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## Enantioselective NHC-catalysed redox [4+2]-hetero-Diels-Alder reactions using $\alpha$ -aroyloxyaldehydes and unsaturated ketoesters

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### ABSTRACT

N-Heterocyclic carbene (NHC)-catalysed redox [4+2]-hetero-Diels-Alder reactions of  $\alpha$ -aroyloxyaldehydes with either  $\beta,\gamma$ -unsaturated  $\alpha$ -ketoesters or  $\alpha,\beta$ -unsaturated  $\gamma$ -ketoesters generates substituted *syn*-dihydropyranones in good yield with excellent enantioselectivity (up to >99:1 er). The product diastereoselectivity is markedly dependent upon the nature of the unsaturated enone substituent. The presence of either electron-neutral or electron-rich aryl substituents gives excellent diastereoselectivity (up to >99:5 dr), while electron-deficient aryl substituents give reduced diastereoselectivity. In these cases, the *syn*-dihydropyranone products are more susceptible to base-promoted epimerisation at the C(4)-position under the reaction conditions, accounting for the lower diastereoselectivity obtained.

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### 1. Introduction

N-Heterocyclic carbenes (NHCs) are versatile organocatalysts that exhibit a wide range of reactivity.<sup>1</sup> Of the multiple activation modes accessible through NHC catalysis, the generation and use of azolium enolates has emerged as a powerful strategy for the enantioselective synthesis of complex small-molecules. A number of methods has been developed for the formation of azolium enolate intermediates (Scheme 1a). For example, addition of an NHC into a substituted ketene directly generates an azolium enolate,<sup>2</sup> while deprotonation of acyl azolium intermediates, themselves generated from either the reaction of NHCs with aldehydes under oxidative conditions<sup>3</sup> or the addition of NHCs into activated carboxylic esters,<sup>4</sup> also leads to enolate formation. Another common strategy for azolium enolate formation is the addition of NHCs into aldehydes bearing  $\alpha$ -reducible functional groups, which subsequently undergo a redox process to form the desired enolate.<sup>5–10</sup> Examples of such  $\alpha$ -reducible aldehydes include  $\alpha$ -chloroaldehydes,<sup>6</sup> enals,<sup>7</sup>  $\alpha$ -aryloxyaldehydes,<sup>8</sup> and formyl cyclopropanes<sup>9</sup> (Scheme 1b). We have previously reported that bench-stable  $\alpha$ -aroyloxyaldehydes **1** are also efficient redox azolium enolate precursors.<sup>10</sup>

Azolium enolates generated from NHCs and  $\alpha$ -reducible aldehydes react with a variety of electrophiles to generate a diverse array of products. Of particular relevance is the reaction of azolium enolates with substituted enones in enantioselective [4+2]-hetero-Diels-Alder processes to form stereodefined dihydropyranone products. For

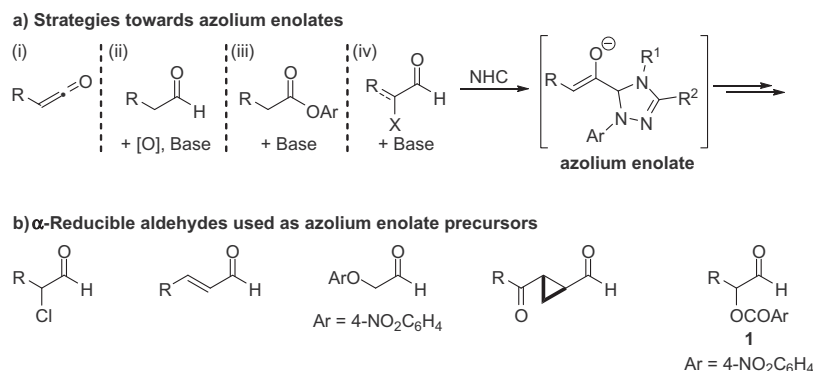
example, Bode and co-workers demonstrated that azolium enolates generated from  $\alpha$ -chloroaldehydes react with both  $\beta,\gamma$ -unsaturated  $\alpha$ -ketoesters and  $\alpha,\beta$ -unsaturated  $\gamma$ -ketoesters to form *syn*-dihydropyranones **3** with excellent enantioselectivity (Scheme 2a).<sup>6b</sup> In this case, the use of unsaturated ketoesters bearing either alkyl or electron-neutral/rich aryl substituents generally formed the product dihydropyranones in high diastereoselectivity. Notably, the presence of electron-deficient aryl (4-BrC<sub>6</sub>H<sub>4</sub>) or heteroaryl (2-furyl) substituents lead to a decrease in diastereoselectivity, although the origin of the reduced dr was not further investigated. This methodology was subsequently extended to the use of the bench-stable sodium bisulfate adducts of  $\alpha$ -chloroaldehydes under biphasic conditions, allowing the use of unsubstituted chloroacetaldehyde sodium bisulfite to form dihydropyranones containing a single stereocentre.<sup>6c</sup> The NHC-catalysed redox hetero-Diels-Alder reaction of enals with unsaturated ketoesters has also been reported to proceed with high levels of stereoselectivity.<sup>7d</sup>

$\alpha$ -Aroyloxyaldehydes have previously been used as azolium enolate precursors in NHC-catalysed [4+2]-hetero-Diels-Alder reactions with various trifluoromethyl enones (Scheme 2b)<sup>10b,d</sup> and  $\alpha,\beta$ -unsaturated trichloromethyl ketones<sup>10e</sup> to form functionalised *syn*-dihydropyranones **4** with high diastereo- and enantioselectivity. Azolium enolates generated from  $\alpha$ -aroyloxyaldehydes also undergo [2+2]<sup>10f</sup> and [3+2]-cycloadditions,<sup>10g</sup> as well as enantioselective  $\alpha$ -aminations to from *N*-aryl amino acid derivatives.<sup>10c</sup>

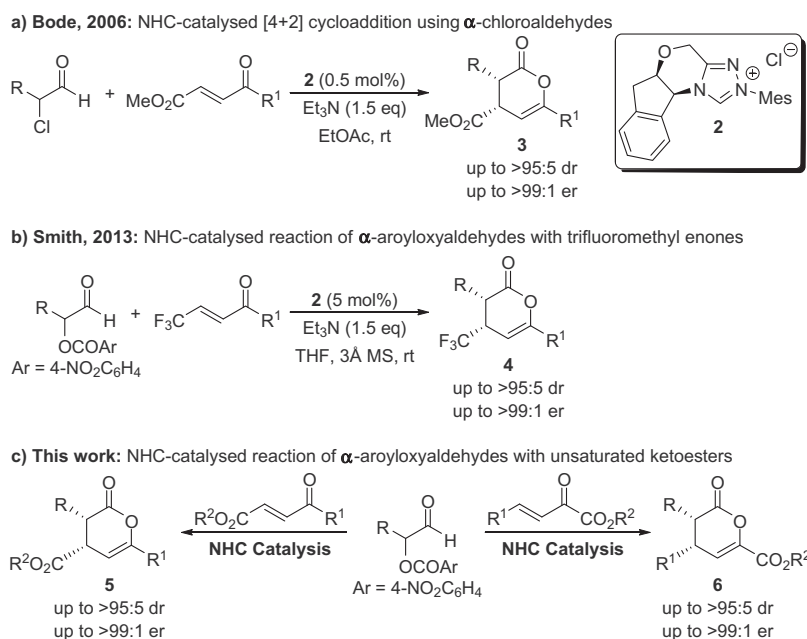
Herein, the NHC-catalysed redox hetero-Diels-Alder reaction of bench-stable  $\alpha$ -aroyloxyaldehydes with both  $\beta,\gamma$ -unsaturated  $\alpha$ -ketoesters and  $\alpha,\beta$ -unsaturated  $\gamma$ -ketoesters is reported to form

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Scheme 1. Generation of azolium enolate intermediates.



Scheme 2. NHC-catalysed redox [4+2]-hetero-Diels-Alder reactions.

*syn*-dihydropyranones **5** and **6** with excellent enantioselectivity (Scheme 2c). The effect of various aryl substituents on the unsaturated ketoesters on the reaction diastereoselectivity is assessed, with control experiments performed to determine the origin of the reduced product diastereoselectivity observed in some cases.

## 2. Results and discussion

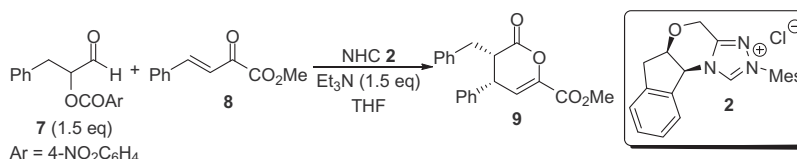
### 2.1. Reaction optimisation

First, the reaction of azolium enolates derived from  $\alpha$ -aroxyaldehydes<sup>11</sup> with  $\beta,\gamma$ -unsaturated  $\alpha$ -ketoesters was studied. Treating  $\alpha$ -aroxyaldehyde **7** and  $\alpha$ -ketoester **8** with NHC precatalyst **2** (20 mol %) and  $Et_3N$  (1.5 equiv) in THF at room temperature gave dihydropyranone **9** in a promising 50% yield and 92:8 dr with excellent enantioselectivity (>99:1 er) for the major *syn*-diastereoisomer (Table 1, entry 1).<sup>12</sup> Lowering the catalyst loading led to increased reaction times and decreased diastereoselectivity, although the enantioselectivity for both diastereoisomers was high (Table 1, entries 2 and 3). Decreasing the reaction temperature to  $-78^\circ\text{C}$  led to an increase in diastereoselectivity (>99:1 dr), but gave lower conversion into the desired product (Table 1, entry 4).

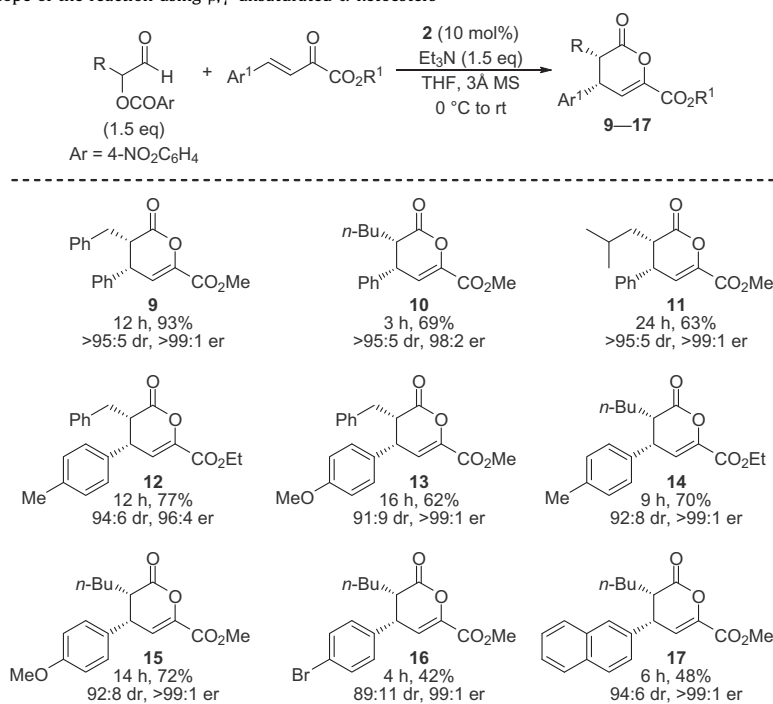
Starting the reaction at  $0^\circ\text{C}$  and allowing it to warm slowly to room temperature using 10 mol % **2** gave an excellent compromise between reactivity and stereoselectivity, with *syn*-dihydropyranone **9** isolated in 93% yield with >95:5 dr and >99:1 er (Table 1, entry 5). The relative and absolute configuration of the major product was assigned by analogy to that of a known derivative formed during investigation of the reaction substrate scope (vide infra).

### 2.2. Reaction scope with $\beta,\gamma$ -unsaturated $\alpha$ -ketoesters

The scope of the NHC-catalysed redox reaction of various  $\alpha$ -aroxyaldehydes with a range of  $\beta,\gamma$ -unsaturated  $\alpha$ -ketoesters was studied under the previously optimised conditions (Table 2). The reaction worked well with different alkyl  $\alpha$ -aroxyaldehyde substituents, forming *syn*-dihydropyranones **10** and **11** in good yields with excellent levels of stereoselectivity (up to >95:5 dr and >99:1 er). The reaction with  $\beta,\gamma$ -unsaturated  $\alpha$ -ketoesters bearing electron-rich aromatic substituents (4-MeC<sub>6</sub>H<sub>4</sub> and 4-MeOC<sub>6</sub>H<sub>4</sub>) gave dihydropyranones **12–15** in high yields, but with slightly reduced levels of *syn*-diastereoselectivity ( $\geq 91:9$  dr) compared with the reaction with phenyl substituted  $\alpha$ -ketoester **8**. However, in each case the major *syn*-diastereoisomer was formed

**Table 1**  
Reaction optimisation

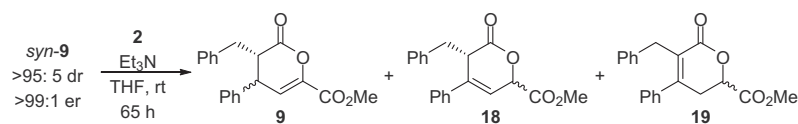
Entry	NHC (mol %)	T (°C)	Time (h)	Conversion <sup>a,b</sup> (%)	dr <sup>a</sup>	er <sup>c</sup>
1	<b>2</b> (20)	rt	5	>90 (50)	92:8	>99:1
2	<b>2</b> (10)	rt	12	>90	85:15	N/D
3	<b>2</b> (1)	rt	48	>90	76:24	>99:1 ( <i>syn</i> )
4	<b>2</b> (10)	−78	12	45	>95:5	N/D
5	<b>2</b> (10)	0 to rt	12	>90 (93)	>95:5	>99:1

<sup>a</sup> Determined by <sup>1</sup>H NMR analysis of the crude reaction mixture.<sup>b</sup> Isolated yield after purification by column chromatography in parentheses.<sup>c</sup> er of major diastereoisomer determined by HPLC analysis.**Table 2**  
Scope of the reaction using β,γ-unsaturated α-ketoesters<sup>a,b,c</sup><sup>a</sup> Isolated yields of single diastereoisomers (>95:5 dr) after column chromatography.<sup>b</sup> dr determined by <sup>1</sup>H NMR analysis of the crude reaction mixtures.<sup>c</sup> er of major diastereoisomer determined by HPLC analysis.

with high levels of enantioselectivity ( $\geq 96:4$  er). The relative configuration of *syn*-dihydropyranone **12** could be confirmed through comparison of its spectroscopic data with the literature,<sup>6b</sup> while the absolute configuration was confirmed through comparison of its specific rotation [ $[\alpha]_D^{20} = +299.4$  (c 0.5, CHCl<sub>3</sub>)] with the reported value [(3*S*,4*S*)-**12**, 98.5:1.5 er,  $[\alpha]_D^{20} = +310.3$  (c 1.0, CHCl<sub>3</sub>)].<sup>6b</sup> The incorporation of a more electron-deficient aryl bromine substituent led to a modest 42% yield of dihydropyranone **16** in a reduced 89:11 dr, although the enantioselectivity remained high (99:1 er). An extended aromatic 2-naphthyl substituent was also successfully incorporated, forming **17** in 48% yield with good stereoselectivity (94:6 dr, >99:1 er).

To investigate the reduced diastereoselectivity observed in certain cases, a series of control experiments was performed (Table 3). Treating isolated *syn*-dihydropyranone **9** (>95:5 dr) with NHC pre-catalyst **2** (15 mol %) and Et<sub>3</sub>N (15 mol %) resulted in epimerisation, returning **9** in 89:11 dr after 65 h at room temperature (Table 3, entry 1). Furthermore, significant amounts of products **18** and **19** arising from double bond isomerisation were also observed, indicating that the initial deprotonation leading to both epimerisation and isomerisation is most likely to occur at the C(4) position in conjugation with the enone.<sup>13,14</sup> The use of Et<sub>3</sub>N (15 mol %) alone resulted in reduced amounts of both epimerisation (93:7 dr after 65 h) and isomerisation, suggesting that the free NHC is capable of deprotonating **9** (Table 3, entry 2). Treating **9** with a stoichio-

**Table 3**  
Investigation into the epimerisation of *syn*-**9**

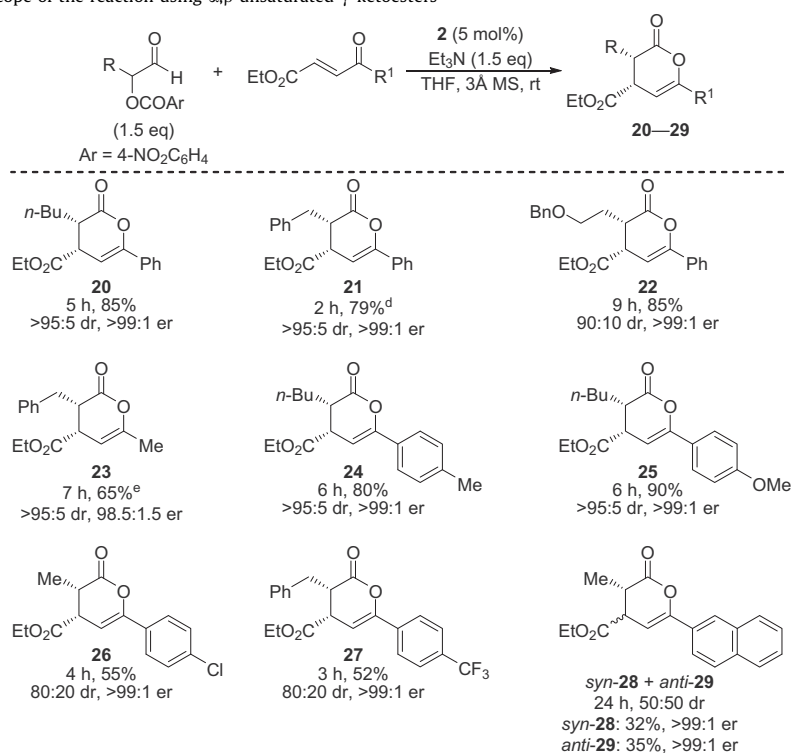


Entry	<b>2</b> (mol %)	Et <sub>3</sub> N (mol %)	<b>9/18/19</b> <sup>a</sup>	dr <b>9</b> <sup>a</sup>	dr <b>18</b> <sup>a</sup>
1	15	15	50:30:20	89:11	59:41
2	—	15	92:8:0	93:7	55:45
3	—	100	48:37:15	94:6	60:40
4 <sup>b</sup>	—	100	27:14:59	80:20	52:48

<sup>a</sup> Determined by <sup>1</sup>H NMR analysis of the crude reaction mixtures.

<sup>b</sup> Entry 3 re-subjected to the same conditions for a further 120 h.

**Table 4**  
Scope of the reaction using  $\alpha,\beta$ -unsaturated  $\gamma$ -ketoesters<sup>a–c</sup>



<sup>a</sup> Isolated yields of single diastereoisomers (>95:5 dr) after column chromatography.

<sup>b</sup> dr determined by <sup>1</sup>H NMR analysis of the crude reaction mixtures.

<sup>c</sup> er of major diastereoisomer determined by HPLC analysis.

<sup>d</sup> 10 mol % **2** used.

<sup>e</sup> Reaction performed at 40 °C using Cs<sub>2</sub>CO<sub>3</sub> instead of Et<sub>3</sub>N.

metric amount of Et<sub>3</sub>N (1 equiv) resulted in increased levels of isomerisation into both **18** and **19** (Table 3, entry 3), while increased reaction times led to further isomerisation and increased epimerisation of the remaining dihydropyranone **9** (Table 3, entry 4). The NHC and base-promoted epimerisation and isomerisation of the product *syn*-dihydropyranones could therefore account for the reduced diastereoselectivity and lower yields obtained in certain instances (Table 2).

### 2.3. Reactions with $\alpha,\beta$ -unsaturated $\gamma$ -ketoesters

Next, the use of  $\alpha,\beta$ -unsaturated  $\gamma$ -ketoesters in the NHC-catalysed redox process with  $\alpha$ -aryloxyaldehydes was investigated (Table 4). In this case, only 5 mol % NHC precatalyst **2** was required

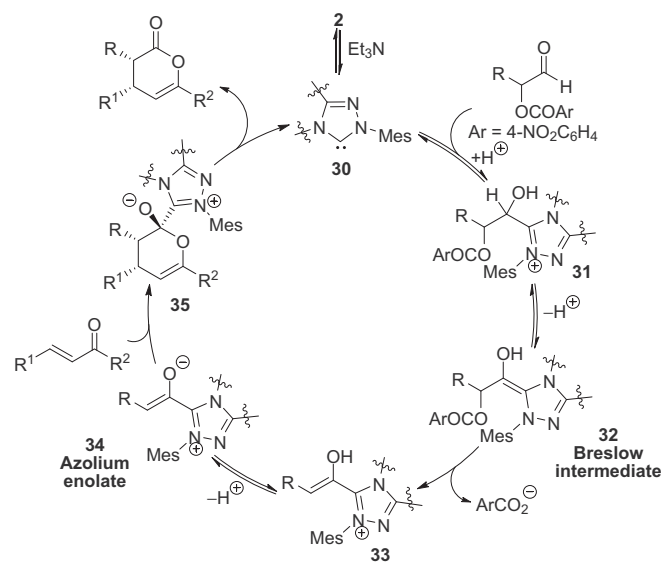
alongside Et<sub>3</sub>N (1.5 equiv) in THF at room temperature to form the corresponding *syn*-dihydropyranones in high yields and with excellent stereoselectivity.  $\alpha$ -Aryloxyaldehydes bearing alkyl and benzyl substituents were well tolerated, forming products **20–22** in high yields with excellent diastereo- and enantioselectivity (>90:10 dr, >99:1 er). The relative and absolute configuration of **21** was confirmed through comparison of its spectroscopic data and specific rotation [ $\alpha$ ]<sub>D</sub><sup>20</sup> = +173 (c 1.05, CHCl<sub>3</sub>) with the literature [ $\alpha$ ]<sub>D</sub><sup>20</sup> = +107 (c 0.82, CHCl<sub>3</sub>),<sup>6c</sup> with all other products in this series assigned by analogy. The reaction using an  $\alpha,\beta$ -unsaturated  $\gamma$ -ketoester bearing a methyl substituent needed to be heated at 40 °C and required the use of Cs<sub>2</sub>CO<sub>3</sub> as base to form *syn*-dihydropyranone **23** in 65% yield as a single diastereoisomer in high enantioselectivity. The absolute

configuration of **23** could also be confirmed through comparison of its specific rotation [ $[\alpha]_D^{20} = +271$  ( $c$  0.32 in  $\text{CHCl}_3$ )] with the literature [ $>99:1$  er,  $[\alpha]_D^{20} = +251$  ( $c$  0.93,  $\text{CHCl}_3$ )].<sup>6c</sup> The use of  $\alpha$ ,  $\beta$ -unsaturated  $\gamma$ -ketoester bearing electron-rich aryl substituents worked particularly well, forming *syn*-dihydropyranones **24** and **25** in high yield with excellent levels of stereoselectivity ( $>95:5$  dr,  $>99:1$  er). However, the incorporation of aryl groups containing electron-withdrawing substituents led to the formation of **26** and **27** in lower yields with reduced diastereoselectivity (80:20 dr), although the enantioselectivity remained high in both cases ( $>99:1$  er). A similar reduction in diastereoselectivity was observed by Bode and co-workers in the related NHC-catalysed redox reaction of an  $\alpha$ -chloroaldehyde with an  $\alpha,\beta$ -unsaturated  $\gamma$ -ketoester bearing a 4-bromo substituted aryl ring.<sup>6b</sup> The reaction of a methyl substituted  $\alpha$ -aroyloxyaldehyde with a 2-naphthyl substituted  $\alpha,\beta$ -unsaturated  $\gamma$ -ketoester under the previously optimised conditions gave the largest reduction in diastereoselectivity, with *syn*-**28** and *anti*-**29** formed as a 50:50 mixture, although both diastereoisomers were obtained in excellent enantioselectivity ( $>99:1$  er).

The dramatic reduction in diastereoselectivity observed with the 2-naphthyl substituted  $\alpha,\beta$ -unsaturated  $\gamma$ -ketoester was probed by treating isolated *syn*-dihydropyranone **28** ( $>95:5$  dr) with  $\text{Et}_3\text{N}$  (1.5 equiv) in THF at room temperature (Scheme 3). After 16 hours, the dihydropyranone had epimerized into a 50:50 mixture of diastereoisomers, with both obtained in  $>99:1$  er. This is consistent with the result from the initial NHC-catalysed process, suggesting that the initially formed *syn*-diastereoisomer is epimerized under the basic reaction conditions. In this case, it is likely that epimerisation occurs at the C (4) position and that the presence of conjugated electron-deficient aryl substituents in the C(6) position increases the propensity for deprotonation, which accounts for the reduced diastereoselectivity observed in these cases. However, selective epimerisation at the C(3) position adjacent to the lactone cannot be unambiguously ruled out.

## 2.4. Proposed mechanism

The proposed reaction mechanism is shown in Scheme 4. Initially, the catalytically active free NHC is generated through deprotonation of NHC precursor **2**. Nucleophilic addition of the free NHC **30** into the  $\alpha$ -aroyloxyaldehyde generates adduct **31**, which is likely to be the catalytic resting state.<sup>10b</sup> Reversible deprotonation of **31** transiently forms Breslow intermediate **32** that can eliminate 4-nitrobenzoate. The resulting enol **33** can be deprotonated to form the key azolium enolate intermediate **34**, which can undergo an enantioselective asynchronous *endo*-hetero-Diels-Alder reaction with an appropriate unsaturated ketoester. Finally, elimination from intermediate **35** releases the product *syn*-dihydropyranone and regenerates the free NHC catalyst. This mechanistic proposal is consistent with the computational studies from Bode and co-workers on related NHC-catalysed [4+2]-hetero-Diels-Alder processes.<sup>15</sup>



Scheme 4. Proposed reaction mechanism.

## 3. Conclusion

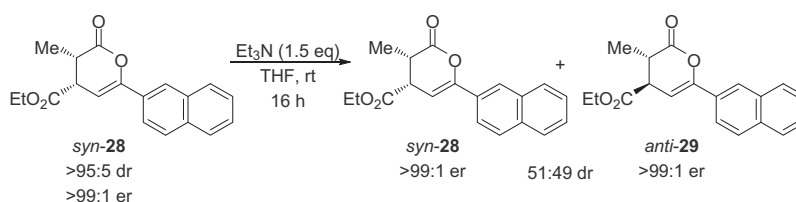
$\alpha$ -Aroyloxyaldehydes are efficient azolium enolate precursors in enantioselective NHC-catalysed [4+2] hetero-Diels-Alder reactions with unsaturated ketoesters. Reactions using either  $\beta,\gamma$ -unsaturated  $\alpha$ -ketoesters or  $\alpha,\beta$ -unsaturated  $\gamma$ -ketoesters form the corresponding *syn*-dihydropyranone products with generally high diastereoselectivity and excellent enantioselectivity. In cases where the unsaturated ketoester bears an electron-deficient aryl substituent, the initially-formed *syn*-dihydropyranones are more susceptible to epimerisation at the C(4)-position under the reaction conditions, which lowers the observed diastereoselectivity of the products.

## 4. Experimental

### 4.1. General

Anhydrous reactions were carried out in flame-dried glassware under an inert atmosphere ( $\text{N}_2$  or Ar) using standard vacuum line techniques. Anhydrous THF and  $\text{Et}_2\text{O}$  were obtained after passing through an alumina column (Mbraun SPS-800). Petrol is defined as petroleum ether 40–60 °C. All other solvents and commercial reagents were used as received without further purification.  $\alpha$ -Aroyloxyaldehydes were prepared according to previously reported procedures.<sup>10</sup>

Room temperature (rt) refers to 20–25 °C and a temperature of 0 °C was obtained using an ice/water bath. Reactions involving heating were performed using DrySyn blocks and a contact thermocouple. Under reduced pressure refers to the use of a rotary evaporator with vacuum controller.



Scheme 3. Base-promoted epimerisation of *syn*-**28**.



Analytical thin layer chromatography was performed on pre-coated aluminium plates (Kieselgel 60 F<sub>254</sub> silica) and visualisation was achieved using ultraviolet light (254 nm) and/or staining with a 1% aqueous KMnO<sub>4</sub> solution. Flash column chromatography was performed on Kieselgel 60 silica in the solvent system stated.

Melting points were recorded on an Electrothermal 9100 melting point apparatus, (dec) refers to decomposition. Optical rotations were measured on a Perkin Elmer Precisely/Model-341 polarimeter operating at the sodium d line with a 100 mm path cell at 20 °C.

HPLC analyses were obtained on either a Gilson HPLC consisting of a Gilson 305 pump, Gilson 306 pump, Gilson 811C dynamic mixer, Gilson 805 manometric module, Gilson 401C dilutor, Gilson 213XL sample injector and sample detection was performed with a Gilson 118 UV/vis detector or a Shimadzu HPLC consisting of a DGU-20A5 degasser, LC-20AT liquid chromatography SIL-20AHT autosampler, CMB-20A communications bus module, SPD-M20A diode array detector and a CTO-20A column oven. Separation was achieved using Chiralcel OD-H and OJ-H columns or a Chiralpak AD-H column. All HPLC traces were compared with an authentic racemic spectrum prepared in analogous fashion using ( $\pm$ )-**2**.

Infrared spectra ( $\nu_{\text{max}}$ ) were recorded on a Shimadzu IRAffinity-1 Fourier transform IR spectrophotometer using either thin film or solid using Pike MIRacle ATR accessory.

<sup>1</sup>H, <sup>13</sup>C{<sup>1</sup>H}, and <sup>19</sup>F{<sup>1</sup>H} NMR spectra were acquired on either a Bruker Avance 300 (<sup>1</sup>H 300 MHz; <sup>13</sup>C{<sup>1</sup>H} 75 MHz; <sup>19</sup>F{<sup>1</sup>H} 282 MHz), a Bruker Avance II 400 (<sup>1</sup>H 400 MHz; <sup>13</sup>C{<sup>1</sup>H} 100 MHz; <sup>19</sup>F{<sup>1</sup>H} 376 MHz), or a Bruker Ultrashield 500 (<sup>1</sup>H 500 MHz) spectrometer at room temperature in the deuterated solvent stated. All chemical shifts are quoted in parts per million (ppm) relative to the residual solvent peak. All coupling constants, *J*, are quoted in Hz. Multiplicities are indicated as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and multiples thereof. The abbreviation Ar denotes aromatic and *app* denotes apparent.

High resolution mass spectrometry (*m/z*) data was acquired by electrospray ionisation (ESI), atmospheric pressure chemical ionisation (APCI) or nanospray ionisation (NSI) at the EPSRC UK National Mass Spectrometry Facility at Swansea University.

## 4.2. General procedure for the synthesis of $\beta,\gamma$ -unsaturated $\alpha$ -ketoesters

**Part 1:** Based upon a literature procedure,<sup>16</sup> KOH (1.5 equiv) in MeOH (6 M) was added to a solution of pyruvic acid (1.0 equiv), the required aryl aldehyde (1.0 equiv) and MeOH (12 M) at 0 °C. The first equivalent of KOH solution was added dropwise over 30 min, the rest was added as one portion. The reaction mixture was heated at 40 °C for 1 h before being cooled to 0 °C and stirred overnight. The precipitate was collected by filtration and washed with cold MeOH ( $\times 2$ ) and Et<sub>2</sub>O before being dried under vacuum to give the desired  $\beta,\gamma$ -unsaturated  $\alpha$ -ketoacid potassium salt.

**Part 2:** Based upon a literature procedure procedure,<sup>17</sup> acetyl chloride (11.5 equiv) was added dropwise to the appropriate alcohol (0.2 M) at 0 °C before the required potassium salt (1.0 equiv) was added. The reaction mixture was warmed to rt and stirred for 2 h before being heated at reflux for 6 h. The solution was cooled to rt, concentrated under reduced pressure and then partitioned between CH<sub>2</sub>Cl<sub>2</sub> and H<sub>2</sub>O. The layers were separated and the aqueous layer extracted with CH<sub>2</sub>Cl<sub>2</sub> ( $\times 2$ ). The combined organic phases were washed with a saturated NaHCO<sub>3</sub> solution and H<sub>2</sub>O before being dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to give the crude  $\beta,\gamma$ -unsaturated  $\alpha$ -ketoester that was purified by column chromatography.

### 4.2.1. (E)-Methyl 2-oxo-4-phenylbut-3-enoate **8**

Following General Procedure 4.2 (part 1), KOH (16.8 g, 300 mmol) in MeOH (60 mL), pyruvic acid (13.8 mL, 200 mmol)

and benzaldehyde (20.4 mL, 200 mmol) in MeOH (15 mL) were reacted to give potassium (E)-2-oxo-4-phenylbut-3-enoate (39.0 g, 91%) as a yellow solid with spectroscopic data in accordance with the literature.<sup>18</sup> Mp 246–248 °C {Lit.<sup>18</sup> 248 °C}; <sup>1</sup>H NMR (400 MHz, D<sub>2</sub>O)  $\delta_{\text{H}}$ : 6.78 (1H, d, *J* 15.0, PhCH=CH), 7.34–7.42 (3H, m, Ar(3,4,5)*H*), 7.39 (1H, d, *J* 15.0, C PhCH=CH), 7.57–7.61 (2H, m, Ar(2,6)*H*).

Following General Procedure 4.2 (part 2), potassium (E)-2-oxo-4-phenylbut-3-enoate (7.48 g, 35 mmol) and acetyl chloride (28.6 mL, 402 mmol) in MeOH (200 mL) were reacted. The crude was purified by column chromatography (90:10 petrol:EtOAc), then recrystallised from MeOH to give **8** (1.16 g, 17%) as a yellow crystalline solid with spectroscopic data in accordance with the literature.<sup>18</sup> Mp 69–71 °C {Lit.<sup>18</sup> 69–70 °C}; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta_{\text{H}}$ : 3.94 (3H, s, OCH<sub>3</sub>), 7.38 (1H, d, *J* 16.1, HC=CH), 7.42–7.49 (3H, m, Ar*H*), 7.61–7.67 (2H, m, Ar*H*), 7.89 (1 H, d, *J* 16.2, HC=CH).

### 4.2.2. (E)-Ethyl 2-oxo-4-(*p*-tolyl)but-3-enoate **36**

Following General Procedure 4.2 (part 1), KOH (1.40 g, 24.9 mmol) in MeOH (5 mL), pyruvic acid (1.15 mL, 16.6 mmol) and *p*-tolualdehyde (1.96 mL, 16.6 mmol) in MeOH (2 mL) were reacted to give potassium (E)-2-oxo-4-(*p*-tolyl)but-3-enoate (2.78 g, 12.2 mmol, 73%) as yellow solid, with spectroscopic data in accordance with the literature.<sup>18</sup> Mp 242–244 °C (dec); <sup>1</sup>H NMR (400 MHz, D<sub>2</sub>O)  $\delta_{\text{H}}$ : 2.28 (3H, s, ArCH<sub>3</sub>), 6.74 (1H, d, *J* 16.4, ArCH=CH), 7.23 (2H, d, *J* 8.1, Ar*H*), 7.51 (2H, d, *J* 8.2, Ar*H*), 7.59 (1H, d, *J* 16.4, ArCH=CH).

Following General Procedure 4.2 (part 2), potassium (E)-2-oxo-4-(*p*-tolyl)but-3-enoate (1.00 g, 4.38 mmol) and acetyl chloride (3.58 mL, 50.4 mmol) in ethanol (30 mL) were reacted. The crude was purified by column chromatography (95:5 petrol:EtOAc) to give **36** (0.560 g, 58%) as a yellow solid, with spectroscopic data in accordance with the literature.<sup>17</sup> Mp 40–42 °C {Lit.<sup>17</sup> 47–48 °C}; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta_{\text{H}}$ : 1.41 (3H, t, *J* 7.1, OCH<sub>2</sub>CH<sub>3</sub>), 2.40 (3H, s, ArCH<sub>3</sub>), 4.39 (2H, q, *J* 7.1, OCH<sub>2</sub>CH<sub>3</sub>), 7.23 (2H, d, *J* 7.9, Ar*H*), 7.32 (1H, d, *J* 16.1, ArCH=CH), 7.53 (2H, d, *J* 8.2, Ar*H*), 7.84 (1H, d, *J* 16.1, ArCH=CH).

### 4.2.3. (E)-Methyl 4-(4-methoxyphenyl)-2-oxobut-3-enoate **37**

Following General Procedure 4.2 (part 1), KOH (1.11 g, 19.8 mmol) in MeOH (4 mL), pyruvic acid (0.917 mL, 13.2 mmol) and *p*-anisaldehyde (1.80 g, 1.61 mL, 13.2 mmol) in MeOH (1.5 mL) were reacted to give potassium (E)-4-(4-methoxyphenyl)-2-oxobut-3-enoate (2.31 g, 72%) as a yellow solid, with spectroscopic data in accordance with the literature.<sup>16</sup> Mp 250–252 °C {Lit.<sup>16</sup> 248 °C}; <sup>1</sup>H NMR (400 MHz, D<sub>2</sub>O)  $\delta_{\text{H}}$ : 6.66 (1H, d, *J* 16.4, CH=CH), 6.95 (2H, d, *J* 8.8, Ar*H*), 7.50–7.69 (3H, m, Ar*H* and CH=CH).

Following General Procedure 4.2 (part 2), potassium (E)-2-oxo-4-(4-methoxyphenyl)but-3-enoate (2.00 g, 8.19 mmol) and acetyl chloride (6.70 mL, 94.2 mmol) in MeOH (60 mL) were reacted. The crude was purified by column chromatography (85:15 petrol:EtOAc) to give **37** (1.37 g, 76%) as a yellow crystalline solid, with spectroscopic data in accordance with the literature.<sup>18</sup> Mp 95–96 °C {Lit.<sup>18</sup> 99–100 °C}; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta_{\text{H}}$ : 3.80 (3H, s, OCH<sub>3</sub>), 3.86 (3H, s, OCH<sub>3</sub>), 6.87 (2H, d, *J* 8.8, Ar*H*), 7.19 (1H, d, *J* 16.0, ArCH=CH), 7.54 (2H, d, *J* 8.5, Ar*H*), 7.79 (1H, d, *J* 16.0, ArCH=CH).

### 4.2.4. (E)-Methyl 4-(4-fluorophenyl)-2-oxobut-3-enoate **38**

Following General Procedure 4.2 (part 1), KOH (1.36 g, 24.2 mmol) in MeOH (6 mL), pyruvic acid (1.12 mL, 16.1 mmol) and 4-fluorobenzaldehyde (2.00 g, 1.73 mL, 16.1 mmol) in MeOH (2 mL) were reacted to give potassium (E)-4-(4-fluorophenyl)-2-oxobut-3-enoate (2.67 g, 71%) as a yellow solid, with spectroscopic data in accordance with the literature.<sup>19</sup> Mp 205–208 °C (dec); <sup>1</sup>H

NMR (500 MHz, D<sub>2</sub>O)  $\delta_{\text{H}}$ : 6.73 (1H, d, *J* 16.3, ArCH=CH), 7.11 (2H, t, *J* 8.2, ArC(2)H), 7.59 (1H, d, *J* 16.4, ArCH=CH), 7.64 (2H, dd, *J* 7.4, 5.2, ArC(3)H); <sup>19</sup>F NMR (376 MHz, D<sub>2</sub>O)  $\delta_{\text{F}}$ : –109.0 (ArC(4)F).

Following General Procedure 4.2 (part 2), potassium (*E*)-4-(4-fluorophenyl)-2-oxobut-3-enoate (1.00 g, 4.31 mmol) and acetyl chloride (3.53 mL, 49.6 mmol) in MeOH (40 mL) were reacted. The crude was purified by column chromatography (95:5 petrol:EtOAc) to give (*E*)-methyl 4-(4-fluorophenyl)-2-oxobut-3-enoate (0.320 g, 36%) as a yellow crystalline solid, with spectroscopic data in accordance with the literature.<sup>20</sup> Mp 86–87 °C;  $\nu_{\text{max}}$  (solid) 1722 (C=O), 1690 (C=O); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta_{\text{H}}$ : 3.87 (3H, s, OCH<sub>3</sub>), 7.06 (2H, t, *J* 8.6, ArC(3)H), 7.25 (1H, dd, *J* 16.2, 0.6, CH=CH), 7.58 (2H, dd, *J* 8.7, 5.4, ArC(2)H), 7.78 (1H, d, *J* 16.1, CH=CH); <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>)  $\delta_{\text{F}}$ : –107.3 (tt, *J* 8.1, 5.5, C(4)F); <sup>13</sup>C{<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>)  $\delta_{\text{C}}$ : 53.1 (OCH<sub>3</sub>), 116.4 (d, *J* 22.0, C(3)), 120.1 (d, *J* 2.2, ArCH=CH), 130.3 (d, *J* 3.1, C(1)), 131.2 (d, *J* 8.8, C(2)), 147.2 (ArCH=CH), 162.5 (CO<sub>2</sub>), 164.7 (d, *J* 253.9, C(4)), 182.1 (CH=CHCO); HRMS (ESI<sup>+</sup>) C<sub>11</sub>H<sub>10</sub>O<sub>3</sub>F [M+H]<sup>+</sup> found 209.0610, requires 209.0608 (+0.7 ppm).

#### 4.2.5. (*E*)-Methyl 4-(4-bromophenyl)-2-oxobut-3-enoate 39

Following General Procedure 4.2 (part 1), KOH (4.55 g, 81.1 mmol) in MeOH (15 mL), pyruvic acid (3.81 mL, 54.1 mmol) and 4-bromobenzaldehyde (10.0 g, 54.1 mmol) in MeOH (15 mL) were reacted to give potassium (*E*)-2-oxo-4-(4-bromophenyl)but-3-enoate (15.9 g, 84%) as a yellow solid, with spectroscopic data in accordance with the literature.<sup>18</sup> Mp 240 °C (dec) [Lit.<sup>18</sup> 233 °C]; <sup>1</sup>H NMR (400 MHz, D<sub>2</sub>O)  $\delta_{\text{H}}$ : 6.91 (1H, d, *J* 17.1, C(3)H), 7.59–7.60 (2H, m, Ar(3,5)H), 7.62 (1H, d, *J* 17.1, C(4)H), 7.65–7.68 (2H, m, Ar(2,6)H).

Following General Procedure 4.2 (part 2), potassium (*E*)-2-oxo-4-(4-bromophenyl)but-3-enoate (2.00 g, 6.82 mmol) and acetyl chloride (5.57 mL, 78.4 mmol) in MeOH (40 mL) were reacted. The crude was purified by column chromatography (95:5 petrol:EtOAc) to give **39** (1.21 g, 66%) as a yellow crystalline solid, with spectroscopic data in accordance with the literature.<sup>18</sup> Mp 109–112 °C [Lit.<sup>18</sup> 120 °C]; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta_{\text{H}}$ : 3.87 (3H, s, OCH<sub>3</sub>), 7.31 (1H, d, *J* 16.1, ArCH=CH), 7.43 (2H, d, *J* 8.5, ArH), 7.50 (2H, d, *J* 8.5, ArH), 7.74 (1H, d, *J* 16.1, ArCH=CH).

#### 4.2.6. (*E*)-Methyl 4-(naphthalen-2-yl)-2-oxobut-3-enoate 40

Following General Procedure 4.2 (part 1), KOH (1.08 g, 19.2 mmol) in MeOH (3 mL), pyruvic acid (0.890 mL, 12.8 mmol) and 2-naphthaldehyde (2.00 g, 12.8 mmol) in MeOH (3 mL) were reacted to give potassium (*E*)-4-(naphthalen-2-yl)-2-oxobut-3-enoate (2.46 g, 73%) as a yellow solid, with spectroscopic data in accordance with the literature.<sup>18</sup> Mp >320 °C [Lit.<sup>18</sup> 270–272 °C (dec)]; <sup>1</sup>H NMR (400 MHz, D<sub>2</sub>O)  $\delta_{\text{H}}$ : 6.85 (1H, d, *J* 16.5, ArCH=CH), 7.50 (2H, s, ArH), 7.65–7.74 (2H, m, ArH, and ArCH=CH), 7.81–7.86 (3H, m, ArH), 7.99 (1H, s, Ar(1)H).

Following General Procedure 4.2 (part 2), potassium (*E*)-4-(naphthalen-2-yl)-2-oxobut-3-enoate (1.00 g, 3.78 mmol) and acetyl chloride (3.08 mL, 43.5 mmol) in MeOH (30 mL) were reacted. The crude was purified by column chromatography (95:5 petrol:EtOAc) to give **40** (0.570 g, 63%) as a yellow solid, with spectroscopic data in accordance with the literature.<sup>18</sup> Mp 94–96 °C [Lit.<sup>18</sup> 70–72 °C]; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta_{\text{H}}$ : 3.96 (3H, s, OCH<sub>3</sub>), 7.49 (1H, d, *J* 16.1, ArCH=CH), 7.52–7.61 (2H, m, ArH), 7.77 (1H, dd, *J* 8.6, 1.8, ArH), 7.84–7.93 (3H, m, ArH), 8.02–8.09 (2H, m, ArCH=CH and ArH).

### 4.3. General procedure for the NHC-catalysed redox hetero-Diels-Alder reaction with $\beta,\gamma$ -unsaturated $\alpha$ -ketoesters

The appropriate  $\alpha$ -aroyloxyaldehyde (1.5 equiv),  $\beta,\gamma$ -unsaturated  $\alpha$ -ketoester (1.0 equiv) and NHC precatalyst **2** (10 mol %)

were dissolved in anhydrous THF (0.075 M) in a sealed vial containing 3 Å molecular sieves. The solution was cooled to 0 °C before Et<sub>3</sub>N (1.5 equiv) was added. The reaction was stirred, allowing to warm to rt, until complete by TLC analysis. The mixture was diluted with EtOAc and washed successively with 1 M HCl, saturated NaHCO<sub>3</sub> and brine. The organic layer was dried with MgSO<sub>4</sub>, filtered and concentrated under reduced pressure to give the crude product, which was purified by column chromatography.

#### 4.3.1. (3*S*,4*S*)-Methyl 3-benzyl-2-oxo-4-phenyl-3,4-dihydro-2H-pyran-6-carboxylate 9

Following General Procedure 4.3, 1-oxo-3-phenylpropan-2-yl 4-nitrobenzoate **7** (50 mg, 0.17 mmol), (*E*)-methyl 2-oxo-4-phenylbut-3-enoate **8** (21.0 mg, 0.11 mmol), NHC precatalyst **2** (4.0 mg, 11  $\mu$ mol), Et<sub>3</sub>N (23  $\mu$ L, 0.17 mmol) and THF (3 mL) were reacted for 12 h. The crude (>95:5 dr) was purified by column chromatography (90:10 petrol:EtOAc) to give **9** (51 mg, 93%) as a colourless solid. Mp 106–107 °C;  $[\alpha]_{\text{D}}^{20}$  = +398 (c 0.23, CHCl<sub>3</sub>); Chiral HPLC analysis, Chiralpak AD-H (90:10 hexane:IPA, flow rate 1.0 mL min<sup>–1</sup>, 254 nm, 30 °C) *t*<sub>R</sub> (R,R) 18.0 min, *t*<sub>R</sub> (S,S) 27.8 min, >99:1 er;  $\nu_{\text{max}}$  (KBr, cm<sup>–1</sup>) 2956, 2925, 1765, 1628, 1664, 1602, 1495, 1435, 1316, 1100; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta_{\text{H}}$ : 2.33 (1H, dd, *J* 10.6, 15.8, C(3)CH<sup>A</sup>H<sup>B</sup>), 3.16–3.23 (2H, m, C(3)CH<sup>A</sup>H<sup>B</sup> and C(3)H), 3.55 (1H, t, *J* 6.8, C(4)H), 3.77 (3H, OCH<sub>3</sub>), 6.58 (1H, d, *J* 6.7, C(5)H), 6.93–7.00 (4H, m, C(3)ArH), 7.15–7.26 (6H, m, C(3)ArH and C(3)CH<sub>2</sub>ArH); <sup>13</sup>C{<sup>1</sup>H} NMR (75 MHz, CDCl<sub>3</sub>)  $\delta_{\text{C}}$ : 32.1 (C(3)CH<sub>2</sub>), 40.6 (C(3)H), 44.8 (C(4)H), 52.7 (OCH<sub>3</sub>), 118.8 (C(5)), 126.8 (C(3)CH<sub>2</sub>ArC(4)), 128.4 (C(4)ArC(4)), 128.4 (ArC), 128.7 (ArC), 128.9 (ArC), 129.2 (ArC), 135.8 (CPh-1), 138.1 (C(3)CH<sub>2</sub>ArC(1)), 141.9 (C(6)), 161.0 (CO<sub>2</sub>Me), 168.5 (C(2)); HRMS (ESI<sup>+</sup>) C<sub>20</sub>H<sub>22</sub>O<sub>4</sub>N [M+NH<sub>4</sub>]<sup>+</sup> found 340.1544, requires 340.1543 (+0.2 ppm).

#### 4.3.2. (3*S*,4*S*)-Methyl 3-butyl-2-oxo-4-phenyl-3,4-dihydro-2H-pyran-6-carboxylate 10

Following General Procedure 4.3, 1-oxohexan-2-yl 4-nitrobenzoate (50 mg, 0.19 mmol), (*E*)-methyl 2-oxo-4-phenylbut-3-enoate **8** (25.2 mg, 0.13 mmol), NHC precatalyst **2** (4.2 mg, 10.0  $\mu$ mol), Et<sub>3</sub>N (28  $\mu$ L, 0.19 mmol) and THF (3 mL) were reacted for 3 h. The crude (>95:5 dr) was purified by column chromatography (95:5 petrol:EtOAc) to give **10** (26 mg, 69%) as a colourless oil.  $[\alpha]_{\text{D}}^{20}$  = +156 (c 0.15, CHCl<sub>3</sub>); Chiral HPLC analysis, Chiralpak AD-H (95:5 hexane:IPA, flow rate 1.0 mL min<sup>–1</sup>, 220 nm) *t*<sub>R</sub> (R,R) 16.2 min, *t*<sub>R</sub> (S,S) 18.3 min, 98:2 er;  $\nu_{\text{max}}$  (ATR, cm<sup>–1</sup>) 2954, 1773, 1734, 1661, 1454, 1437, 1323, 1259, 1045; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta_{\text{H}}$ : 0.81 (3H, t, *J* 7.1, CH<sub>2</sub>CH<sub>3</sub>), 1.08–1.40 (5H, m, CH<sub>2</sub>  $\times$  2 and C(3)CH<sup>A</sup>H<sup>B</sup>), 1.60–1.70 (1H, m, C(3)CH<sup>A</sup>H<sup>B</sup>), 2.79 (1H, d, *J* 6.9, C(3)H), 3.79 (1H, t, *J* 6.7, C(4)H), 3.83 (3H, s, OCH<sub>3</sub>), 6.68 (1H, d, *J* 6.4, C(5)H), 7.06 (2H, dt, *J* 1.8, 5.8, ArC(2)H), 7.23–7.29 (3H, m, ArC(3)H and ArC(4)H); <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>)  $\delta_{\text{C}}$ : 13.9 (CH<sub>3</sub>), 22.5 (CH<sub>2</sub>), 26.0 (CH<sub>2</sub>), 29.4 (CH<sub>2</sub>), 41.5 (C(4)), 43.4 (C(3)), 52.7 (OCH<sub>3</sub>), 118.4 (C(5)), 128.1 (CPhH-2,6), 128.1 (CPh-4), 129.1 (ArC(3)), 136.0 (ArC(1)), 142.1 (C(6)), 161.1 (CO<sub>2</sub>Me), 168.8 (C(2)); HRMS (ESI<sup>+</sup>) C<sub>17</sub>H<sub>24</sub>O<sub>4</sub>N [M+NH<sub>4</sub>]<sup>+</sup> found 306.1702, requires 306.1700 (+0.7 ppm).

#### 4.3.3. (3*S*,4*S*)-Methyl 3-isobutyl-2-oxo-4-phenyl-3,4-dihydro-2H-pyran-6-carboxylate 11

Following General Procedure 4.3, 4-methyl-1-oxopentan-2-yl 4-nitrobenzoate **7** (133 mg, 0.50 mmol), (*E*)-methyl 2-oxo-4-phenylbut-3-enoate **8** (63.0 mg, 0.33 mmol), NHC precatalyst **2** (12.0 mg, 33  $\mu$ mol), Et<sub>3</sub>N (70  $\mu$ L, 0.50 mmol) and THF (5 mL) were reacted for 24 h. The crude (>95:5 dr) was purified by column chromatography (95:5 petrol:EtOAc) to give **11** (60 mg, 63%) as a colourless oil.  $[\alpha]_{\text{D}}^{20}$  = +279 (c 0.14, CHCl<sub>3</sub>); Chiral HPLC analysis, Chiralpak AD-H (95:5 hexane:IPA, flow rate 1.0 mL min<sup>–1</sup>, 220 nm) *t*<sub>R</sub> (R,R)

11.9 min,  $t_R$  (S,S) 13.0 min, >99:1 er;  $\nu_{\max}$  (KBr,  $\text{cm}^{-1}$ ) 2959, 1769, 1708, 1661, 1317, 1265, 1094, 1082;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$ : 0.83 (3H, d,  $J$  6.6,  $\text{CH}_3$ ), 0.88 (3H, d,  $J$  6.6,  $\text{CH}_3$ ), 1.04 (1H, app dt,  $J$  7.0, 14.0,  $i\text{-BuCH}$ ), 1.56 (2H, dt,  $J$  7.0, 13.9,  $\text{C}(3)\text{CH}^{\text{A}}\text{H}^{\text{B}}$ ), 1.72 (1H, dd,  $J$  7.0, 14.0,  $\text{C}(3)\text{CH}_2\text{H}_a$ ), 2.93 (1H, app q,  $J$  6.9,  $\text{C}(3)\text{H}$ ), 3.77 (1H, t,  $J$  6.7,  $\text{C}(4)\text{H}$ ), 3.87 (3H, s,  $\text{OCH}_3$ ), 6.72 (1H, d,  $J$  6.4,  $\text{C}(5)\text{H}$ ), 7.07–7.10 (2H, dt,  $J$  1.8, 5.8,  $\text{ArC}(2)\text{H}$ ), 7.27–7.34 (3H, m,  $\text{ArC}(3)\text{H}$  and  $\text{ArC}(4)\text{H}$ );  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$ : 22.2 ( $(\text{CH}_3)_2\text{CH}$ ), 22.5 ( $(\text{CH}_3)_2\text{CH}$ ), 25.2 ( $(\text{CH}_3)_2\text{CH}$ ), 35.2 ( $\text{C}(3)\text{CH}_2$ ), 41.2 ( $\text{C}(3)$ ), 41.7 ( $\text{C}(4)$ ), 52.7 ( $\text{OCH}_3$ ), 118.4 ( $\text{C}(5)$ ), 128.1 ( $\text{ArC}(2)$ ), 128.1 ( $\text{ArC}(4)$ ), 129.1 ( $\text{ArC}(3)$ ), 136.0 ( $\text{ArC}(1)$ ), 142.1 ( $\text{C}(6)$ ), 161.1 ( $\text{CO}_2\text{Me}$ ), 168.9 ( $\text{C}(2)$ ); HRMS (ESI+)  $\text{C}_{17}\text{H}_{24}\text{O}_4\text{N}$ ,  $[\text{M}+\text{NH}_4]^+$  found 306.1704; requires 306.1700 (+1.4 ppm).

#### 4.3.4. (3S,4S)-Ethyl 3-benzyl-2-oxo-4-(*p*-tolyl)-3,4-dihydro-2H-pyran-6-carboxylate 12

Following General Procedure 4.3, 1-oxohexan-2-yl 4-nitrobenzoate **7** (202 mg, 0.675 mmol), (*E*)-ethyl 4-(*p*-tolyl)-2-oxobut-3-enoate **36** (98.2 mg, 0.450 mmol), NHC precatalyst **2** (16.6 mg, 45.0  $\mu\text{mol}$ ),  $\text{Et}_3\text{N}$  (94.1  $\mu\text{L}$ , 0.675 mmol) and THF (10 mL) were reacted for 12 h. The crude (94:6 dr) was purified by column chromatography (95:5 petrol:EtOAc) to give **12** (122 mg, 77%) as a pale yellow oil, with spectroscopic data in accordance with the literature.<sup>6b</sup>  $[\alpha]_{\text{D}}^{20} = +299.4$  (c 0.5,  $\text{CHCl}_3$ ) {Lit.<sup>6b</sup>  $[\alpha]_{\text{D}}^{20} = +310.3$  (c 1.0,  $\text{CHCl}_3$ )}; Chiral HPLC analysis, Chiralcel OD-H (90:10 hexane:IPA, flow rate 0.5 mL  $\text{min}^{-1}$ , 254 nm, 30 °C)  $t_R$  (3R,4R): 19.7 min,  $t_R$  (3S,4S): 23.5 min, 96:4 er;  $\nu_{\max}$  (film,  $\text{cm}^{-1}$ ) 2981, 1773, 1732;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$ : 1.34 (3H, t,  $J$  7.1,  $\text{OCH}_2\text{CH}_3$ ), 2.36 (3H, s,  $\text{C}(4)\text{ArC}(4)\text{CH}_3$ ), 2.43 (1H, dd,  $J$  15.8, 10.5,  $\text{C}(3)\text{H}$ ), 3.22–3.32 (2H, m,  $\text{C}(3)\text{CH}_2$ ), 3.60 (1H, t,  $J$  6.8,  $\text{C}(4)\text{H}$ ), 4.31 (2H, q,  $J$  7.1,  $\text{OCH}_2\text{CH}_3$ ), 6.66 (1H, d,  $J$  6.7,  $\text{C}(5)\text{H}$ ), 6.93 (2H, d,  $J$  8.1,  $\text{C}(3)\text{CH}_2\text{ArC}(2)\text{H}$ ), 7.09 (2H, d,  $J$  6.8,  $\text{C}(4)\text{ArC}(2)\text{H}$ ), 7.16 (2H, d,  $J$  7.8,  $\text{C}(4)\text{ArC}(3)\text{H}$ ), 7.21–7.36 (3H, m,  $\text{C}(3)\text{CH}_2\text{ArC}(3)\text{H}$  and  $\text{C}(3)\text{CH}_2\text{ArC}(4)\text{H}$ );  $^{13}\text{C}\{^1\text{H}\}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$ : 14.2 ( $\text{OCH}_2\text{CH}_3$ ), 21.1 ( $\text{C}(4)\text{ArC}(4)\text{CH}_3$ ), 32.1 ( $\text{C}(3)\text{CH}_2$ ), 40.2 ( $\text{C}(4)$ ), 44.9 ( $\text{C}(3)$ ), 61.9 ( $\text{OCH}_2\text{CH}_3$ ), 118.8 ( $\text{C}(5)$ ), 126.7 ( $\text{C}(3)\text{CH}_2\text{ArC}(4)$ ), 128.3 ( $\text{C}(3)\text{CH}_2\text{ArC}(3)$ ), 128.6 ( $\text{C}(3)\text{CH}_2\text{ArC}(2)$ ), 129.0 ( $\text{C}(4)\text{ArC}(2)$ ), 129.9 ( $\text{C}(4)\text{ArC}(3)$ ), 132.7 ( $\text{C}(4)\text{ArC}(1)$ ), 138.1 ( $\text{C}(4)\text{ArC}(4)$ ), 138.2 ( $\text{C}(3)\text{CH}_2\text{ArC}(4)$ ), 141.9 ( $\text{C}(6)$ ), 160.5 ( $\text{CO}_2\text{Et}$ ), 168.7 ( $\text{C}(2)$ ).

#### 4.3.5. (3S,4S)-Methyl 3-benzyl-4-(4-methoxyphenyl)-2-oxo-3,4-dihydro-2H-pyran-6-carboxylate 13

Following General Procedure 4.3, 1-oxo-3-phenylpropan-2-yl 4-nitrobenzoate **7** (202 mg, 0.675 mmol), (*E*)-methyl 4-(4-methoxyphenyl)-2-oxobut-3-enoate **37** (99.1 mg, 0.450 mmol), NHC precatalyst **2** (16.6 mg, 45.0  $\mu\text{mol}$ ),  $\text{Et}_3\text{N}$  (94.1  $\mu\text{L}$ , 0.675 mmol) and THF (10 mL) were reacted for 16 h. The crude (91:9 dr) was purified by column chromatography (90:10 petrol:EtOAc) to give **13** (98.3 mg, 62%) as a pale yellow oil.  $[\alpha]_{\text{D}}^{20} = +277.3$  (c 0.5,  $\text{CHCl}_3$ ); Chiral HPLC analysis, Chiralcel OD-H (90:10 hexane:IPA, flow rate 0.5 mL  $\text{min}^{-1}$ , 220 nm, 30 °C)  $t_R$  (3R,4R): 40.7 min,  $t_R$  (3S,4S): 45.0 min, >99:1 er;  $\nu_{\max}$  (film,  $\text{cm}^{-1}$ ) 2955, 1771, 1734;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$ : 2.41 (1H, dd,  $J$  15.7, 10.6,  $\text{C}(3)\text{H}$ ), 3.21–3.30 (2H, m,  $\text{C}(3)\text{CH}_2$ ), 3.58 (1H, t,  $J$  6.7,  $\text{C}(4)\text{H}$ ), 3.80 (3H, s,  $\text{OCH}_3$ ), 3.84 (3H, s,  $\text{CO}_2\text{CH}_3$ ), 6.65 (1H, d,  $J$  6.8,  $\text{C}(5)\text{H}$ ), 6.86 (2H, d,  $J$  8.8,  $\text{C}(4)\text{ArC}(2)\text{H}$ ), 6.93 (2H, d,  $J$  8.8,  $\text{C}(4)\text{ArC}(3)\text{H}$ ), 7.04–7.11 (2H, m,  $\text{C}(3)\text{CH}_2\text{ArC}(2)\text{H}$ ), 7.20–7.35 (3H, m,  $\text{C}(3)\text{CH}_2\text{ArC}(3)\text{H}$  and  $\text{C}(3)\text{CH}_2\text{ArC}(4)\text{H}$ );  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$ : 30.9 ( $\text{C}(3)\text{CH}_2$ ), 38.7 ( $\text{C}(4)$ ), 43.9 ( $\text{C}(3)$ ), 51.6 ( $\text{CO}_2\text{CH}_3$ ), 54.3 ( $\text{C}(4)\text{ArC}(4)\text{OCH}_3$ ), 113.5 ( $\text{C}(4)\text{ArC}(2)$ ), 118.1 ( $\text{C}(5)$ ), 125.7 ( $\text{C}(3)\text{CH}_2\text{ArC}(1)$ ), 126.4 ( $\text{C}(4)\text{ArC}(1)$ ), 127.6 ( $\text{C}(3)\text{CH}_2\text{ArC}(3)$ ), 127.9 ( $\text{C}(3)\text{CH}_2\text{ArC}(2)$ ), 128.9 ( $\text{C}(4)\text{ArC}(3)$ ), 137.1 ( $\text{C}(3)\text{CH}_2\text{ArC}(1)$ ), 140.5 ( $\text{C}(6)$ ), 158.5 ( $\text{C}(4)\text{ArC}(4)$ ), 160.0 ( $\text{CO}_2\text{Me}$ ), 167.6 ( $\text{C}(2)$ ); HRMS (ESI+)  $\text{C}_{21}\text{H}_{24}\text{O}_5\text{N}_1$   $[\text{M}+\text{NH}_4]^+$  found 370.1655, requires 370.1649 (+1.6 ppm).

#### 4.3.6. (3S,4S)-Ethyl 3-butyl-2-oxo-4-(*p*-tolyl)-3,4-dihydro-2H-pyran-6-carboxylate 14

Following General Procedure 4.3, 1-oxohexan-2-yl 4-nitrobenzoate (200 mg, 0.750 mmol), (*E*)-ethyl 2-oxo-4-(*p*-tolyl)but-3-enoate **36** (109 mg, 0.500 mmol), NHC precatalyst **2** (18.4 mg, 50.0  $\mu\text{mol}$ ),  $\text{Et}_3\text{N}$  (105  $\mu\text{L}$ , 0.750 mmol) and THF (10 mL) were reacted for 9 h. The crude (92:8 dr) was purified by column chromatography (95:5 petrol:EtOAc) to give **14** (110 mg, 70%) as a pale yellow oil.  $[\alpha]_{\text{D}}^{20} = +249.2$  (c 0.5,  $\text{CHCl}_3$ ); Chiral HPLC analysis, Chiralpak AD-H (95:5 hexane:IPA, flow rate 1 mL  $\text{min}^{-1}$ , 254 nm, 30 °C)  $t_R$  (3S,4S): 11.3 min,  $t_R$  (3R,4R): 13.7 min, >99:1 er;  $\nu_{\max}$  (film,  $\text{cm}^{-1}$ ) 2957, 1773, 1732;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$ : 0.78 (3H, t,  $J$  7.2,  $\text{CH}_2\text{CH}_3$ ), 1.04–1.38 (7H, m,  $(\text{CH}_2)_2$  and  $\text{OCH}_2\text{CH}_3$ ), 1.54–1.71 (2H, m,  $\text{CH}_2$ ), 2.24 (3H, s,  $\text{ArC}(4)\text{CH}_3$ ), 2.73 (1H, q,  $J$  7.0,  $\text{C}(3)\text{H}$ ), 3.70 (1H, t,  $J$  6.8,  $\text{C}(4)\text{H}$ ), 4.24 (2H, q,  $J$  7.1,  $\text{OCH}_2\text{CH}_3$ ), 6.62 (1H, d,  $J$  6.4,  $\text{C}(5)\text{H}$ ), 6.91 (2H, d,  $J$  8.1,  $\text{ArC}(2)\text{H}$ ), 7.04 (2H, d,  $J$  7.8,  $\text{ArC}(3)\text{H}$ );  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$ : 13.9 ( $\text{OCH}_2\text{CH}_3$ ), 14.2 ( $\text{CH}_2\text{CH}_3$ ), 21.1 ( $\text{ArC}(4)\text{CH}_3$ ), 22.5 ( $\text{CH}_2$ ), 26.0 ( $\text{CH}_2$ ), 29.4 ( $\text{CH}_2$ ), 41.1 ( $\text{C}(4)$ ), 43.4 ( $\text{C}(3)$ ), 61.9 ( $\text{OCH}_2\text{CH}_3$ ), 118.4 ( $\text{C}(5)$ ), 127.9 ( $\text{ArC}(2)$ ), 129.8 ( $\text{ArC}(3)$ ), 132.9 ( $\text{ArC}(1)$ ), 137.9 ( $\text{ArC}(4)$ ), 142.1 ( $\text{C}(6)$ ), 160.6 ( $\text{CO}_2\text{Et}$ ), 169.0 ( $\text{C}(2)$ ); HRMS (ESI+)  $\text{C}_{19}\text{H}_{28}\text{O}_4\text{N}$   $[\text{M}+\text{NH}_4]^+$  found 334.2019, requires 334.2013 (+1.8 ppm).

#### 4.3.7. (3S,4S)-Methyl 3-butyl-4-(4-methoxyphenyl)-2-oxo-3,4-dihydro-2H-pyran-6-carboxylate 15

Following General Procedure 4.3, 1-oxohexan-2-yl 4-nitrobenzoate (200 mg, 0.750 mmol), (*E*)-methyl 4-(4-methoxyphenyl)-2-oxobut-3-enoate **37** (110 mg, 0.500 mmol), NHC precatalyst **2** (18.4 mg, 50.0  $\mu\text{mol}$ ),  $\text{Et}_3\text{N}$  (105  $\mu\text{L}$ , 0.750 mmol) and THF (10 mL) were reacted for 14 h. The crude (92:8 dr) was purified by column chromatography (95:5 petrol:EtOAc) to give **15** (114 mg, 72%) as a pale yellow oil.  $[\alpha]_{\text{D}}^{20} = +245.1$  (c 0.5,  $\text{CHCl}_3$ ); Chiral HPLC analysis, Chiralpak AD-H (90:10 hexane:IPA, flow rate 0.5 mL  $\text{min}^{-1}$ , 220 nm, 30 °C)  $t_R$  (3S,4S): 30.5 min,  $t_R$  (3R,4R): 32.6 min, >99:1 er;  $\nu_{\max}$  (film,  $\text{cm}^{-1}$ ) 2955, 1771, 1734;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$ : 0.84 (3H, t,  $J$  7.1,  $\text{CH}_2\text{CH}_3$ ), 1.09–1.43 (5H, m,  $(\text{CH}_2)_2$  and  $\text{C}(3)\text{CH}^{\text{A}}\text{H}^{\text{B}}$ ), 1.58–1.76 (1H, m,  $\text{C}(3)\text{CH}^{\text{A}}\text{H}^{\text{B}}$ ), 2.78 (1H, q,  $J$  6.9,  $\text{C}(3)\text{H}$ ), 3.73–3.80 (4H, m,  $\text{ArC}(4)\text{OCH}_3$  and  $\text{C}(4)\text{H}$ ), 3.85 (3H, s,  $\text{CO}_2\text{CH}_3$ ), 6.69 (1H, d,  $J$  6.5,  $\text{C}(5)\text{H}$ ), 6.83 (2H, d,  $J$  8.7,  $\text{ArC}(2)\text{H}$ ), 7.00 (2H, d,  $J$  8.7,  $\text{ArC}(3)\text{H}$ );  $^{13}\text{C}\{^1\text{H}\}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$ : 12.8 ( $\text{CH}_2\text{CH}_3$ ), 21.4 ( $\text{CH}_2$ ), 24.9 ( $\text{CH}_2$ ), 28.3 ( $\text{CH}_2$ ), 39.6 ( $\text{C}(4)$ ), 42.5 ( $\text{C}(3)$ ), 51.6 ( $\text{CO}_2\text{CH}_3$ ), 54.3 ( $\text{ArC}(4)\text{OCH}_3$ ), 113.4 ( $\text{ArC}(2)$ ), 117.7 ( $\text{C}(5)$ ), 126.7 ( $\text{ArC}(1)$ ), 128.1 ( $\text{ArC}(3)$ ), 140.8 ( $\text{C}(6)$ ), 158.3 ( $\text{ArC}(4)$ ), 160.1 ( $\text{CO}_2\text{Me}$ ), 167.9 ( $\text{C}(2)$ ); HRMS (ESI+)  $\text{C}_{18}\text{H}_{26}\text{O}_5\text{N}$   $[\text{M}+\text{NH}_4]^+$  found 336.1812, requires 336.1805 (+1.9 ppm).

#### 4.3.8. (3S,4S)-Methyl 4-(4-bromophenyl)-3-butyl-2-oxo-3,4-dihydro-2H-pyran-6-carboxylate 16

Following General Procedure 4.3, 1-oxohexan-2-yl 4-nitrobenzoate (200 mg, 0.750 mmol), (*E*)-methyl 4-(4-bromophenyl)-2-oxobut-3-enoate **39** (135 mg, 0.500 mmol), NHC precatalyst **2** (18.4 mg, 50.0  $\mu\text{mol}$ ),  $\text{Et}_3\text{N}$  (105  $\mu\text{L}$ , 0.750 mmol) and THF (10 mL) were for 4 h. The crude (89:11 dr) was purified by column chromatography (95:5 petrol:EtOAc) to give **16** (77.1 mg, 42%) as a pale yellow oil.  $[\alpha]_{\text{D}}^{20} = +205.3$  (c 0.5,  $\text{CHCl}_3$ ); Chiral HPLC analysis, Chiralpak AD-H (95:5 hexane:IPA, flow rate 1 mL  $\text{min}^{-1}$ , 220 nm, 30 °C)  $t_R$  (3S,4S): 15.1 min,  $t_R$  (3R,4R): 17.7 min, 99:1 er;  $\nu_{\max}$  (film,  $\text{cm}^{-1}$ ) 2955, 1773, 1732;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$ : 0.78–1.00 (3H, m,  $\text{CH}_2\text{CH}_3$ ), 1.06–1.47 (5H, m,  $(\text{CH}_2)_2$  and  $\text{C}(3)\text{CH}^{\text{A}}\text{H}^{\text{B}}$ ), 1.54–1.77 (1H, m,  $\text{C}(3)\text{CH}^{\text{A}}\text{H}^{\text{B}}$ ), 2.82 (1H, q,  $J$  7.0,  $\text{C}(3)\text{H}$ ), 3.79 (1H, t,  $J$  6.7,  $\text{C}(4)\text{H}$ ), 3.87 (3H, s,  $\text{ArC}(4)\text{OCH}_3$ ), 6.67 (1H, d,  $J$  6.4,  $\text{C}(5)\text{H}$ ), 6.97 (2H, d,  $J$  8.4,  $\text{ArC}(3)\text{H}$ ), 7.44 (2H, d,  $J$  8.5,  $\text{ArC}(2)\text{H}$ );  $^{13}\text{C}\{^1\text{H}\}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$ : 12.8 ( $\text{CH}_2\text{CH}_3$ ), 21.4 ( $\text{CH}_2$ ), 24.9 ( $\text{CH}_2$ ), 28.3 ( $\text{CH}_2$ ), 39.7 ( $\text{C}(4)$ ), 42.2 ( $\text{C}(3)$ ), 51.7 ( $\text{CO}_2\text{CH}_3$ ), 116.6 ( $\text{C}(5)$ ), 121.1 ( $\text{ArC}(4)$ ), 128.7 ( $\text{ArC}(3)$ ), 131.3 ( $\text{ArC}(2)$ ), 134.0 ( $\text{ArC}(1)$ ),



141.3 (C(6)), 159.8 (CO<sub>2</sub>Me), 167.4 (C(2)); HRMS (NSI<sup>+</sup>) C<sub>17</sub>H<sub>23</sub>BrO<sub>5</sub>-N [M+NH<sub>4</sub>]<sup>+</sup> found 384.0813, requires 384.0805 (+2.1 ppm).

#### 4.3.9. (3S,4S)-Methyl 3-butyl-4-(naphthalen-2-yl)-2-oxo-3,4-dihydro-2H-pyran-6-carboxylate **17**

Following General Procedure 4.3, 1-oxohexan-2-yl 4-nitrobenzoate (200 mg, 0.750 mmol), (E)-methyl 4-(naphthalen-2-yl)-2-oxobut-3-enoate **40** (120 mg, 0.500 mmol), NHC precatalyst **2** (18.4 mg, 50.0 μmol), Et<sub>3</sub>N (105 μL, 0.750 mmol) and THF (10 mL) were reacted for 6 h. The crude (94:6 dr) was purified by column chromatography (95:5 petrol:EtOAc) to give **17** (81.7 mg, 48%) as a colourless solid. Mp 99–101 °C; [α]<sub>D</sub><sup>20</sup> = +297.0 (c 0.5, CHCl<sub>3</sub>); Chiral HPLC analysis, Chiralpak AD-H (95:5 hexane:IPA, flow rate 1 mL min<sup>-1</sup>, 254 nm, 30 °C) t<sub>R</sub> (3R,4R): 22.0 min, t<sub>R</sub> (3S,4S): 25.0 min, >99:1 er; ν<sub>max</sub> (solid) 2951, 1757, 1736; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ<sub>H</sub>: 0.83 (3H, t, J 7.3, CH<sub>2</sub>CH<sub>3</sub>), 1.11–1.49 (5H, m, (CH<sub>2</sub>)<sub>2</sub> and C(3)CH<sup>A</sup>H<sup>B</sup>), 1.63–1.78 (1H, m, C(3)CH<sup>A</sup>H<sup>B</sup>), 2.90 (1H, q, J 7.0, C(3)H), 3.88 (3H, s, CO<sub>2</sub>CH<sub>3</sub>), 3.99 (1H, t, J 6.7, C(4)H), 6.77 (1H, d, J 6.3, C(5)H), 7.19 (1H, dd, J 8.5, 1.9, ArH), 7.44–7.52 (2H, m, ArH), 7.57 (1H, d, J 1.8, ArC(2)H), 7.74–7.85 (3H, m, ArH); <sup>13</sup>C{<sup>1</sup>H} NMR (75 MHz, CDCl<sub>3</sub>) δ<sub>C</sub>: 12.8 (CH<sub>3</sub>CH<sub>2</sub>), 21.4 (CH<sub>2</sub>), 25.0 (CH<sub>2</sub>), 28.4 (CH<sub>2</sub>), 40.6 (C(4)), 42.4 (C(3)), 51.7 (CO<sub>2</sub>CH<sub>3</sub>), 117.2 (C(5)), 124.5 (ArC(8)), 125.3 (ArC), 125.5 (ArC), 126.1 (ArC(2)), 126.6 (ArC(6)), 126.8 (ArC), 127.7 (ArC(2a)), 128.0 (ArC), 131.9 (ArC(1)), 132.4 (ArC(6a)), 141.1 (C(5)), 163.3 (CO<sub>2</sub>CH<sub>3</sub>), 167.7 (C(2)); HRMS (NSI<sup>+</sup>) C<sub>21</sub>H<sub>26</sub>O<sub>4</sub>N<sub>1</sub> [M+NH<sub>4</sub>]<sup>+</sup> found 356.1862, requires 356.1856 (+1.6 ppm).

#### 4.4. General procedure for the synthesis of α,β-unsaturated γ-ketoesters

Based upon a literature procedure,<sup>21</sup> periodic acid (1 equiv.) was added portionwise to a solution of (+)-diethyl L-tartrate (1 equiv.) in anhydrous Et<sub>2</sub>O (0.5 M). The solution was stirred at rt for 3 h before being filtered into a dried two-necked round-bottomed flask containing MgSO<sub>4</sub> (1.0 g/7 mL Et<sub>2</sub>O), washing with THF (1 mL/0.8 mL EtO). The resulting solution was cooled to 0 °C before the appropriate phosphorane (1.5 equiv.) was added in one portion. The reaction was stirred overnight (cf. 16 h), allowing to warm slowly to rt. The reaction was filtered and concentrated under reduced pressure to give the crude product, which was purified by column chromatography.

##### 4.4.1. (E)-Ethyl 4-oxopent-2-enoate **41**

Following General Procedure 4.4, periodic acid (0.95 g, 4.2 mmol) and (+)-diethyl L-tartrate (0.72 mL, 4.2 mmol) in Et<sub>2</sub>O (8.5 mL) were stirred for 3 h at rt. The reaction was filtered into a two-necked round-bottomed flask containing MgSO<sub>4</sub> (1.0 g), washing with THF (10.5 mL), before 1-(triphenylphosphoranylidene)propan-2-one (2.0 g, 6.3 mmol) was added at 0 °C. The crude product was purified by column chromatography (80:20 hexane:Et<sub>2</sub>O, R<sub>f</sub> 0.24) to give **41** (0.61 g, 68%) as a colourless oil, with spectroscopic data in accordance with the literature.<sup>22</sup> <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ<sub>H</sub>: 1.32 (3H, t, J 7.2 CH<sub>2</sub>CH<sub>3</sub>), 2.36 (3H, s, COCH<sub>3</sub>), 4.26 (2H, q, J 7.2, OCH<sub>2</sub>), 6.64 (1H, d, J 16.1, EtO<sub>2</sub>CCH), 7.01 (1H, d, J 16.1, CHCOMe).

##### 4.4.2. (E)-Ethyl 4-oxo-4-(p-tolyl)but-2-enoate **42**

Following General Procedure 4.4, periodic acid (0.39 g, 1.7 mmol) and (+)-diethyl L-tartrate (0.35 g, 1.7 mmol) in Et<sub>2</sub>O (3.5 mL) were stirred for 3 h at rt. The reaction was filtered into a two-necked round-bottomed flask containing MgSO<sub>4</sub> (0.5 g), washing with THF (4.3 mL), before 1-(p-tolyl)-2-(triphenylphosphoranylidene)ethanone (1.0 g, 2.5 mmol) was added at 0 °C. The crude product was purified by column chromatography (95:5 petrol:EtOAc, R<sub>f</sub> 0.36) to give **42** (0.39 g, 78%) as a yellow oil, with

spectroscopic data in accordance with the literature.<sup>21</sup> <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ<sub>H</sub>: 1.35 (3H, t, J 7.1, CH<sub>2</sub>CH<sub>3</sub>), 2.44 (3H, s, ArC(4)CH<sub>3</sub>), 4.30 (2H, q, J 7.1, OCH<sub>2</sub>), 6.87 (1H, d, J 15.6, EtO<sub>2</sub>CCH), 7.31 (2H, d, J 8.2, ArC(3,5)H), 7.91 (1H, d, J 15.5, CHCOAr), 7.91 (1H, d, J 8.2, ArC(2,6)H).

##### 4.4.3. (E)-Ethyl 4-(4-methoxyphenyl)-4-oxobut-2-enoate **43**

Following General Procedure 4.4, periodic acid (0.37 g, 1.6 mmol) and (+)-diethyl L-tartrate (0.34 g, 1.6 mmol) in Et<sub>2</sub>O (3.2 mL) were stirred for 3 h at rt. The reaction was filtered into a two-necked round-bottomed flask containing MgSO<sub>4</sub> (0.5 g), washing with THF (4.1 mL), before 1-(4-methoxyphenyl)-2-(triphenylphosphoranylidene)ethanone (1.0 g, 2.4 mmol) was added at 0 °C. The crude product was purified by column chromatography (70:30 petrol:Et<sub>2</sub>O, R<sub>f</sub> 0.25) to give **43** (0.48 g, 83%) as a yellow oil, which solidified over time, with spectroscopic data in accordance with the literature.<sup>21</sup> Mp 40–42 °C; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ<sub>H</sub>: 1.35 (3H, t, J 7.2 CH<sub>2</sub>CH<sub>3</sub>), 3.90 (3H, s, OCH<sub>3</sub>), 4.30 (2H, q, J 7.1, OCH<sub>2</sub>), 6.87 (1H, d, J 15.5, EtO<sub>2</sub>CCH), 6.98 (2H, d, J 9.0, ArC(3,5)H), 7.92 (1H, d, J 15.5, CHCOAr), 8.01 (2H, d, J 9.0, ArC(2,6)H).

##### 4.4.4. (E)-Ethyl 4-(4-chlorophenyl)-4-oxobut-2-enoate **44**

Following General Procedure 4.4, periodic acid (0.37 g, 1.6 mmol) and (+)-diethyl L-tartrate (0.33 g, 1.6 mmol) in Et<sub>2</sub>O (3.2 mL) were stirred for 3 h at rt. The reaction was filtered into a two-necked round-bottomed flask containing MgSO<sub>4</sub> (0.5 g), washing with THF (4.0 mL), before 1-(4-chlorophenyl)-2-(triphenylphosphoranylidene)ethanone (1.0 g, 2.4 mmol) was added at 0 °C. The crude product was purified by column chromatography (95:5 petrol:EtOAc, R<sub>f</sub> 0.29) to give **44** (0.57 g, 99%) as a yellow solid, with spectroscopic data in accordance with the literature.<sup>21</sup> Mp 62–63 °C; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ<sub>H</sub>: 1.35 (3H, t, J 7.1, CH<sub>3</sub>), 4.30 (2H, q, J 7.1, OCH<sub>2</sub>), 6.90 (1H, d, J 15.5, EtO<sub>2</sub>CCH), 7.49 (2H, d, J 8.7, ArC(3,5)H), 7.87 (1H, d, J 15.6, CHCOAr), 7.95 (1H, d, J 8.7, ArC(2,6)H).

##### 4.4.5. (E)-Ethyl 4-oxo-4-(4-(trifluoromethyl)phenyl)but-2-enoate **45**

Following General Procedure 4.4, periodic acid (0.68 g, 3.0 mmol) and (+)-diethyl L-tartrate (0.51 mL, 3.0 mmol) in Et<sub>2</sub>O (6.0 mL) were stirred for 3 h at rt. The reaction was filtered into a two-necked round-bottomed flask containing MgSO<sub>4</sub> (1.0 g), washing with THF (7.5 mL), before 1-(4-(trifluoromethyl)phenyl)-2-(triphenylphosphoranylidene)ethanone (2.0 g, 4.5 mmol) was added at 0 °C. The crude product was purified by column chromatography (90:10 petrol:Et<sub>2</sub>O, R<sub>f</sub> 0.24) to **45** (0.85 g, 70%) as a yellow solid. Mp 61–63 °C; ν<sub>max</sub> (film, cm<sup>-1</sup>) 1721, 1672, 1630, 1414, 1315, 1294, 1163, 1123, 1111; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ<sub>H</sub>: 1.35 (3H, t, J 7.1 CH<sub>3</sub>), 4.31 (2H, q, J 7.1, OCH<sub>2</sub>), 6.91 (1H, d, J 15.6, EtO<sub>2</sub>-CCH), 7.78 (2H, d, J 8.4, ArC(3,5)H), 7.87 (1H, d, J 15.5, CHCOAr), 8.09 (2H, d, J 8.3, ArC(2,6)H); <sup>13</sup>C{<sup>1</sup>H} NMR (75 MHz, CDCl<sub>3</sub>) δ<sub>C</sub>: 14.3 (CH<sub>3</sub>), 61.7 (OCH<sub>2</sub>), 123.6 (q, <sup>1</sup>J<sub>CF</sub> 272.8, CF<sub>3</sub>), 126.1 (q, <sup>3</sup>J<sub>CF</sub> 3.7, ArC(2)H), 129.3 (ArC(3)H), 133.8 (EtO<sub>2</sub>C=CH), 135.1 (q, <sup>2</sup>J<sub>CF</sub> 32.8, ArC(1)), 135.7 (C=CHCOAr), 139.4 (ArC(4)), 165.4 (CO<sub>2</sub>Et), 188.9 (COAr); <sup>19</sup>F{<sup>1</sup>H} NMR (282 MHz, CDCl<sub>3</sub>) δ<sub>F</sub>: -63.69 (CF<sub>3</sub>); HRMS (APCI<sup>+</sup>) C<sub>13</sub>H<sub>12</sub>O<sub>3</sub>F<sub>3</sub> [M+H]<sup>+</sup> found 273.0732, requires 273.0733 (-0.4 ppm).

##### 4.4.6. (E)-Ethyl 4-(naphthalen-2-yl)-4-oxobut-2-enoate **46**

Following General Procedure 4.4, periodic acid (1.06 g, 4.6 mmol) and (+)-diethyl L-tartrate (0.80 mL, 4.6 mmol) in Et<sub>2</sub>O (9.0 mL) were stirred for 3 h at rt. The reaction was filtered into a two-necked round-bottomed flask containing MgSO<sub>4</sub> (1.5 g), washing with THF (11.5 mL), before 1-(naphthalen-2-yl)-2-(triphenylphosphoranylidene)ethanone (3.00 g, 7.0 mmol) was added

at 0 °C. The crude product was purified by column chromatography (80:20 hexane:Et<sub>2</sub>O, *R<sub>f</sub>* 0.38) to give **46** (1.24 g, 70%) as a yellow solid. Mp 57–59 °C;  $\nu_{\max}$  (film, cm<sup>-1</sup>) 1717, 1667, 1624, 1464, 1364, 1304, 1246, 1175, 1123; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$ <sub>H</sub>: 1.38 (3H, t, *J* 7.2 CH<sub>3</sub>), 4.33 (2H, q, *J* 7.2, OCH<sub>2</sub>), 6.96 (1H, d, *J* 15.5, EtO<sub>2</sub>CCH), 7.52–7.68 (2H, m, ArH), 7.86–8.10 (4H, m, ArH), 8.09 (1H, d, *J* 15.5, CHCOAr), 8.46–8.55 (1H, m, ArH); <sup>13</sup>C{<sup>1</sup>H} NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$ <sub>C</sub>: 14.4 (CH<sub>3</sub>), 61.6 (OCH<sub>2</sub>), 124.2 (ArC), 127.2 (ArC), 128.0 (ArC), 129.1 (ArC), 129.2 (ArC), 129.9 (ArC), 131.3 (ArC), 132.6 (C=CCO<sub>2</sub>), 132.7 (ArC), 134.2 (ArC), 136.0 (ArC), 136.6 (C=CCO), 165.9 (CO<sub>2</sub>), 189.4 (CO); HRMS (ESI<sup>+</sup>) C<sub>16</sub>H<sub>15</sub>O<sub>3</sub> [M+H]<sup>+</sup> found 255.1017, requires 255.1016 (+0.5 ppm).

#### 4.5. General procedure for the NHC-catalysed redox hetero-Diels-Alder reaction with $\alpha,\beta$ -unsaturated $\gamma$ -ketoesters

The appropriate  $\alpha$ -aroyloxyaldehyde (1.5 equiv),  $\alpha,\beta$ -unsaturated  $\gamma$ -ketoester (1.0 equiv) and NHC precatalyst **2** (5 mol %) were dissolved in anhydrous THF (0.075 M) in a sealed vial containing 3 Å molecular sieves. Et<sub>3</sub>N (1.5 equiv.) was added and the reaction stirred until complete by TLC analysis. The mixture was diluted with EtOAc and washed successively with 1 M HCl, saturated NaHCO<sub>3</sub> and brine. The organic layer was dried with MgSO<sub>4</sub>, filtered and concentrated under reduced pressure to give the crude product, which was purified by column chromatography.

##### 4.5.1. (3*S*,4*S*)-Ethyl 3-butyl-2-oxo-6-phenyl-3,4-dihydro-2*H*-pyran-4-carboxylate **20**

Following General Procedure 4.5, 1-oxohexan-2-yl 4-nitrobenzoate (200 mg, 0.75 mmol), (*E*)-ethyl 4-oxo-4-phenylbut-2-enoate (102 mg, 0.500 mmol), NHC precatalyst **2** (18.4 mg, 50.0  $\mu$ mol), Et<sub>3</sub>N (105  $\mu$ L, 0.75 mmol) and THF (10 mL) were reacted for 5 h. The crude (>95:5 dr) was purified by column chromatography (95:5 petrol:EtOAc) to give **20** (129 mg, 85%) as colourless solid. Mp 61–63 °C;  $[\alpha]_{\text{D}}^{20}$  = +185.5 (*c* 0.5, CHCl<sub>3</sub>); Chiral HPLC analysis, Chiralcel OJ-H (95:5 hexane:IPA, flow rate 1 mL min<sup>-1</sup>, 254 nm, 30 °C) *t<sub>R</sub>* (3*S*,4*S*): 17.2 min, *t<sub>R</sub>* (3*R*,4*R*): 22.3 min, >99:1 er;  $\nu_{\max}$  (solid) 2953 (C–H), 1761 (C=O), 1719 (C=O); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ <sub>H</sub>: 0.91 (3H, t, *J* 7.1, CH<sub>2</sub>CH<sub>3</sub>), 1.25 (3H, t, *J* 7.1, OCH<sub>2</sub>CH<sub>3</sub>), 1.31–1.54 (5H, m, (CH<sub>2</sub>)<sub>2</sub> and C(3)CH<sup>A</sup>H<sup>B</sup>), 1.99–2.13 (1H, m, C(3)CH<sup>A</sup>H<sup>B</sup>), 2.68–2.79 (1H, m, C(3)H), 3.53 (1H, t, *J* 6.3, C(4)H), 4.17 (2H, qd, *J* 7.1, 2.5, OCH<sub>2</sub>CH<sub>3</sub>), 5.88 (1H, d, *J* 6.5, C(5)H), 7.32–7.41 (3H, m, ArC(2)H and ArC(4)H), 7.61–7.66 (2H, m, ArC(3)H); <sup>13</sup>C {<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$ <sub>C</sub>: 12.8 (CH<sub>2</sub>CH<sub>3</sub>), 13.0 (OCH<sub>2</sub>CH<sub>3</sub>), 21.5 (CH<sub>2</sub>), 25.8 (CH<sub>2</sub>), 28.3 (CH<sub>2</sub>), 39.5 (C(3)), 40.8 (C(4)), 60.5 (OCH<sub>2</sub>CH<sub>3</sub>), 96.9 (C(5)), 123.8 (ArC(3)), 127.5 (ArC(2)), 128.4 (ArC(4)), 130.9 (ArC(1)), 151.1 (C(6)), 168.2 (C(2)), 169.2 (CO<sub>2</sub>Et); HRMS (ESI<sup>+</sup>) C<sub>18</sub>H<sub>26</sub>O<sub>4</sub>N [M+NH<sub>4</sub>]<sup>+</sup> found 320.1864, requires 320.1856 (+2.4 ppm).

##### 4.5.2. (3*S*,4*S*)-Ethyl 3-benzyl-2-oxo-6-phenyl-3,4-dihydro-2*H*-pyran-4-carboxylate **21**

Following General Procedure 4.5, 1-oxo-3-phenylpropan-2-yl 4-nitrobenzoate **7** (238 mg, 0.80 mmol), (*E*)-ethyl 4-oxo-4-phenylbut-2-enoate (108 mg, 0.53 mmol), NHC precatalyst **2** (19.5 mg, 53  $\mu$ mol), Et<sub>3</sub>N (0.11 mL, 0.80 mmol) and THF (5 mL) were reacted for 2 h. The crude (>95:5 dr) was purified by column chromatography (95:5 petrol:EtOAc) to give **21** (140 mg, 79%) as a colourless oil, with spectroscopic data in accordance with the literature.<sup>6c</sup>  $[\alpha]_{\text{D}}^{20}$  = +173.0 (*c* 1.05, CHCl<sub>3</sub>) {Lit.<sup>6c</sup> = +107.2 (*c* 0.82, CHCl<sub>3</sub>)}; Chiral HPLC analysis Chiralpak AD-H (90:10 hexane:IPA, flow rate 1.0 mL min<sup>-1</sup>, 254 nm, 30 °C) >99:1 er; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$ <sub>H</sub>: 1.29 (3H, t, *J* 7.1, OCH<sub>2</sub>CH<sub>3</sub>) 2.77 (1H, dd, *J* 14.2, 10.2, PhCH<sup>A</sup>H<sup>B</sup>), 2.97–3.03 (1H, m, C(3)H), 3.25 (1H, dd, *J* 6.9, 5.9, C(4)H) 3.55 (1H, dd, *J* 14.2, 4.6, PhCH<sup>A</sup>H<sup>B</sup>), 4.22 (2H, q, *J* 7.1,

OCH<sub>2</sub>CH<sub>3</sub>), 5.80 (1H, d, *J* 7.0, C(5)H), 7.16–7.21 (2H, m, ArH), 7.26–7.40 (6H, m, ArH), 7.60–7.63 (2H, m, ArH).

##### 4.5.3. (3*S*,4*S*)-Ethyl 3-(2-(benzyloxy)ethyl)-2-oxo-6-phenyl-3,4-dihydro-2*H*-pyran-4-carboxylate **22**

Following General Procedure 4.5, 4-(benzyloxy)-1-oxobutan-2-yl 4-nitrobenzoate (257 mg, 0.75 mmol), (*E*)-ethyl 4-oxo-4-phenylbut-2-enoate (102 mg, 0.50 mmol), NHC precatalyst **2** (9.2 mg, 25.0  $\mu$ mol), Et<sub>3</sub>N (105  $\mu$ L, 0.75 mmol) and THF (5 mL) were reacted for 9 h. The crude (90:10 dr) was purified by column chromatography (85:15 petrol:EtOAc, *R<sub>f</sub>* 0.25) to give **22** (161 mg, 85%) as white solid. Mp 77–78 °C (hexane);  $[\alpha]_{\text{D}}^{20}$  = +169.1 (*c* 0.55, CHCl<sub>3</sub>); Chiral HPLC analysis, Chiralcel OD-H (95:5 hexane:IPA, flow rate 1 mL min<sup>-1</sup>, 254 nm, 30 °C) *t<sub>R</sub>* (3*R*,4*R*): 23.2 min, *t<sub>R</sub>* (3*S*,4*S*): 25.1 min, >99:1 er;  $\nu_{\max}$  (film, cm<sup>-1</sup>) 1767 (C=O), 1715 (C=O), 1657 (C=C); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$ <sub>H</sub>: 1.23 (3H, t, *J* 7.1, OCH<sub>2</sub>CH<sub>3</sub>), 1.72–1.83 (1H, m, C(3)CH<sup>A</sup>H<sup>B</sup>), 2.37–2.48 (1H, m, C(3)CH<sup>A</sup>H<sup>B</sup>), 3.04 (1H, q, *J* 6.7, C(3)H), 3.50 (1H, t, *J* 6.5, C(4)H), 3.60–3.72 (2H, m, C(3)CH<sub>2</sub>CH<sub>2</sub>), 4.09–4.20 (2H, m, OCH<sub>2</sub>CH<sub>3</sub>), 4.50 (2H, d, *J* 2.1, OCH<sub>2</sub>Ar), 5.86 (1H, d, *J* 6.9, C(5)H), 7.27–7.40 (8H, m, ArH), 7.61–7.66 (2H, m, ArH); <sup>13</sup>C{<sup>1</sup>H} NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$ <sub>C</sub>: 14.2 (CH<sub>3</sub>), 27.8 (CH<sub>2</sub>), 37.6 (C(3)H), 42.1 (C(4)H), 61.7 (OCH<sub>2</sub>CH<sub>3</sub>), 67.4 (OCH<sub>2</sub>CH<sub>2</sub>), 73.2 (OCH<sub>2</sub>Ph), 98.2 (C(5)H), 125.0 (ArCH), 127.8 (ArCH), 128.5 (ArCH), 128.6 (ArCH), 129.6 (ArCH), 132.0 (ArC), 138.2 (ArC), 152.4 (C(6)), 169.4 (C(2)), 170.4 (CO<sub>2</sub>Et); HRMS (ESI<sup>+</sup>) C<sub>23</sub>H<sub>25</sub>O<sub>5</sub> [M+H]<sup>+</sup> found 381.1697, requires 381.1697 (+0.1 ppm).

##### 4.5.4. (3*S*,4*S*)-Ethyl 3-benzyl-6-methyl-2-oxo-3,4-dihydro-2*H*-pyran-4-carboxylate **23**

In a modified procedure, 1-oxo-3-phenylpropan-2-yl 4-nitrobenzoate **7** (196 mg, 0.65 mmol), (*E*)-ethyl 4-oxopent-2-enoate **41** (62 mg, 0.44 mmol), NHC precatalyst **2** (8.0 mg, 21.8  $\mu$ mol), and Cs<sub>2</sub>CO<sub>3</sub> (142 mg, 0.44 mmol) were dissolved in THF (4.4 mL) in a sealed vial and heated at 40 °C for 7 h. The mixture was then diluted with EtOAc and washed successively with 1 M HCl ( $\times$ 2), NaHCO<sub>3</sub> ( $\times$ 2), and brine ( $\times$ 2) before being dried over MgSO<sub>4</sub> and concentrated under reduced pressure. The crude (>95:5 dr) was purified by column chromatography (95:5 petrol:EtOAc, *R<sub>f</sub>* 0.20) to give **23** (79 mg, 65%) as white solid, with spectroscopic data in accordance to the literature.<sup>6c</sup> Mp 88–89 °C (hexane);  $[\alpha]_{\text{D}}^{20}$  = +270.9 (*c* 0.32, CHCl<sub>3</sub>) {Lit.<sup>6c</sup> = +250.6 (*c* 0.93, CHCl<sub>3</sub>)}; Chiral HPLC analysis, Chiralcel AD-H (95:5 hexane:IPA, flow rate 1 mL min<sup>-1</sup>, 254 nm, 30 °C) *t<sub>R</sub>* (3*R*,4*R*): 11.0 min, *t<sub>R</sub>* (3*S*,4*S*): 13.2 min, 98.5:1.5 er;  $\nu_{\max}$  (film, cm<sup>-1</sup>) 1771 (C=O), 1726 (C=O), 1688 (C=C); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$ <sub>H</sub>: 1.21 (3H, t, *J* 7.1, OCH<sub>2</sub>CH<sub>3</sub>), 1.83 (3H, s, C(6)CH<sub>3</sub>), 2.61 (1H, dd, *J* 14.3, 10.1, C(3)CH<sup>A</sup>H<sup>B</sup>), 2.75–2.82 (1H, m, C(3)H), 2.92 (1H, t, *J* 6.4, C(4)H), 3.42 (1H, dd, *J* 14.2, 4.6, C(3)CH<sup>A</sup>H<sup>B</sup>), 4.13 (2H, q, *J* 7.2, OCH<sub>2</sub>), 4.95 (1H, dd, *J* 6.8, 1.1, C(5)H), 7.04–7.10 (2H, m, ArC(2)H), 7.12–7.27 (3H, m, ArC(3)H and ArC(4)H); <sup>13</sup>C{<sup>1</sup>H} NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$ <sub>C</sub>: 14.2 (CH<sub>2</sub>CH<sub>3</sub>), 18.9 (CCH<sub>3</sub>), 33.3 (CH<sub>2</sub>), 40.4 (C(3)H), 42.8 (C(4)H), 61.5 (OCH<sub>2</sub>), 98.7 (C(5)H), 126.9 (ArCH), 128.8 (ArCH), 129.1 (ArCH), 138.3 (ArC), 152.4 (C(6)), 169.3 (C(2)), 170.7 (CO<sub>2</sub>Et); HRMS (ESI<sup>+</sup>) C<sub>16</sub>H<sub>19</sub>O<sub>4</sub> [M+H]<sup>+</sup> found 275.1280, requires 275.1278 (+0.8 ppm).

##### 4.5.5. (3*S*,4*S*)-Ethyl 3-butyl-2-oxo-6-(*p*-tolyl)-3,4-dihydro-2*H*-pyran-4-carboxylate **24**

Following General Procedure 4.5, 1-oxohexan-2-yl 4-nitrobenzoate (200 mg, 0.75 mmol), (*E*)-ethyl 4-oxo-4-(*p*-tolyl)but-2-enoate **42** (109 mg, 0.50 mmol), NHC precatalyst **2** (9.2 mg, 25.0  $\mu$ mol), Et<sub>3</sub>N (105  $\mu$ L, 0.75 mmol) and THF (5 mL) were reacted for 6 h. The crude (>95:5 dr) was purified by column chromatography (90:10 hexane:Et<sub>2</sub>O, *R<sub>f</sub>* 0.19) to give **24** (127 mg, 80%) as colourless needles. Mp 64–65 °C (hexane);  $[\alpha]_{\text{D}}^{20}$  = +158.4 (*c* 0.38, CHCl<sub>3</sub>); Chiral HPLC analysis, Chiralcel OD-H (95:5 hexane:IPA,

flow rate 1 mL min<sup>-1</sup>, 254 nm, 30 °C) *t*<sub>R</sub> (3S,4S): 8.3 min, *t*<sub>R</sub> (3R,4R): 9.0 min, >99:1 er; *v*<sub>max</sub> (film, cm<sup>-1</sup>) 1763 (C=O), 1719 (C=O), 1684 (C=C); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$ <sub>H</sub>: 0.91 (3H, t, *J* 7.1, (CH<sub>2</sub>)<sub>3</sub>CH<sub>3</sub>), 1.25 (3H, t, *J* 7.2, OCH<sub>2</sub>CH<sub>3</sub>), 1.31–1.52 (5H, m, C(3)H<sub>a</sub>H<sub>b</sub> and CH<sub>2</sub> × 2), 1.98–2.15 (1H, m, C(3)H<sub>a</sub>H<sub>b</sub>), 2.36 (3H, s, ArC(4)CH<sub>3</sub>), 2.73 (1H, q, *J* 6.5, C(3)H), 3.51 (1H, t, *J* 6.3, C(4)H), 4.17 (2H, qd, *J* 7.2, 1.9, OCH<sub>2</sub>), 5.82 (1H, d, *J* 6.5, C(5)H), 7.18 (2H, d, *J* 8.1, ArC(3)H), 7.53 (2H, d, *J* 8.3, ArC(2)H); <sup>13</sup>C{<sup>1</sup>H} NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$ <sub>C</sub>: 14.0 (CH<sub>3</sub>), 14.2 (CH<sub>3</sub>), 21.4 (CH<sub>3</sub>), 22.6 (CH<sub>2</sub>), 26.9 (CH<sub>2</sub>), 29.5 (CH<sub>2</sub>), 40.7 (C(3)H), 42.0 (C(4)H), 61.6 (OCH<sub>2</sub>), 97.1 (C(5)H), 124.9 (ArC), 129.2 (ArCH), 129.3 (ArCH), 139.7 (ArC), 152.4 (C(6)), 169.6 (C(2)), 170.5 (CO<sub>2</sub>Et); HRMS (NSI<sup>+</sup>) C<sub>19</sub>H<sub>25</sub>O<sub>4</sub> [M+H]<sup>+</sup> found 317.1751, requires 317.1747 (+1.1 ppm).

#### 4.5.6. (3S,4S)-Ethyl 3-butyl-6-(4-methoxyphenyl)-2-oxo-3,4-dihydro-2H-pyran-4-carboxylate 25

Following General Procedure 4.5, 1-oxohexan-2-yl 4-nitrobenzoate (200 mg, 0.75 mmol), (E)-ethyl 4-(4-methoxyphenyl)-4-oxobut-2-enoate **43** (117 mg, 0.50 mmol), NHC precatalyst **2** (9.2 mg, 25.0  $\mu$ mol), Et<sub>3</sub>N (105  $\mu$ L, 0.75 mmol) and THF (5 mL) were reacted for 6 h. The crude (>95:5 dr) was purified by column chromatography (85:15 hexane:Et<sub>2</sub>O, *R*<sub>f</sub> 0.17) to give **25** (149 mg, 90%) as white solid. Mp 61–62 °C (hexane); [ $\alpha$ ]<sub>D</sub><sup>20</sup> = +123.6 (c 0.39, CHCl<sub>3</sub>); Chiral HPLC analysis, Chiralcel OD-H (95:5 hexane:IPA, flow rate 1 mL min<sup>-1</sup>, 254 nm, 30 °C) *t*<sub>R</sub> (3R,4R): 13.9 min, *t*<sub>R</sub> (3S,4S): 14.5 min, >99:1 er; *v*<sub>max</sub> (film, cm<sup>-1</sup>) 1751 (C=O), 1726 (C=O), 1661 (C=C); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$ <sub>H</sub>: 0.91 (3H, t, *J* 7.1, CH<sub>2</sub>-CH<sub>3</sub>), 1.25 (3H, t, *J* 7.2, OCH<sub>2</sub>CH<sub>3</sub>), 1.31–1.49 (5H, m, C(3)H<sub>a</sub>H<sub>b</sub>), 1.99–2.11 (1H, m, C(3)H<sub>a</sub>H<sub>b</sub>), 2.72 (1H, q, *J* 6.5, C(3)H), 3.50 (1H, t, *J* 6.3, C(4)H), 3.82 (3H, s, ArC(4)OCH<sub>3</sub>), 4.17 (2H, qd, *J* 7.1, 1.9, OCH<sub>2</sub>), 5.74 (1H, d, *J* 6.5, C(5)H), 6.89 (2H, d, *J* 8.9, ArC(3)H), 7.57 (2H, d, *J* 9.0, ArC(2)H); <sup>13</sup>C{<sup>1</sup>H} NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$ <sub>C</sub>: 14.0 (CH<sub>3</sub>), 14.2 (CH<sub>3</sub>), 22.6 (CH<sub>2</sub>), 26.9 (CH<sub>2</sub>), 29.5 (CH<sub>2</sub>), 40.8 (C(3)H), 41.9 (C(4)H), 55.5 (OCH<sub>3</sub>), 61.6 (OCH<sub>2</sub>), 96.0 (C(5)H), 114.0 (ArC), 124.6 (ArCH), 126.4 (ArCH), 152.1 (C(6)), 160.7 (ArC), 169.6 (C(2)), 170.6 (CO<sub>2</sub>Et); HRMS (NSI<sup>+</sup>) C<sub>19</sub>H<sub>25</sub>O<sub>5</sub> [M+H]<sup>+</sup> found 333.1699, requires 333.1697 (+0.7 ppm).

#### 4.5.7. (3S,4S)-Ethyl 6-(4-chlorophenyl)-3-methyl-2-oxo-3,4-dihydro-2H-pyran-4-carboxylate 26

Following General Procedure 4.5, 1-oxopropan-2-yl 4-nitrobenzoate (167 mg, 0.75 mmol), (E)-ethyl 4-(4-chlorophenyl)-4-oxobut-2-enoate **44** (119 mg, 0.50 mmol), NHC precatalyst **2** (9.2 mg, 25.0  $\mu$ mol), Et<sub>3</sub>N (105  $\mu$ L, 0.75 mmol) and THF (5 mL) were reacted for 4 h. The crude (80:20 dr) was purified by column chromatography (70:30 hexane:Et<sub>2</sub>O, minor-*anti* *R*<sub>f</sub> 0.29, major-*syn* *R*<sub>f</sub> 0.23) to give **26** (81 mg, 55%) as white solid. Mp 93–95 °C (hexane); [ $\alpha$ ]<sub>D</sub><sup>20</sup> = +248.5 (c 0.27, CHCl<sub>3</sub>); Chiral HPLC analysis, Chiralcel OD-H (95:5 hexane:IPA, flow rate 1 mL min<sup>-1</sup>, 254 nm, 30 °C) *t*<sub>R</sub> (3R,4R): 14.3 min, *t*<sub>R</sub> (3S,4S): 15.7 min, >99:1 er; *v*<sub>max</sub> (film, cm<sup>-1</sup>) 1765 (C=O), 1721 (C=O), 1657 (C=C); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$ <sub>H</sub>: 1.26 (3H, t, *J* 7.2, OCH<sub>2</sub>CH<sub>3</sub>), 1.34 (3H, d, *J* 7.0, C(3)CH<sub>3</sub>), 2.92 (1H, pent, *J* 6.7, C(3)H), 3.44 (1H, t, *J* 6.3, C(4)H), 4.19 (2H, qd, *J* 7.1, 3.2, OCH<sub>2</sub>), 5.86 (1H, d, *J* 6.6, C(5)H), 7.35 (2H, d, *J* 8.7, ArC(2)H), 7.57 (2H, d, *J* 8.8, ArC(3)H); <sup>13</sup>C{<sup>1</sup>H} NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$ <sub>C</sub>: 12.6 (C(3)CH<sub>3</sub>), 14.2 (CH<sub>2</sub>CH<sub>3</sub>), 35.6 (C(3)H), 43.8 (C(4)H), 61.8 (OCH<sub>2</sub>), 98.4 (C(5)H), 126.3 (ArC), 128.9 (ArCH), 130.5 (ArCH), 135.6 (ArC), 151.6 (C(6)), 169.6 (C(2)), 170.2 (CO<sub>2</sub>Et); HRMS (NSI<sup>+</sup>) C<sub>15</sub>H<sub>16</sub>O<sub>4</sub>Cl [N+H]<sup>+</sup> found 295.0735, requires 295.0732 (+1.1 ppm).

#### 4.5.8. (3S,4S)-Ethyl 3-benzyl-2-oxo-6-(4-(trifluoromethyl)phenyl)-3,4-dihydro-2H-pyran-4-carboxylate 27

Following General Procedure 4.5, 1-oxo-3-phenylpropan-2-yl 4-nitrobenzoate **7** (224 mg, 0.75 mmol), (E)-ethyl 4-oxo-4-(4-(trifluoromethyl)phenyl)but-2-enoate **45** (136 mg, 0.50 mmol), NHC precatalyst **2** (18.3 mg, 50.0  $\mu$ mol), Et<sub>3</sub>N (105  $\mu$ L, 0.75 mmol) and THF

(5 mL) were reacted for 3 h. The crude (80:20 dr) was purified by column chromatography (90:10 petrol:EtOAc, major-*syn* *R*<sub>f</sub> 0.16, minor-*anti* *R*<sub>f</sub> 0.09) to give **27** (105 mg, 52%) as white solid. Mp 145–147 °C (hexane); [ $\alpha$ ]<sub>D</sub><sup>20</sup> = +172.9 (c 0.31 in CHCl<sub>3</sub>); Chiral HPLC analysis, Chiralcel OD-H (95:5 hexane:IPA, flow rate 1 mL min<sup>-1</sup>, 254 nm, 30 °C) *t*<sub>R</sub> (3S,4S): 18.8 min, *t*<sub>R</sub> (3R,4R): 15.4 min, >99:1 er; *v*<sub>max</sub> (film, cm<sup>-1</sup>) 1775 (C=O), 1719 (C=O), 1659 (C=C); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$ <sub>H</sub>: 1.30 (3H, t, *J* 7.2, OCH<sub>2</sub>CH<sub>3</sub>), 2.78 (1H, dd, *J* 14.4, 9.9, C(3)H<sub>a</sub>H<sub>b</sub>), 2.98–3.06 (1H, m, C(3)H), 3.30 (1H, t, *J* 6.4, C(4)H), 3.55 (1H, dd, *J* 14.2, 4.7, C(3)H<sub>a</sub>H<sub>b</sub>), 4.23 (2H, q, *J* 7.2, OCH<sub>2</sub>), 5.92 (1H, d, *J* 7.0, C(5)H), 7.17–7.19 (2H, m, C(3)CH<sub>2</sub>ArC(2)H), 7.24–7.36 (3H, m, C(3)CH<sub>2</sub>ArC(3)H and C(3)CH<sub>2</sub>ArC(4)H), 7.63 (2H, d, *J* 8.5, C(6)ArC(2)H), 7.73 (2H, d, *J* 8.5, C(6)ArC(3)H); <sup>13</sup>C{<sup>1</sup>H} NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$ <sub>C</sub>: 14.3 (CH<sub>3</sub>), 33.3 (CH<sub>2</sub>Ph), 40.8 (C(3)H), 42.8 (C(4)H), 62.0 (OCH<sub>2</sub>), 100.3 (C(5)H), 124.0 (q, <sup>1</sup>J<sub>CF</sub> 272, CF<sub>3</sub>), 125.2 (ArCH), 125.7 (q, <sup>3</sup>J<sub>CF</sub> 3.8, C(6)ArC(3,5)H), 127.1 (ArCH), 129.0 (ArCH), 129.1 (ArCH), 131.4 (q, <sup>2</sup>J<sub>CF</sub> 32.5, C(6)ArC(4)), 135.2 (ArC), 137.9 (ArC), 151.4 (C(6)), 168.4 (C(2)), 170.0 (CO<sub>2</sub>Et); HRMS (NSI<sup>+</sup>) C<sub>22</sub>H<sub>23</sub>-O<sub>4</sub>NF<sub>3</sub> [M+NH<sub>4</sub>]<sup>+</sup> found 422.1574, requires 422.1574 (+0.1 ppm).

#### 4.5.9. (3S,4S)-Ethyl 3-methyl-6-(naphthalen-2-yl)-2-oxo-3,4-dihydro-2H-pyran-4-carboxylate 28 and (3S,4R)-Ethyl 3-methyl-6-(naphthalen-2-yl)-2-oxo-3,4-dihydro-2H-pyran-4-carboxylate 29

Following General Procedure 4.5, 1-oxopropan-2-yl 4-nitrobenzoate (167 mg, 0.75 mmol), (E)-ethyl 4-(naphthalen-2-yl)-4-oxobut-2-enoate **46** (127 mg, 0.50 mmol), NHC precatalyst **2** (9.2 mg, 25.0  $\mu$ mol), Et<sub>3</sub>N (105  $\mu$ L, 0.75 mmol) and THF (5 mL) were reacted for 24 h. The crude (50:50 dr) was purified by column chromatography (90:10 petrol:EtOAc, *anti* *R*<sub>f</sub> 0.29, *syn* *R*<sub>f</sub> 0.23) to give *syn*-**28** (49 mg, 32%) as white solid and *anti*-**29** (55 mg, 35%) as white solid. *syn*-**28**: Mp 101–103 °C (hexane); [ $\alpha$ ]<sub>D</sub><sup>20</sup> = +220.3 (c 0.34, CHCl<sub>3</sub>); Chiral HPLC analysis, Chiralcel OD-H (95:5 hexane:IPA, flow rate 1 mL min<sup>-1</sup>, 254 nm, 30 °C) *t*<sub>R</sub> (3S,4S): 26.7 min, *t*<sub>R</sub> (3R,4R): 24.1 min, >99:1 er; *v*<sub>max</sub> (film, cm<sup>-1</sup>) 1771 (C=O), 1715 (C=O), 1651 (C=C); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$ <sub>H</sub>: 1.27 (3H, t, *J* 7.2, OCH<sub>2</sub>-CH<sub>3</sub>), 1.37 (3H, d, *J* 6.9, C(3)CH<sub>3</sub>), 2.97 (1H, pent, *J* 6.7, C(3)H), 3.49 (1H, t, *J* 6.3, C(4)H), 4.15–4.26 (2H, m, OCH<sub>2</sub>), 6.02 (1H, d, *J* 6.6, C(5)H), 7.48–7.53 (2H, m, ArH), 7.65 (1H, dd, *J* 8.7, 1.9, ArC(2)H), 7.78–7.91 (3H, m, ArH), 8.16–8.22 (1H, m, ArH); <sup>13</sup>C{<sup>1</sup>H} NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$ <sub>C</sub>: 12.7 (C(3)CH<sub>3</sub>), 14.2 (CH<sub>2</sub>CH<sub>3</sub>), 35.7 (C(3)H), 43.9 (C(4)H), 61.8 (OCH<sub>2</sub>), 98.5 (C(5)H), 122.1 (ArCH), 124.6 (ArCH), 126.8 (ArCH), 127.1 (ArCH), 127.7 (ArCH), 128.4 (ArCH), 128.8 (ArCH), 129.0 (ArC), 133.1 (ArC), 133.7 (ArC), 152.4 (C(6)), 170.0 (C(2)), 170.3 (CO<sub>2</sub>Et); HRMS (NSI<sup>+</sup>) C<sub>19</sub>H<sub>19</sub>O<sub>4</sub> [M+H]<sup>+</sup> found 311.1282, requires 311.1278 (+1.3 ppm).

*anti*-**29**: Mp 92–94 °C (hexane); [ $\alpha$ ]<sub>D</sub><sup>20</sup> = -91.9 (c 0.37, CHCl<sub>3</sub>); Chiral HPLC analysis, Chiralcel OD-H (95:5 hexane:IPA, flow rate 1 mL min<sup>-1</sup>, 254 nm, 30 °C) *t*<sub>R</sub> (3R,4S): 15.2 min, *t*<sub>R</sub> (3S,4R): 15.9 min, >99:1 er; *v*<sub>max</sub> (film, cm<sup>-1</sup>) 1769 (C=O), 1728 (C=O), 1661 (C=C); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$ <sub>H</sub>: 1.33 (3H, t, *J* 7.2, OCH<sub>2</sub>-CH<sub>3</sub>), 1.40 (3H, d, *J* 6.9, C(3)CH<sub>3</sub>), 3.10–3.20 (1H, m, C(3)H), 3.38 (1H, dd, *J* 9.1, 4.0, C(4)H), 4.27 (2H, q, *J* 7.2, OCH<sub>2</sub>), 5.86 (1H, d, *J* 4.2, C(5)H), 7.48–7.53 (2H, m, ArH), 7.65 (1H, dd, *J* 8.7, 1.7, ArC(2)H), 7.79–7.93 (3H, m, ArH), 8.15–8.23 (1H, m, ArH); <sup>13</sup>C{<sup>1</sup>H} NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$ <sub>C</sub>: 14.3 (CH<sub>2</sub>CH<sub>3</sub>), 15.0 (C(3)CH<sub>3</sub>), 35.7 (C(3)H), 45.0 (C(4)H), 62.0 (OCH<sub>2</sub>), 98.0 (C(5)H), 122.0 (ArCH), 124.5 (ArCH), 126.8 (ArCH), 127.0 (ArCH), 127.7 (ArCH), 128.4 (ArCH), 128.8 (ArCH), 128.8 (ArC), 133.1 (ArC), 133.7 (ArC), 150.9 (C(6)), 170.3 (CO<sub>2</sub>Et), 171.5 (C(2)); HRMS (NSI<sup>+</sup>) C<sub>19</sub>H<sub>19</sub>O<sub>4</sub> [M+H]<sup>+</sup> found 311.1282, requires 311.1278 (+1.3 ppm).

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## A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.tetasy.2017.01.002>.

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- The ee of the products arising from epimerisation and isomerisation of *syn*-**9** could not be determined as the complex mixtures were inseparable by HPLC analysis.
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