CH<sub>3</sub>)CH<sub>3</sub>), 6.93-6.97 (3H, m, NAr(2,6)*H* and NAr(4)*H*), 7.26-7.30 (2H, m, NAr(3,5)*H*), 7.46-7.49 (2H, m, C(O)Ar(3,5)*H*), 7.54-7.58 (1H, m, C(O)Ar(4)*H*), 7.85-7.88 (2H, m, C(O)Ar(2,6)*H*), 8.64 (1H, s, NH);  $\delta_{\text{C}}$  (100 MHz, CDCl<sub>3</sub>) 21.8 (CH(CH<sub>3</sub>)CH<sub>3</sub>), 22.0 (CH(CH<sub>3</sub>)CH<sub>3</sub>), 31.1 (CH(CH<sub>3</sub>)CH<sub>3</sub>), 52.3 (OCH<sub>3</sub>), 64.4 (C(2)), 114.8 (NArC(2,6)), 120.0 (CH=CHCH(CH<sub>3</sub>)CH<sub>3</sub>), 121.5 (NArC(4)), 127.3 (C(O)ArC(2,6)), 128.8 (C(O)ArC(3,5)), 129.4 (NArC(3,5)), 132.1 (C(O)ArC(4)), 133.0 (C(O)ArC(1)), 143.9 (CH=CHCH(CH<sub>3</sub>)CH<sub>3</sub>), 148.2 (NArC(1)), 167.3 (NHC=O), 173.4 (MeOC=O); Selected data for minor rotamer:  $\delta_{\text{H}}$  (500 MHz, CDCl<sub>3</sub>) 3.66 (3H, s, OCH<sub>3</sub>), 5.01 (1H, d, *J* 7.0, C(2)*H*);  $\delta_{\text{C}}$  (100 MHz, CDCl<sub>3</sub>) 21.4 (CH(CH<sub>3</sub>)CH<sub>3</sub>), 21.5 (CH(CH<sub>3</sub>)CH<sub>3</sub>), 31.1 (CH(CH<sub>3</sub>)CH<sub>3</sub>), 52.2 (OCH<sub>3</sub>), 66.3 (C(2)), 115.2 (NArC(2,6)), 146.1 (CH=CHCH<sub>2</sub>CH<sub>3</sub>), 148.8 (NArC(1)), 172.0 (MeOC=O); *m/z* (NSI<sup>+</sup>) 353 ([M+H]<sup>+</sup>, 100%); HRMS (NSI<sup>+</sup>) C<sub>21</sub>H<sub>25</sub>N<sub>2</sub>O<sub>3</sub><sup>+</sup> ([M+H]<sup>+</sup>) requires 353.1860; found 353.1862 (+0.7 ppm).

#### **(2R)-(E)-methyl 2-(2-benzoyl-1-phenylhydrazinyl)-5-phenylpent-3-enoate 44**

Following general procedure A, (*E*)-5-phenylpent-3-enoic acid **66** (70.4 mg, 0.40 mmol), *i*Pr<sub>2</sub>NEt (104  $\mu$ L, 0.60 mmol) and pivaloyl chloride (74.0  $\mu$ L, 0.60 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2 mL), HBTM-2.1 (2*S*,3*R*)-**23** (1.23 mg, 0.004 mmol, 1 mol%), (NE)-N-(phenylimino)benzamide **60** (84.0 mg, 0.40 mmol) and *i*Pr<sub>2</sub>NEt (174  $\mu$ L, 1.00 mmol) for 15 min at rt, followed by addition of MeOH (2 mL) and stirring for 1 h at rt gave, after chromatographic purification (eluent Et<sub>2</sub>O:petrol 50:50) a rotameric mixture (ratio 96:4) of (2*R*)-**44** as a white solid (123 mg, 77%); mp 136-138 °C; [ $\alpha$ ]<sub>D</sub><sup>20</sup> -70.8 (*c* 0.5, CH<sub>2</sub>Cl<sub>2</sub>); Chiral HPLC Chiralpak IB (5% IPA:hexane, flow rate 1 mL min<sup>-1</sup>, 220 nm, 30 °C) *t*<sub>R</sub>(2*S*): 28.5 min, *t*<sub>R</sub>(2*R*): 41.2 min, 99% *ee*;  $\nu_{\text{max}}$  (ATR)/cm<sup>-1</sup> 3323 (N-H), 2890 (C-H), 1730 (C=O Ester), 1686 (C=O Amide), 1599, 1514; Data for major rotamer:  $\delta_{\text{H}}$  (500 MHz, CDCl<sub>3</sub>) 3.41 (2H, d, *J* 6.1, CHHPh and CHHPh), 3.78 (3H, s, OCH<sub>3</sub>), 5.34-5.35 (1H, m, C(2)*H*), 5.89-6.00 (2H, m, CH=CHBn and CH=CHBn), 6.96-6.99 (3H, m, NAr(2,6)*H* and NAr(4)*H*), 7.05-7.03 (CH<sub>2</sub>Ar(2,6)*H*), 7.12-7.15 (CH<sub>2</sub>Ar(3,5)*H* and CH<sub>2</sub>Ar(4)*H*), 7.28-7.32 (2H, m,



NAr(3,5)H), 7.48-7.51 (2H, m, C(O)Ar(3,5)H), 7.58-7.62 (1H, m, C(O)Ar(4)H), 7.85-7.86 (2H, m, C(O)Ar(2,6)H), 8.68 (1H, s, NH);  $\delta_C$  (100 MHz, CDCl<sub>3</sub>) 38.9 (CH<sub>2</sub>Ph), 52.4 (OCH<sub>3</sub>), 64.5 (C(2)), 114.7 (NArC(2,6)), 121.6 (NArC(4)), 124.1 (CH=CHBn), 126.2 (CH<sub>2</sub>ArC(4)), 127.3 (C(O)ArC(2,6)), 128.4 (ArC), 128.6 (ArC), 128.8 (C(O)ArC(3,5)), 129.4 (NArC(3,5)), 132.1 (C(O)ArC(4)), 132.8 (C(O)ArC(1)), 135.7 (CH=CHBn), 138.9 (CH<sub>2</sub>ArC(1)), 148.1 (NArC(1)), 167.1 (NHC=O), 173.1 (MeOC=O); Selected data for minor rotamer  $\delta_H$  (500 MHz, CDCl<sub>3</sub>) 3.67 (3H, s, OCH<sub>3</sub>), 5.06-5.08 (1H, m, C(2)H);  $\delta_C$  (100 MHz, CDCl<sub>3</sub>) 38.8 (CH<sub>2</sub>Ph), 52.3 (OCH<sub>3</sub>), 66.2 (C(2)), 115.2 (NArC(2,6)), 148.7 (NArC(1));  $m/z$  (NSI<sup>+</sup>) 401 ([M+H]<sup>+</sup>, 100%); HRMS (NSI<sup>+</sup>) C<sub>25</sub>H<sub>25</sub>N<sub>2</sub>O<sub>3</sub><sup>+</sup> ([M+H]<sup>+</sup>) requires 401.1860; found 401.1859 (-0.2 ppm).

### **(2R)-(E)-methyl 2-(2-benzoyl-1-phenylhydrazinyl)-4-phenylbut-3-enoate 45**

Following general procedure A, (*E*)-4-phenylbut-3-enoic acid **16** (64.9 mg, 0.40 mmol), *i*Pr<sub>2</sub>NEt (104  $\mu$ L, 0.60 mmol) and pivaloyl chloride (74.0  $\mu$ L, 0.60 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2 mL), HBTM-2.1 (2*S*,3*R*)-**23** (1.23 mg, 0.004 mmol, 1 mol%), (NE)-N-(phenylimino)benzamide **60** (84.0 mg, 0.40 mmol) and *i*Pr<sub>2</sub>NEt (174  $\mu$ L, 1.00 mmol) for 15 min at rt, followed by addition of MeOH (2 mL) and stirring for 1 h at rt gave, after chromatographic purification (eluent Et<sub>2</sub>O:petrol 40:60) a rotameric mixture (ratio 95:5) of (2*R*)-**45** as an off-white solid (109 mg, 71%); mp 116-118 °C;  $[\alpha]_D^{20}$  -19.6 (*c* 0.25, CH<sub>2</sub>Cl<sub>2</sub>); Chiral HPLC Chiralpak IB (5% IPA:hexane, flow rate 1 mL min<sup>-1</sup>, 211 nm, 30 °C)  $t_R$ (2*S*): 22.0 min,  $t_R$ (2*R*): 27.9 min, 91% *ee*;  $\nu_{\max}$  (ATR)/cm<sup>-1</sup> 3325 (N-H), 3057, 2959 (C-H), 1728 (C=O), 1693 (C=O), 1599; Data for major rotamer:  $\delta_H$  (500 MHz, CDCl<sub>3</sub>) 3.84 (3H, s, CH<sub>3</sub>), 5.50 (1H, d, *J* 5.1, C(2)H), 6.54 (1H, dd, *J* 16.3, 5.7, CH=CHPh), 6.76 (1H, d, *J* 16.3, CH=CHPh), 6.99-7.04 (3H, m, ArH), 7.24-7.41 (7H, m, ArH), 7.44 (2H, t, *J* 8.7, C(O)Ar(3,5)H), 7.54 (1H, t, *J* 7.4, C(O)Ar(4)H), 7.83 (2H, d, *J* 7.4, C(O)Ar(2,6)H), 8.72 (1H, s, NH);  $\delta_C$  (125 MHz, CDCl<sub>3</sub>) 52.6 (CH<sub>3</sub>), 64.9 (C(2)), 114.8 (NArC(2,6)), 121.7 (NArC(4)), 122.1 (CH=CHPh), 126.8 (=CHArC(4)), 127.2 (C(O)ArC(2,6)), 128.3 (ArC), 128.7 (ArC), 128.8 (C(O)ArC(3,5)), 129.5 NArC(3,5), 132.1 (C(O)ArC(4)), 133.0 (C(O)ArC(1)), 135.0 (CH=CHPh), 135.9 (=CHArC(1)), 148.0 (NArC(1)), 167.6 (NHC=O), 172.8 (MeOC=O); Selected data for minor rotamer:  $\delta_H$  (500 MHz, CDCl<sub>3</sub>)

3.73 (3H, s, CH<sub>3</sub>), 5.21 (1H, d, *J* 7.2, C(2)*H*), 6.02 (1H, dd, *J* 16.1, 7.2, CH=CHPh), 7.98 (1H, s, NH); δ<sub>C</sub> (125 MHz, CDCl<sub>3</sub>) 52.5 (CH<sub>3</sub>), 66.1 (C(2)), 115.1 (NArC(2,6)), 137.5 (CH=CHPh); *m/z* (NSI<sup>+</sup>) 387 ([M+H]<sup>+</sup>, 100%); HRMS (NSI<sup>+</sup>) C<sub>24</sub>H<sub>23</sub>N<sub>2</sub>O<sub>3</sub><sup>+</sup> ([M+H]<sup>+</sup>) requires 387.1703; found 387.1704 (-0.2 ppm).

#### **(2*R*)-(Z)-methyl 2-(2-benzoyl-1-phenylhydrazinyl)pent-3-enoate 46**

Following general procedure A, (*Z*)-pent-3-enoic acid **68** (40.0 mg, 0.40 mmol), *i*Pr<sub>2</sub>NEt (104 μL, 0.60 mmol) and pivaloyl chloride (74.0 μL, 0.60 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2 mL), HBTM-2.1 (2*S*,3*R*)-**23** (1.23 mg, 0.004 mmol, 1 mol%), (NE)-*N*-(phenylimino)benzamide **60** (84.0 mg, 0.40 mmol) and *i*Pr<sub>2</sub>NEt (174 μL, 1.00 mmol) for 15 min at rt, followed by addition of MeOH (2 mL) and stirring for 1 h at rt gave, after chromatographic purification (eluent Et<sub>2</sub>O:petrol 50:50) a rotameric mixture (ratio 95:5) of (*2R*)-**46** (94:6 (*Z*):(*E*)) as a colourless oil (93.7 mg, 72%); [α]<sub>D</sub><sup>20</sup> -76.8 (*c* 0.5, CH<sub>2</sub>Cl<sub>2</sub>); Chiral HPLC Chiralpak AD-H (20% IPA:hexane, flow rate 1 mL min<sup>-1</sup>, 220 nm, 30 °C) t<sub>R</sub>(*2S*): 19.1 min, t<sub>R</sub>(*2R*): 23.6 min, 99% *ee*; ν<sub>max</sub> (ATR)/cm<sup>-1</sup> 3291 (N-H), 2953 (C-H), 1732 (C=O Ester), 1674 (C=O Amide), 1599; Data for major isomer (*Z*) and major rotamer: δ<sub>H</sub> (400 MHz, CDCl<sub>3</sub>) 1.88 (3H, dd, *J* 7.0, 1.8, CH<sub>3</sub>CH=), 3.75 (3H, s, OCH<sub>3</sub>), 5.48 (1H, d, *J* 8.2, C(2)*H*), 5.61-5.67 (1H, m, CH=CHCH<sub>3</sub>), 5.91 (1H, dqd, *J* 10.7, 7.0, 1.0, CH=CHCH<sub>3</sub>), 6.93-6.99 (3H, m, NAr(2,6)*H* and NAr(4)*H*), 7.26-7.30 (2H, m, NAr(3,5)*H*), 7.46-7.51 (2H, m, C(O)Ar(3,5)*H*), 7.54-7.59 (1H, m, C(O)Ar(4)*H*), 7.88-7.91 (2H, m, C(O)Ar(2,6)*H*), 8.67 (1H, s, NH); δ<sub>C</sub> (100 MHz, CDCl<sub>3</sub>) 14.1 (CH<sub>3</sub>CH=), 52.6 (OCH<sub>3</sub>), 59.8 (C(2)), 114.7 (NArC(2,6)), 121.6 (NArC(4)), 121.7 (CH=CHCH<sub>3</sub>), 127.4 (C(O)ArC(2,6)), 128.9 (C(O)ArC(3,5)), 129.5 (NArC(3,5)), 132.2 (C(O)ArC(4)), 132.7 (CH=CHCH<sub>3</sub>), 132.8 (C(O)ArC(1)), 148.3 (NArC(1)), 167.0 (NHC=O), 173.6 (MeOC=O); *m/z* (NSI<sup>+</sup>) 325 ([M+H]<sup>+</sup>, 100%); HRMS (NSI<sup>+</sup>) C<sub>19</sub>H<sub>21</sub>N<sub>2</sub>O<sub>3</sub><sup>+</sup> ([M+H]<sup>+</sup>) requires 325.1547; found 325.1548 (+0.4 ppm).

#### **(2*R*)-(E)-methyl 2-(2-(4-fluorobenzoyl)-1-phenylhydrazinyl)pent-3-enoate 47**

Following general procedure A, (*E*)-pent-3-enoic acid **24** (40.6 μL, 0.40 mmol), *i*Pr<sub>2</sub>NEt (104 μL, 0.60 mmol) and pivaloyl chloride (74.0 μL, 0.60 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2 mL), HBTM-2.1 (2*S*,3*R*)-**23** (1.23 mg,

0.004 mmol, 1 mol%), (NE)-4-fluoro-N-(phenylimino)benzamide **61** (91.2 mg, 0.40 mmol) and *i*Pr<sub>2</sub>NEt (174 μL, 1.00 mmol) for 15 min at rt, followed by addition of MeOH (2 mL) and stirring for 1 h at rt gave, after chromatographic purification (eluent Et<sub>2</sub>O:petrol 40:60) a rotameric mixture (ratio 92:8) of (2*R*)-**47** as a white solid (109 mg, 79%); mp 102-104 °C;  $[\alpha]_D^{20}$ -57.8 (*c* 0.5, CH<sub>2</sub>Cl<sub>2</sub>); Chiral HPLC Chiralpak IB (5% IPA:hexane, flow rate 1 mL min<sup>-1</sup>, 211 nm, 30 °C) *t*<sub>R</sub>(2*S*): 13.2 min, *t*<sub>R</sub>(2*R*): 17.1 min, 99% *ee*; *v*<sub>max</sub> (ATR)/cm<sup>-1</sup> 3522 (N-H), 2951 (C-H), 1751 (C=O), 1661 (C=O), 1599; Data for major rotamer:  $\delta_H$  (500 MHz, CDCl<sub>3</sub>) 1.68-1.69 (3H, m, CH<sub>3</sub>CH=), 3.76 (3H, s, OCH<sub>3</sub>), 5.21-5.22 (1H, m, C(2)*H*), 5.74-5.84 (2H, m, CH=CHCH<sub>3</sub> and CH=CHCH<sub>3</sub>), 6.91-6.95 (3H, m, NAr(2,6)*H* and NAr(4)*H*), 7.13-7.17 (2H, t, *J* 8.4, NAr(3,5)*H*), 7.24-7.27 (2H, m, C(O)Ar(3,5)*H*), 7.84-7.87 (2H, m, C(O)Ar(2,6)*H*), 8.60 (1H, s, NH);  $\delta_C$  (125 MHz, CDCl<sub>3</sub>) 18.2 (CH<sub>3</sub>CH=), 52.4 (OCH<sub>3</sub>), 64.6 (C(2)), 114.8 (NArC(2,6)), 116.0 (d, *J* 21.8, C(O)ArC(3,5)), 121.7 (NArC(4)), 123.7 (CH=CHCH<sub>3</sub>), 129.2 (d, *J* 3.5, C(O)ArC(1)), 129.5 (NArC(3,5)), 129.7 (d, *J* 8.7, C(O)ArC(2,6)), 132.4 (CH=CHCH<sub>3</sub>), 148.1 (NArC(1)), 165.2 (d, *J* 252, C(O)ArC(4)), 166.4 (NHC=O), 173.4 (MeOC=O);  $\delta_F$  (376 MHz, CDCl<sub>3</sub>) -107.6 (ArF); Selected data for minor rotamer:  $\delta_H$  (500 MHz, CDCl<sub>3</sub>) 1.61-1.62 (3H, m, CH<sub>3</sub>CH=), 3.65 (3H, s, OCH<sub>3</sub>), 4.95 (1H, d, *J* 7.3, C(2)*H*), 7.36 (2H, dd, *J* 8.8, 7.4, C(O)Ar(3,5)*H*), 7.58-7.61 (2H, C(O)Ar(2,6)*H*);  $\delta_C$  (125 MHz, CDCl<sub>3</sub>) 18.2 (CH<sub>3</sub>CH=), 52.4 (OCH<sub>3</sub>), 66.0 (C(2)), 114.8 (NArC(2,6));  $\delta_F$  (376 MHz, CDCl<sub>3</sub>) -108.8 (ArF); *m/z* (NSI<sup>+</sup>) 343 ([M+H]<sup>+</sup>, 100%); HRMS (NSI<sup>+</sup>) C<sub>19</sub>H<sub>20</sub>FN<sub>2</sub>O<sub>3</sub><sup>+</sup> ([M+H]<sup>+</sup>) requires 343.1452; found 343.1458 (+1.6 ppm).

### (2*R*)-(E)-methyl 2-(2-(furan-2-yl)-1-phenylhydrazinyl)pent-3-enoate **48**

Following general procedure A, (E)-pent-3-enoic acid **24** (40.6 μL, 0.40 mmol), *i*Pr<sub>2</sub>NEt (104 μL, 0.60 mmol) and pivaloyl chloride (74.0 μL, 0.60 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2 mL), HBTM-2.1 (2*S*,3*R*)-**23** (1.23 mg, 0.004 mmol, 1 mol%), (NE)-N-(phenylimino)furan-2-carboxamide **62** (80.0 mg, 0.40 mmol) and *i*Pr<sub>2</sub>NEt (174 μL, 1.00 mmol) for 15 min at rt, followed by addition of MeOH (2 mL) and stirring for 1 h at rt gave, after chromatographic purification (eluent Et<sub>2</sub>O:petrol 50:50) a rotameric mixture (ratio 94:6) of (2*R*)-**48** as a colourless oil (109 mg, 87%);  $[\alpha]_D^{20}$ -82.4 (*c* 0.5, CH<sub>2</sub>Cl<sub>2</sub>); Chiral HPLC Chiralpak IB (5%

IPA:hexane, flow rate 1 mL min<sup>-1</sup>, 211 nm, 30 °C)  $t_R(2S)$ : 16.0 min,  $t_R(2R)$ : 22.2 min, 99% *ee*;  $v_{max}$  (ATR)/cm<sup>-1</sup> 3335 (N-H), 2953 (C-H), 1730 (C=O), 1688 (C=O), 1589; Data for major rotamer:  $\delta_H$  (500 MHz, CDCl<sub>3</sub>) 1.70 (3H, dt, *J* 6.4, 1.3, CH<sub>3</sub>CH=), 3.76 (3H, s, OCH<sub>3</sub>), 5.20-5.21 (1H, m, C(2)H), 5.75 (1H, ddq, *J* 15.6, 6.0, 1.5, CH=CHCH<sub>3</sub>), 5.74 (1H, dqd, *J* 15.6, 6.4, 1.2, CH=CHCH<sub>3</sub>), 6.56 (1H, dd, *J* 3.5, 1.8, C(O)Ar(4)H), 6.92-6.95 (3H, m, NAr(2,6)H and NAr(4)H), 7.24-7.27 (3H, m, NAr(3,5)H and C(O)Ar(3)H), 7.52 (1H, dd, *J* 1.7, 0.8, C(O)Ar(5)H), 8.75 (1H, s, NH);  $\delta_C$  (125 MHz, CDCl<sub>3</sub>) 18.2 (CH<sub>3</sub>CH=), 52.4 (OCH<sub>3</sub>), 64.7 (C(2)), 112.2 (C(O)ArC(4)), 114.8 (NArC(2,6)), 115.9 (C(O)ArC(3)), 121.6 (NArC(4)), 123.3 (CH=CHCH<sub>3</sub>), 129.4 (NArC(3,5)), 132.8 (CH=CHCH<sub>3</sub>), 144.7 (C(O)ArC(5)), 146.6 (C(O)ArC(2)), 148.1 (NArC(1)), 158.2 (NHC=O), 173.0 (MeOC=O); Selected data for minor rotamer:  $\delta_H$  (500 MHz, CDCl<sub>3</sub>) 3.69 (3H, s, OCH<sub>3</sub>), 5.10 (1H, d, *J* 7.1, C(2)H), 6.38 (1H, dd, *J* 3.5, 1.7, C(O)Ar(3)H);  $\delta_C$  (125 MHz, CDCl<sub>3</sub>) 18.1 (CH<sub>3</sub>CH=), 52.4 (OCH<sub>3</sub>), 65.5 (C(2)), 111.6 (C(O)ArC(4)), 115.0 (NArC(2,6)), 129.8 (NArC(3,5)), 145.6 (C(O)ArC(5)); *m/z* (NSI<sup>+</sup>) 315 ([M+H]<sup>+</sup>, 100%); HRMS (NSI<sup>+</sup>) C<sub>17</sub>H<sub>19</sub>N<sub>2</sub>O<sub>4</sub><sup>+</sup> ([M+H]<sup>+</sup>) requires 315.1339; found 315.1335 (-1.4 ppm).

**(3R,4R,5R)-N'-(4-hydroxy-5-methyl-2-oxooxolan-3-yl)-N'-phenylbenzohydrazide amine 49 and (3R,4S,5S)-N'-(4-hydroxy-5-methyl-2-oxooxolan-3-yl)-N'-phenylbenzohydrazide amine 50**

To a solution of hydrazide (2R)-**41** (1.12 g, 3.44 mmol) in acetone:water (9:1, 40 mL) was added 2,6-lutidine (0.80 mL, 6.88 mmol), *N*-methylmorpholine-*N*-oxide (0.60 g, 5.16 mmol) and OsO<sub>4</sub> (4% wt in H<sub>2</sub>O, 0.44 mL, 0.07 mmol) and the reaction mixture was stirred at rt for 5 h after which time it was quenched by addition of sat. aq. Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub>. The reaction mixture was extracted with EtOAc (x 3) and the combined organic fractions were washed with HCl (2M in H<sub>2</sub>O), dried (MgSO<sub>4</sub>), filtered and concentrated *in vacuo* to give a mixture of crude diols (2R,3R,4R)-**49** and (2R,3S,4S)-**50** which were used directly in the next reaction without purification. The crude reaction mixture was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (50 mL) and treated with *p*-toluenesulfonic acid (0.65 g, 3.44 mmol). The reaction mixture was stirred at rt for 2 h before being quenched by addition of H<sub>2</sub>O. The reaction mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (x 3) and the

combined organic fractions were dried (MgSO<sub>4</sub>), filtered and concentrated *in vacuo* to give crude lactones (3*R*,4*R*,5*R*)-**49** and (3*R*,4*S*,5*S*)-**50** (70:30 dr).

Major diastereoisomer: Chromatographic purification (eluent Et<sub>2</sub>O:petrol 60:40 to 100% Et<sub>2</sub>O) gave lactone (3*R*,4*R*,5*R*)-**49** (>99:1 dr) as a white solid (0.59 g, 53%); mp 58-60 °C;  $[\alpha]_D^{20} +37.0$  (*c* 0.5, CH<sub>2</sub>Cl<sub>2</sub>); Chiral HPLC Chiralcel OJ-H (10% IPA:hexane, flow rate 1 mL min<sup>-1</sup>, 211 nm, 30 °C) *t<sub>R</sub>*(3*S*,4*S*,5*S*): 13.5 min, *t<sub>R</sub>*(3*R*,4*R*,5*R*): 19.3 min, 99% *ee*;  $\nu_{\max}$  (ATR)/cm<sup>-1</sup> 3306 (N-H and O-H), 2980 (C-H), 1767 (lactone C=O), 1661 (amide C=O), 1597;  $\delta_H$  (500 MHz, CDCl<sub>3</sub>) 1.44 (3H, d, *J* 6.3, CH<sub>3</sub>), 4.73-4.79 (3H, m, C(3)*H*, C(4)*H* and C(5)*H*), 5.02 (1H, br s, OH), 6.93-6.96 (3H, m, NAr(2,6)*H* and NAr(4)*H*), 7.24 (2H, td, *J* 9.1, 1.7, NAr(3,5)*H*), 7.43-7.46 (2H, m, C(O)Ar(3,5)*H*), 7.58 (1H, tt, *J* 7.5, 1.4, C(O)Ar(4)*H*), 7.79-7.81 (2H, m, C(O)Ar(2,6)*H*), 8.58 (1H, br s, NH);  $\delta_C$  (125 MHz, CDCl<sub>3</sub>) 14.9 (CH<sub>3</sub>), 66.8 (C(3)), 69.3 (C(4)), 77.3 (C(5)), 114.7 (NArC(2,6)), 121.7 (NArC(4)), 127.6 (ArC), 129.0 (ArC), 129.5 (ArC), 131.4 (C=OArC(1)), 133.0 (C=OArC(4)), 148.0 (NArC(1)), 168.8 (NHC=O), 172.0 (MeOC=O); *m/z* (NSI<sup>+</sup>) 327 ([M+H]<sup>+</sup>, 86%); HRMS (NSI<sup>+</sup>) C<sub>18</sub>H<sub>19</sub>N<sub>2</sub>O<sub>4</sub><sup>+</sup> ([M+H]<sup>+</sup>) requires 327.1339; found 327.1345 (+1.7 ppm).

Minor diastereoisomer: Chromatographic purification (eluent Et<sub>2</sub>O:petrol 60:40 to 100% Et<sub>2</sub>O) gave lactone (3*R*,4*S*,5*S*)-**50** (>99:1 dr) as a white solid (0.28 g, 25%); mp 110-112 °C;  $[\alpha]_D^{20} -266.4$  (*c* 0.5, CH<sub>2</sub>Cl<sub>2</sub>); Chiral HPLC Chiralpak IA (40% IPA:hexane, flow rate 1 mL min<sup>-1</sup>, 211 nm, 30 °C) *t<sub>R</sub>*(3*S*,4*R*,5*R*): 8.9 min, *t<sub>R</sub>*(3*R*,4*S*,5*S*): 14.8 min, 99% *ee*;  $\nu_{\max}$  (ATR)/cm<sup>-1</sup> 3238 (N-H and O-H), 2938 (C-H), 1776 (lactone C=O), 1668 (amide C=O), 1597, 1510;  $\delta_H$  (500 MHz, CDCl<sub>3</sub>) 1.51 (3H, d, *J* 6.3, CH<sub>3</sub>), 4.61-4.65 (2H, m, C(4)*H* and C(5)*H*), 4.76 (1H, d, *J* 4.3, C(3)*H*), 4.95 (1H, s, OH), 6.88 (2H, d, *J* 8.0, NAr(2,6)*H*), 6.97 (1H, t, *J* 7.4, NAr(4)*H*), 7.30 (2H, tt, *J* 7.2, 1.8, NAr(3,5)*H*), 7.48-7.51 (2H, m, C(O)Ar(3,5)*H*), 7.58-7.62 (1H, m, C(O)Ar(4)*H*), 7.89-7.91 (2H, m, C(O)Ar(2,6)*H*), 8.92 (1H, s, NH);  $\delta_C$  (125 MHz, CDCl<sub>3</sub>) 13.9 (CH<sub>3</sub>), 67.7 (C(3)), 70.3 (C(4)), 79.4 (C(5)), 113.0 (NArC(2,6)), 121.5 (NArC(4)), 127.6 (ArC), 129.1 (ArC), 129.8 (ArC), 131.4 (C=OArC(1)), 133.1 (C=OArC(4)), 147.3 (NArC(1)), 168.9

(NHC=O), 172.0 (MeOC=O);  $m/z$  (NSI<sup>+</sup>) 327 ([M+H]<sup>+</sup>, 100%); HRMS (NSI<sup>+</sup>) C<sub>18</sub>H<sub>19</sub>N<sub>2</sub>O<sub>4</sub><sup>+</sup> ([M+H]<sup>+</sup>) requires 327.1339; found 327.1346 (+2.0 ppm).

### **(3R,4R,5R)-4-hydroxy-5-methyl-2-(phenylamino)dihydrofuran-2(3H)-one 79**

To a solution of lactone (3R,4R,5R)-**49** (65.2 g, 0.20 mmol) in MeOH (2 mL) at -78 °C was added SmI<sub>2</sub> (0.1 M in THF, 6.00 mL, 0.60 mmol) and the reaction mixture was stirred at -78 °C for 10 minutes after which time it was quenched by addition of sat. aq. NaHCO<sub>3</sub>. The reaction mixture was extracted with EtOAc (x 3) and the combined organic fractions were dried (MgSO<sub>4</sub>), filtered and concentrated *in vacuo*. Chromatographic purification (eluent Et<sub>2</sub>O:petrol 60:40) gave lactone (3R,4R,5R)-**79** as a colourless oil (29.0 mg, 70%);  $[\alpha]_D^{20} +18.0$  (*c* 0.1, CH<sub>2</sub>Cl<sub>2</sub>);  $\nu_{\max}$  (ATR)/cm<sup>-1</sup> 3381 (N-H or O-H), 2986 (C-H), 1761 (C=O), 1603, 1499;  $\delta_H$  (500 MHz, CDCl<sub>3</sub>) 1.45 (3H, d, *J* 6.8, CH<sub>3</sub>), 2.74 (1H, d, *J* 4.9, OH or NH), 4.13 (1H, s, OH or NH), 4.18-4.19 (1H, m, C(3)H), 4.41 (1H, td, *J* 7.0, 4.8, C(4)H), 4.73 (1H, app. quintet, *J* 6.7, C(5)H), 6.80-6.85 (3H, m, NAr(2,6)H and NAr(4)H), 7.19-7.23 (2H, m, NAr(3,5)H);  $\delta_C$  (125 MHz, CDCl<sub>3</sub>) 14.7 (CH<sub>3</sub>), 59.6 (C(3)), 74.9 (C(4)), 77.4 (C(5)), 114.1 (NArC(2,6)), 119.6 (NArC(4)), 129.6 (NArC(3,5)), 146.8 (NArC(1)), 174.2 (C=O);  $m/z$  (NSI<sup>+</sup>) 208 ([M+H]<sup>+</sup>, 100%); HRMS (NSI<sup>+</sup>) C<sub>11</sub>H<sub>14</sub>NO<sub>3</sub><sup>+</sup> ([M+H]<sup>+</sup>) requires 208.0968; found 208.0968 (-0.1 ppm).

### **(3R,4S,5S)-4-hydroxy-5-methyl-2-(phenylamino)dihydrofuran-2(3H)-one 80**

To a solution of lactone (3R,4S,5S)-**50** (65.2 g, 0.20 mmol) in MeOH (2 mL) at -78 °C was added SmI<sub>2</sub> (0.1 M in THF, 6.00 mL, 0.60 mmol) and the reaction mixture was stirred at -78 °C for 10 minutes after which time it was quenched by addition of sat. aq. NaHCO<sub>3</sub>. The reaction mixture was extracted with EtOAc (x 3) and the combined organic fractions were dried (MgSO<sub>4</sub>), filtered and concentrated *in vacuo*. Chromatographic purification (eluent Et<sub>2</sub>O:petrol 60:40) gave lactone (3R,4S,5S)-**80** as a colourless oil (31.4 mg, 76%);  $[\alpha]_D^{20} -98.0$  (*c* 0.1, CH<sub>2</sub>Cl<sub>2</sub>);  $\nu_{\max}$  (ATR)/cm<sup>-1</sup> 3389 (N-H or O-H), 2982 (C-H), 1761 (C=O), 1603, 1506;  $\delta_H$  (400 MHz, CDCl<sub>3</sub>) 1.47 (3H, d, *J* 6.5, CH<sub>3</sub>), 2.76 (1H, br s, OH or NH), 4.08 (1H, d, *J* 4.4, C(3)H), 4.40 (1H, dd, *J* 4.4, 2.9, C(4)H), 4.58 (1H, qd, *J* 6.5, 2.9, C(5)H), 6.67-6.70 (2H, m,

NAr(2,6)H), 6.84 (1H, tt,  $J$  7.4, 1.0, NAr(4)H), 7.16-7.21 (2H, m, NAr(3,5)H);  $\delta_C$  (100 MHz, CDCl<sub>3</sub>) 13.8 (CH<sub>3</sub>), 60.4 (C(3)), 69.8 (C(4)), 78.6 (C(5)), 114.2 (NArC(2,6)), 120.5 (NArC(4)), 129.6 (NArC(3,5)), 146.0 (NArC(1)), 174.6 (C=O);  $m/z$  (NSI<sup>+</sup>) 208 ([M+H]<sup>+</sup>, 100%); HRMS (NSI<sup>+</sup>) C<sub>11</sub>H<sub>14</sub>NO<sub>3</sub><sup>+</sup> ([M+H]<sup>+</sup>) requires 208.0968; found 208.0968 (-0.1 ppm).

**Acknowledgements:** We thank the Royal Society for a University Research Fellowships (A.D.S) and The Carnegie Trust for the Universities of Scotland (L.C.M) for funding. The research leading to these results has received funding from the European Research Council under the European Union's Seventh Framework Programme (FP7/2007-2013) / ERC grant agreement n° 279850. We also thank the EPSRC National Mass Spectrometry Service Centre (Swansea). SMS Funding?

**Supporting Information Available:**  $\beta$ -lactam epimerization studies, Assignments of aza sugar relative configurations, X-ray structural data, spectral and HPLC data for all new compounds are provided. This material is available free of charge via the Internet at <http://pubs.acs.org>.

## REFERENCES

- (1) For selected reviews on dienamine catalysis, see: (a) Jensen, K. L.; Dickmeiss, G.; Jiang, H.; Albrecht, L.; Jørgensen, K. A. *Acc. Chem. Res.*, **2012**, *45*, 248-264; (b) Nielsen, M.; Worgull, D.; Zweifel, T.; Gschwend, B.; Bertelsen, S.; Jørgensen, K. A. *Chem. Commun.*, **2011**, *47*, 632-649; (c) Ramachary, D. B.; Reddy, Y. V. *Eur. J. Org. Chem.* **2012**, 865-887.
- (2) (a) Tiseni, P. S.; Peters, R. *Angew. Chem. Int. Ed.* **2007**, *46*, 5325-5328; (b) Tiseni, P. S.; Peters, R. *Org. Lett.* **2008**, *10*, 2019-2022; (c) Tiseni, P. S.; Peters, R. *Chem. Eur. J.* **2010**, *16*, 2503-2517.
- (3) (a) Shen, L-T.; Sun, L-H.; Ye, S. *J. Am. Chem. Soc.* **2011**, *133*, 15894-15897; (b) Shen, L-T.; Jia, W-Q.; Ye, S. *Angew. Chem. Int. Ed.* **2013**, *52*, 585-588.
- (4) Shen, L-T.; Shao, P-L.; Ye, S. *Adv. Synth. Catal.* **2011**, *353*, 1943-1948.

- (5) Mo, J.; Chen, X.; Chi, Y. R. *J. Am. Chem. Soc.* **2012**, *134*, 8810-8813.
- (6) Chen, X.; Yang, S.; Song, B-A.; Chi, Y. R. *Angew. Chem. Int. Ed.* **2013**, *52*, 11134-11137.
- (7) Xu, J.; Jin, Z.; Chi, Y. R. *Org. Lett.* **2013**, *15*, 5028-5031.
- (8) Yao, C.; Xiao, Z.; Liu, R.; Li, T.; Jiao, W.; Yu, C. *Chem. Eur. J.*, **2013**, *19*, 456-459.
- (9) C1-azolium dienolates accessed from  $\alpha,\beta$ -unsaturated acid chlorides **4** may also be formed *via* a mechanism involving dehydrohalogenation to form a vinyl ketene intermediate which is subsequently intercepted by the NHC.
- (10) Zhao, Y-M.; Cheung, M. S.; Lin, Z.; Sun, J. *Angew. Chem. Int. Ed.* **2012**, *51*, 10359-10363.
- (11) Chen, X-Y.; Xia, F.; Chen, J-T.; Ye, S. *Angew. Chem. Int. Ed.* **2013**, *52*, 10644-10647.
- (12) For the pioneering work of Romo regarding the activation of carboxylic acids towards *intramolecular* nucleophile catalysed aldol-lactonisation (NCAL) reactions see: (a) Cortez, G. S.; Tennyson, R. L.; Romo, D. *J. Am. Chem. Soc.* **2001**, *123*, 7945-7946; (b) Cortez, G. S.; Oh, S. H.; Romo, D. *Synthesis* **2001**, 1731-1736; (c) Oh, S. H.; Cortez, G. S.; Romo, D. *J. Org. Chem.* **2005**, *70*, 2835-2838; (d) Henry-Riyad, H.; Lee, C.; Purohit, V. C.; Romo, D. *Org. Lett.* **2006**, *8*, 4363-4366; (e) Ma, G.; Nguyen, H.; Romo, D. *Org. Lett.* **2007**, *9*, 2143-2146; (f) Purohit, V. C.; Matla, A. S.; Romo, D. *J. Am. Chem. Soc.* **2008**, *130*, 10478-10479; (g) Nguyen, H.; Ma, G.; Romo, D. *Chem. Commun.* **2010**, *46*, 4803-4805; (h) Morris, K. A.; Arendt, K. M.; Oh, S. H.; Romo, D. *Org. Lett.* **2010**, *12*, 3764-3767; (i) Leverett, C.; Purohit, V. C.; Romo, D. *Angew. Chem. Int. Ed.* **2010**, *49*, 9479-9483; (j) Nguyen, H.; Oh, S.; Henry-Riyad, H.; Sepulveda, D.; Romo, D. *Org. Synth.* **2011**, *88*, 121;-137 (k) Nguyen, H.; Ma, G.; Gladysheva, T.; Fremgen, T.; Romo, D. *J. Org. Chem.* **2011**, *76*, 2-12; (l) Liu, G.; Romo, D. *Angew. Chem. Int. Ed.* **2011**, *50*, 7537-7540; (m) Leverett, C. A.; Purohit, V. C.; Johnson, A. G.; Davis, R. L.; Tantillo, D. J.; Romo, D. *J. Am. Chem. Soc.* **2012**, *134*, 13348-13356; (n) Liu, G.; Shirley, M. E.; Romo, D. *J. Org. Chem.* **2012**, *77*, 2496-2500.



- (13) For a recent review detailing the use of isothioureas in nucleophilic catalysis see Taylor, J. E.; Bull, S. D.; Williams, J. M. J. *Chem. Soc. Rev.* **2012**, *14*, 2109-2121.
- (14) For pioneering work demonstrating the utility of isothioureas as efficient *O*-acyl transfer agents see: (a) Birman, V. B.; Li, X. *Org. Lett.*, **2006**, *8*, 1351-1354; (b) Kobayashi, M.; Okamoto, S. *Tetrahedron Lett.*, **2006**, *47*, 4347-4350.
- (15) For an excellent review of ammonium enolate chemistry see Gaunt, M. J.; Johansson, C. C. C. *Chem. Rev.*, **2007**, *107*, 5596-5605.
- (16) For examples see: (a) Belmessieri, D.; Morrill, L. C.; Simal, C.; Slawin, A. M. Z.; Smith, A. D. *J. Am. Chem. Soc.* **2011**, *133*, 2714-2720; (b) Simal, C.; Lebl, T.; Slawin, A. M. Z.; Smith, A. D. *Angew. Chem. Int. Ed.* **2012**, *51*, 3653-3657; (c) Morrill, L. C.; Lebl, T.; Slawin, A. M. Z.; Smith, A. D. *Chem. Sci.* **2012**, *3*, 2088-2093; (d) Morrill, L. C.; Douglas, J.; Lebl, T.; Slawin, A. M. Z.; Fox D. J.; Smith, A. D. *Chem. Sci.*, **2013**, *4*, 4146-4155; (e) Belmessieri, D.; Cordes, D. B.; Slawin, A. M. Z.; Smith, A. D. *Org. Lett.*, **2013**, *15*, 3472-3475; (f) D. G. Stark, L. C. Morrill, P-P. Yeh, T. J. O’Riordan, *Angew. Chem. Int. Ed.*, **2013**, *52*, 11642-11646.
- (17) In Ref 16(c), using specific reaction conditions, selected non-arylacetic acids could be used - namely (thiophenyl)acetic acid, methoxyacetic acid and 3-phenylpropionic acid - when a highly reactive *N*-aryl-*N*-aroyldiazene Michael acceptor was used.
- (18) For a recent report from our research group detailing the use of 2-arylacetic anhydrides as ammonium enolate precursors see Morrill, L. C.; Ledingham, L. A.; Couturier, J-P.; Bickel, J.; Harper, A. D.; Fallan, C.; Smith, A. D. *Org. Biomol. Chem.* **2013**, *12*, 624-636.
- (19) Smith, S. R.; Douglas, J.; Prevet, H.; Shapland, P.; Slawin, A. M. Z.; Smith, A. D. *J. Org. Chem.* preceding publication.
- (20) All experiments were carried out under air using bench grade solvents as standard.

(21) Other carboxylic acid starting materials, namely (*E*)-3-phenylbut-2-enoic acid **70** and (*E*)-3,4-diphenylbut-2-enoic acid **72** were tested to attempt to access ammonium dienolates which react at the  $\gamma$ -position but none were successful.

(22) The relative configurations of  $\beta$ -lactones (*anti* **21**, *syn* **73**) and  $\beta$ -lactams (*anti* **22**, *syn* **74**) in table 1 were confirmed unambiguously by X-ray crystallography. Crystallographic data for all diastereoisomers **21**, **22**, **73** and **74** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 968689, 968690, 968692 and 968693.

(23) Although we describe these reactions as formal [2+2] cycloadditions, they may also be considered as intermolecular enolate-imine cyclisation reactions, or Gilman-Speeter reactions. For representative examples see: (a) Hiroki, F.; Kanai, M.; Kambara, T.; Iida, A.; Tomioka, K. *J. Am. Chem. Soc.* **1997**, *119*, 2060-2061; (b) Tomioka, K.; Fujieda, H.; Hayashi, S.; Hussein, M. A.; Kambara, T.; Nomura, Y.; Kanai, M.; Koga, K. *Chem. Commun.* **1999**, 715-716; (c) Hussein, M. A.; Iida, A.; Tomioka, K. *Tetrahedron* **1999**, *55*, 11219-11228; (d) Kambara, T.; Tomioka, K. *Chem. Pharm. Bull.* **2000** *48*, 1577-1580; (e) Evans C. D.; Mahon, M. R.; Andrews, P. C.; Muir, J.; Bull, S. D. *Org. Lett.* **2011**, *13*, 6276-6279. For the Gilman-Speeter reaction see: Gilman, H.; Speeter, M. *J. Am. Chem. Soc.*, **1943**, *65*, 2255-2256.

(24) For selected alternative methods for accessing  $\beta$ -lactams bearing an olefin at C(3), see: (a) Torii, S.; Okumoto, H.; Sadakane, M.; Hai, A. K. M. A.; Tanaka, H. *Tetrahedron Lett.* **1993**, *34*, 6553-6556; (b) Taggi, A. E.; Hafez, A. M.; Wack, H.; Young, B.; Ferraris, D.; Lectka, T. *J. Am. Chem. Soc.* **2002**, *124*, 6626-6635; (c) Fontana, F.; Tron, G. C.; Barbero, N.; Ferrini, S.; Thomas, S. P.; Aggarwal, V. K. *Chem. Commun.* **2010**, *46*, 267-269; (d) Xia, P.; Qian, B.; Huang, H. *Tetrahedron Lett.* **2012**, *53*, 1613-1616. For discussions regarding the biological importance of the  $\beta$ -lactam motif, see: (a) Morin, R. B.; Gorman, M. *Chemistry and biology of beta-lactam antibiotics*; Academic Press, 1982; (b) Jastrzebski, J. T. B. H.; VanKoten, G. In *Comprehensive Heterocyclic Chemistry II*; Editors-in-Chief: Alan, R. K., Charles, W.

R., Eric F.V. Scriven - Editors-in-Chief: Alan R. Katritzky, C. W. R., Eric, F. V. S., Eds.; Pergamon: Oxford, 1996, p 623-658; (c) Zhang, T. Y.; Hatfield, L. D. In *Comprehensive Heterocyclic Chemistry II*; Editors-in-Chief: Alan, R. K., Charles, W. R., Eric F.V. Scriven - Editors-in-Chief: Alan R. Katritzky, C. W. R., Eric, F. V. S., Eds.; Pergamon: Oxford, 1996, p 591-622.

(25) Racemic samples of all  $\beta$ -lactams in tables 2 and 3 were prepared using achiral catalyst DHPB **17**.

(26) The absolute configuration of *syn*- $\beta$ -lactam **27** was confirmed unambiguously by X-ray crystallography as (3*S*,4*S*). Crystallographic data for **27** has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 968691.

(27) See SI for full details of the epimerization experiment.

(28) Poor conversion to  $\beta$ -lactams **28** and **29** is observed when the reactions are carried out at  $-78$  °C.

(29) All reactions quoted at  $-78$  °C were also carried out at rt, typically giving lower enantioselectivities for  $\beta$ -lactam products. See SI for these results.

(30) Racemic ( $\pm$ )-**36** was prepared using ( $\pm$ )-HBTM-2.1 **23**. Racemic samples of all products in Table 4 were made using ( $\pm$ )-HBTM-2.1 **23** as a catalyst.

(31) The minor diastereoisomer was formed in 15% ee. The enantioselectivities of all minor diastereoisomers in Table 4 can be found in the SI.

(32) The relative and absolute configuration of  $\delta$ -lactone **36** was assigned by comparison with the literature Ref 16(d). All other products in Table 4 were assigned by analogy.

(33) The initial heterocyclic products were immediately ring-opened with methanol due to their instability towards chromatographic purification on silica.

(34) The absolute configuration of hydrazide **41** was assigned by comparison with the literature Ref 16(c). All other products in Table 5 were assigned by analogy.

- (35) Racemic ( $\pm$ )-**41** was prepared using the achiral isothioureia DHPB **17**. Racemic samples of all products in Table 5 were made using DHPB **17** as a catalyst.
- (36) The N-N bond in lactones **49** and **50** were cleaved using SmI<sub>2</sub> in 70% and 76% yield respectively. Coupling constant analysis in addition to NOE studies of these products allowed the relative configurations of lactones **49** and **50** to be assigned. See SI for details.
- (37) McKay, W. R.; Proctor, G. R.; *J. Chem. Soc. Perkin Trans I*, **1981**, 2435-2442.
- (38) Smith III, A. B.; Toder, B. H.; Branca, S. J.; Dieter, R. K.; *J. Am. Chem. Soc.*, **1981**, *103*, 1996-2008.
- (39) Augustyns, K.; Haemers, A.; Kertesz, I.; Senten, K.; Van Der Veken, P.; De Meester, I.; Lambeir, A-M.; Maes, M-B.; Scharpe, S.; *J. Med. Chem.*, **2005**, *48*, 1768-1780.
- (40) Kantorowski, E. J.; Le, D. D.; Hunt, C. J.; Barry-Holson, K. Q.; Lee, J. P.; Ross, L. N. *J. Org. Chem.*, **2008**, *73*, 1593-1596.
- (41) Miyashi, T.; Nishizawa, Y.; Fujii, Y.; Yamakawa, K.; Kamata, M.; Akao, S.; Mukai, T. *J. Am. Chem. Soc.*, **1986**, *108*, 1617-1632.
- (42) Smith, S. M.; Thacker, N. C.; Takacs, J. M. *J. Am. Chem. Soc.*, **2008**, *130*, 3734-3735.
- (43) Loy, N. S. Y.; Singh, A.; Xu, X.; Park, C-M. *Angew. Chem. Int. Ed.*, **2013**, *52*, 2212-2216.
- (44) Smejkal, T.; Breit, B. *Angew. Chem. Int. Ed.*, **2008**, *47*, 311-315.
- (45) Maleczka, R. E.; Rahaim, R. *J. Org. Lett.*, **2011**, *13*, 584-587.
- (46) Tellier, F.; Sauvetre, R. *Tetrahedron Letters*, **1993**, *34*, 5433-5436.
- (47) Takimoto, M.; Shimizu, K.; Mori, M. *Org. Lett.*, **2001**, *3*, 3345-3347.
- (48) Duan, X-G.; Duan, X-L.; Rees, C. W. *J. Chem Soc., Perkin Trans. I*, **1997**, 2831-2836.

(49) Abarbri, M.; Thibonnet, J; Parrain, J-L.; Duchene, A.; *Synthesis*, **2002**, 543-551.