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Article

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NHC-promoted asymmetric β-lactone formation from arylalkylketenes and electron-deficient benzaldehydes or pyridinecarboxaldehydes

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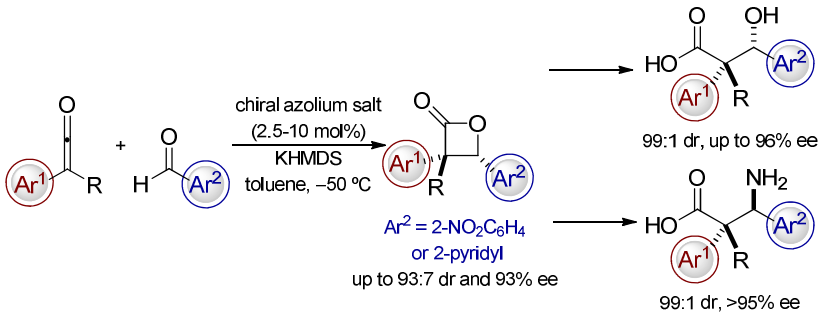


A chiral NHC catalyses the asymmetric formal [2+2]-cycloaddition of alkylarylketenes with both electron deficient benzaldehydes and 2- and 4-pyridinecarboxaldehydes to generate stereodefined β-lactones. In the benzaldehyde series, optimal product diastereo- and enantiocontrol is observed using 2-nitrobenzaldehyde (up to 93:7 dr (*syn*:*anti*) and 93% ee). Substituted 2- and 4-pyridinecarboxaldehydes are also tolerated in this process, generating the corresponding β-lactones in good yield and enantioselectivity, although the diastereocontrol in these processes is highly dependent upon the aldehyde substitution.

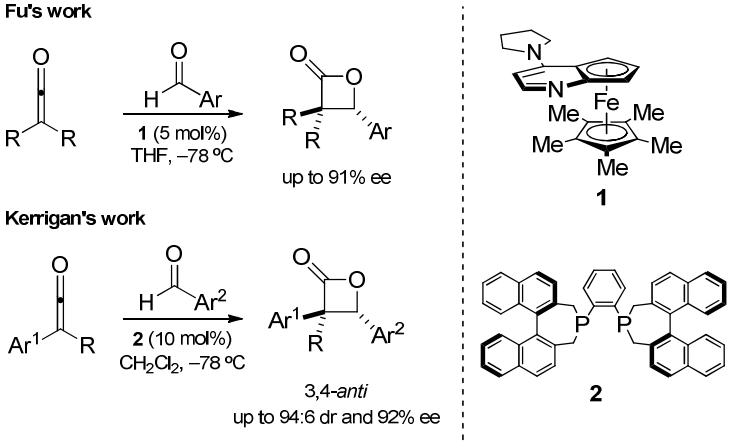
These processes are readily scalable, allowing multi-gram quantities of the β-lactone products to be prepared. Derivatisation of these products, either through ring-opening into the corresponding stereodefined β-hydroxy- and β-amino acid derivatives without loss of stereochemical integrity, or *via* cross-coupling, is demonstrated.

Introduction:

The β-lactone motif is of widespread interest in chemistry, serving as versatile starting materials in complex molecule[1] and building block synthesis,[1b,2] monomers in biodegradable polymer synthesis,[3] as well as being the core structure in a range of natural products with notable pharmacological properties.[4] A number of synthetic methods have been used to prepare these scaffolds in enantioenriched form,[5] ranging from substrate[5b] and chiral auxiliary[6] controlled processes to catalytic asymmetric methods.[7] Within the area of asymmetric Lewis base catalysis, a variety of strategies have been utilised to promote the catalytic asymmetric formation of β-lactones from ketenes and aldehydes.[8] Building on the pioneering work of Wynberg using cinchona alkaloid catalysts,[9] the work of the Nelson,[10] Romo[11] and Calter[12] groups has expanded this approach, with a range of elegant intra- and intermolecular strategies developed. Although versatile, typical limitations of the intermolecular process using cinchona derivatives include the requirement for parent or mono-substituted ketene(s) and aliphatic aldehydes for good reactivity. To date, relatively few studies have been reported that use disubstituted ketenes and benzaldehydes in catalytic asymmetric β-lactone formation. In this area, Fu has shown that planar chiral 4-(pyrrolidino)pyridine (PPY) derivative **1** promotes asymmetric β-lactone formation from symmetrical dialkylketenes and benzaldehydes with high enantioselectivity (up to 91% ee, Scheme 1).[13] Kerrigan has recently shown that BINAPHANE **2** can be

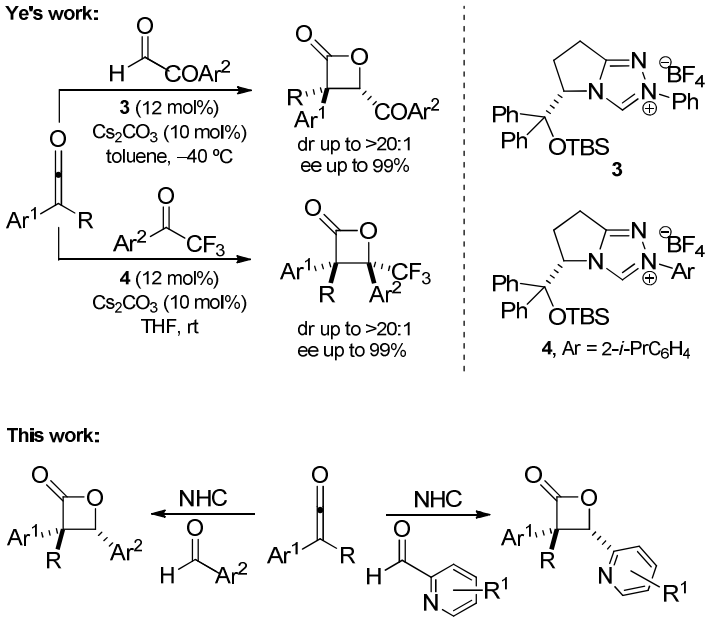
used to promote asymmetric β-lactone formation from alkylarylketenes and 4-substituted benzaldehydes, giving preferentially *anti*-β-lactones with high diastereo- and enantiocontrol (up to 94:6 dr and 92% ee).[14]

Scheme 1. Previous Lewis base-promoted asymmetric β-lactone formation from disubstituted ketenes and benzaldehydes



Ye has previously utilized NHCs to promote β-lactone formation from alkylarylketenes using trifluoromethylketones[15] (up to >20:1 dr, 99% ee) or activated 2-oxo-aldehydes[16] (up to 20:1 dr, 99% ee, Scheme 2). Notably, the use of ethyl-2-chloro-phenylketene is a necessary substrate constraint for high diastereoselectivity in the latter process, with 4-chloro-benzaldehyde proving inactive to β-lactone formation in this study. Building upon these precedents and our interest in NHC-mediated asymmetric processes,[17] we now report the development of an alternative and scalable NHC-promoted asymmetric β-lactone synthesis from alkylarylketenes and both benzaldehydes bearing electron withdrawing substituents and pyridinecarboxaldehydes. Furthermore, derivatisation of the β-lactone products, either through ring-opening into the corresponding stereodefined β-hydroxy- and β-amino acid derivatives, or *via* cross-coupling, is demonstrated.

Scheme 2. Previous and proposed asymmetric β-lactone formation from disubstituted ketenes and aldehydes using NHCs



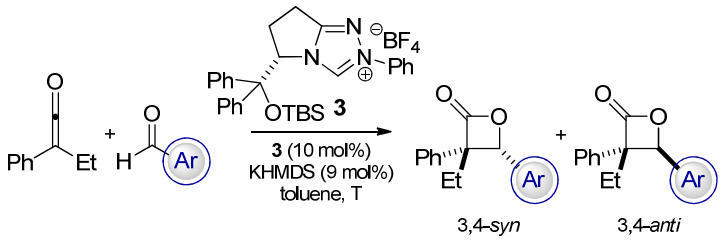
Results and Discussion:

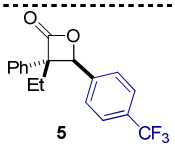
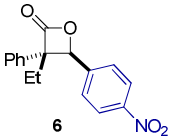
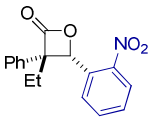
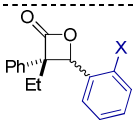
Evaluating NHC-promoted β-lactone formation using benzaldehydes

As NHCs are known to promote benzoin reactions of benzaldehydes[18] as well as ketene dimerisation processes,[19] at the outset of our investigations these were recognised as possible competitive reaction manifolds. NHC precatalyst **3** was chosen for our studies given its precedent to participate in enantioselective cycloaddition processes using ketenes, yet its moderate reactivity in benzoin reactions.[20] Initial studies employed ethylphenylketene and triazolium precatalyst **3** with a range of substituted benzaldehydes (Table 1). Whilst benzaldehyde gave no β-lactone products (giving only ketene dimer), promising reactivity was observed with electron-deficient benzaldehydes utilizing dropwise ketene addition to minimise dimerisation. The reactions using 4-trifluoromethyl- or 4-nitrobenzaldehyde performed at 0 °C gave

good yields of β-lactone product (**5** and **6**) with moderate levels of *anti*-diastereoselectivity (entries 2 and 3).[21] Improved enantiocontrol was achieved at the detriment of product conversion at −78 °C using 4-nitrobenzaldehyde (entry 4).[22] Using 2-nitrobenzaldehyde, high *syn*-diastereoselectivity (89:11 *syn*:*anti*) was observed at 0 °C, giving major *syn*-diastereoisomer **7** in 94% ee (entry 5). Further optimization using 2-nitrobenzaldehyde was achieved through lowering the reaction temperature, with consistently high levels of diastereo- and enantioselectivity observed (entries 6 to 7). Interestingly, lowering the reaction temperature below −50 °C had a detrimental effect on product ee (entry 8), postulated to be due to a competitive KHMDS-catalysed racemic pathway at this temperature.[23] The absolute and relative configuration within **7** was proven through X-ray crystallographic analysis.[24] Following the promising reactivity and stereoselectivity observed using 2-nitrobenzaldehyde, the ability of 2-halobenzaldehydes to participate in this reaction process was investigated. 2-Fluoro-, 2-chloro- and 2-bromobenzaldehyde all gave the corresponding β-lactones (**8**-**10**) with poor dr (entries 9-11),[25] consistent with the 2-nitro substituent being a necessary constraint for optimal diastereoselectivity.[26]

Table 1. Initial screening of benzaldehydes for NHC-promoted β-lactone synthesis



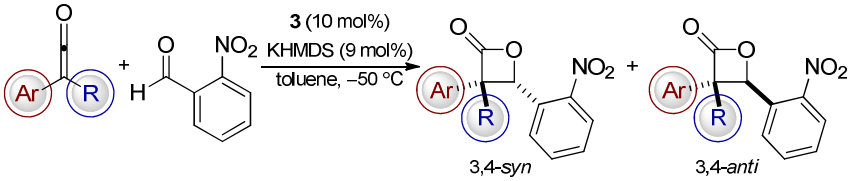
Entry	Ar	T / °C	dr[a] (*syn*:*anti*)	Major product	Yield %[b] (*syn*,*anti*)	ee %[c] (*syn*,*anti*)
1[d]	Ph	0	–:–	–	–,–	–,–
2[e]	4-$CF_3C_6H_4$	0	30:70	 **5**	27,55	80,38
3[f]	4-$NO_2C_6H_4$	0	40:60	 **6**	30,50	81,14
4[f]		–78 to rt	40:60		7,34	97,54
5[f]	2-$NO_2C_6H_4$	0	89:11	 **7**	86,–	94,–
6		–25	92:8		77,–	97,–
7		–50	93:7		83,–	93,–
8		–78	89:11		86,–	82,–
9[g]	2-FC_6H_4	–50	50:50	 **8** X=F **9** X=Cl **10** X=Br	29	87,69
10[g]	2-ClC_6H_4	–50	52:48		36	87,76
11[g]	2-BrC_6H_4	–50	56:44		25	95,71

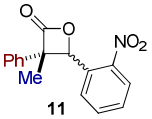
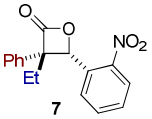
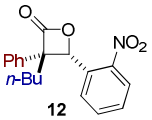
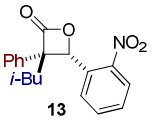
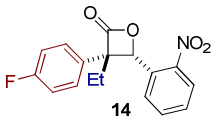
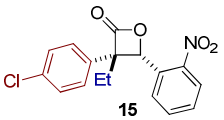
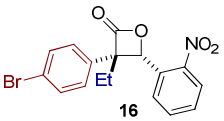
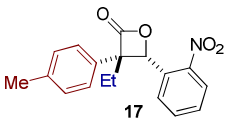
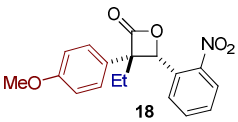
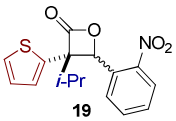
Unless stated, ketene added dropwise as a solution in toluene. [a]dr determined by ^{1}H NMR analysis of the crude reaction mixture. [b]Isolated yield of single diastereoisomer. [c]ee determined by HPLC analysis. [d]Ketene added in a single portion. [e]1.5 equiv of aldehyde. [f]1.2 equiv of aldehyde. [g]Isolated yield and ee of products after ring opening into the corresponding β-hydroxy acids and derivatisation.

With 2-nitrobenzaldehyde identified as giving optimum diastereo- and enantiocontrol in this process, its scope and limitations were explored through variation of the ketene component (Table 2). Firstly, a series of alkylphenylketenes were reacted under the optimized conditions. Incorporation of a methyl substituent led to a decrease in dr

while maintaining high levels of enantioselectivity for both diastereoisomers of product **11** (entry 1). Ethyl and *n*-butyl substitution gave β-lactones **7** and **12** in high dr and ee, while *i*-butyl incorporation leads to high dr but poor ee (entries 2-4). Variation of the aryl unit within a series of ethylarylketenes was also investigated, with the incorporation of both electron-withdrawing and electron-donating substituents providing β-lactones **14-18** in high dr and ee (entries 5-9). Further substrate variation showed that *iso*-propyl-3-thiopheneketene gave β-lactone **19** with poor dr, although the *anti*-diastereoisomer was formed in high ee (entry 10). The NHC-catalysed reaction of either ethyl-2-tolyl- or ethyl-1-naphthylketene with 2-nitrobenzaldehyde gave no β-lactone products, returning the aldehyde starting material (entries 11 and 12). Notably, the observed trend in product diastereoselectivity using NHC-mediated catalysis (reduced dr for methylarylketenes) is opposite to that observed by Kerrigan using phosphine catalysis (high dr for methylarylketenes, reduced dr for *n*-butylarylketenes).[14]

Table 2. Reaction scope and limitations employing 2-nitrobenzaldehyde



Entry	Ar	R	dr[a] (*syn*:*anti*)	Major product	Yield %[b]	ee %[c] (*syn*,*anti*)
1	Ph	Me	43:57	 **11**	65	90,90
2[d]	Ph	Et	93:7	 **7**	83	93,–
3[d,e]	Ph	*n*-Bu	94:6	 **12**	74	89, –
4	Ph	*i*-Bu	94:6	 **13**	30	<10%,–
5	4-FC_6H_4	Et	93:7	 **14**	69	85, –
6	4-ClC_6H_4	Et	93:7	 **15**	79	86, –
7	4-BrC_6H_4	Et	94:6	 **16**	68	92, –
8	4-MeC_6H_4	Et	90:10	 **17**	52	83, –
9[f]	4-$MeOC_6H_4$	Et	86:14	 **18**	75	86, –
10	2-thienyl	*i*-Pr	45:55	 **19**	35	58,92
11	2-$CH_3C_6H_4$	Et	–	–	–	–
12	1-naphthyl	Et	–	–	–	–

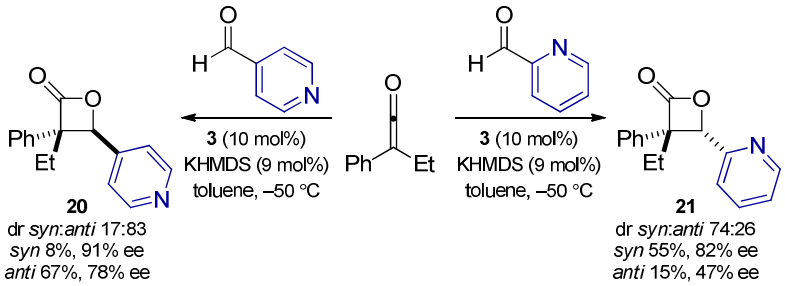
Ketene added dropwise as a solution in toluene. [a]dr determined by ^{1}H NMR analysis of the crude reaction mixture. [b]Isolated yield of mixture of diastereoisomers. [c]ee determined by HPLC analysis. [d]Isolated yield of single diastereoisomer. [e]ee determined by HPLC analysis *via* ring-oepning with NaN_3. [f]1.2 equiv of ketene and 1.0 equiv of aldehyde used.

Evaluating NHC-promoted β-lactone formation using pyridinecarboxaldehydes

Although the use of 2-nitrobenzaldehyde allows efficient access to a range of β-lactones in good yield and typically excellent diastereo- and enantiocontrol, the limited scope of this methodology due to the requirement for a 2-nitro substituent for reasonable diastereoselectivity reduces its synthetic versatility. To address this, the ability of heteroaromatic aldehydes to participate in this methodology was investigated.[27] Accordingly, furfural and all isomers of pyridinecarboxaldehyde were identified as possible participants in this protocol. The formation of chiral pyridine containing compounds is of significance due to their use in both asymmetric catalysis[28] and appearance in biologically relevant molecules.[29] Although a number of methods have previously been developed to prepare these motifs,[30] enantiomerically enriched pyridyl substituted β-lactones, to the best of our knowledge, are unreported.[31]

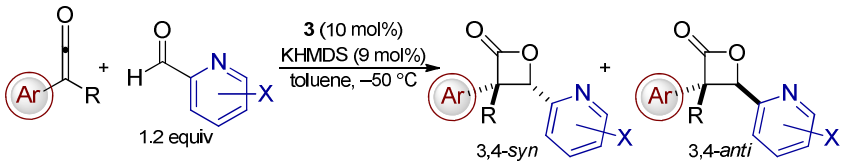
While both furfural and 3-pyridinecarboxaldehyde gave the corresponding β-lactone products with unsatisfactory levels of conversion (<10%), 2- and 4-pyridinecarboxaldehyde both proved efficient coupling partners with ethylphenylketene (Scheme 3). Notably, 2-pyridinecarboxaldehyde preferentially gave the *syn*-diastereoisomer **21** (74:26 *syn*:*anti*), while 4-pyridinecarboxaldehyde preferentially gave the *anti*-diastereoisomer **20** (17:83 *syn*:*anti*), consistent with the differences in *syn*:*anti* product distributions previously observed using 2- and 4-nitrobenzaldehydes.[32] The absolute and relative configuration within β-lactone **21** was unambiguously identified *via* X-ray crystallographic analysis,[33] consistent with the sense of asymmetric induction previously observed using 2-nitrobenzaldehyde.

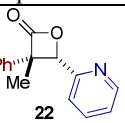
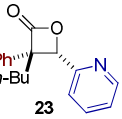
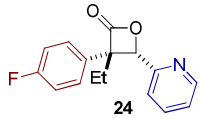
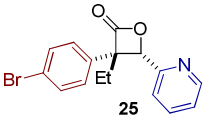
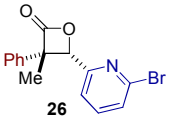
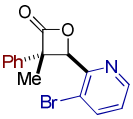
Scheme 3. Initial reactivity employing 2- and 4-pyridinecarboxaldehydes



Subsequent studies probed the generality of this process through variation of the alkylarylketene and through the effect of substitution within the 2-pyridinecarboxaldehyde (Table 3).[33] Using 2-pyridinecarboxaldehyde, variation of either the aryl unit within the ketene or the alkyl chain length had little effect upon reaction stereoselectivity, with *syn*-β-lactones **22**-**25** formed in good dr and ee (entries 1-4). The effect of both electronic and steric perturbation within the 2-pyridyl motif was next investigated. Using methylphenylketene, 6-bromo-2-pyridinecarboxaldehyde gave *syn*-β-lactone **26** (70% combined yield, 80:20 dr *syn*:*anti*, 86% ee *syn*), while 3-bromo-2-pyridinecarboxaldehyde displayed a reversal in diastereoselectivity (18:82 *syn*:*anti*) and excellent enantioselectivity for the major *anti* diastereoisomer **27** (91% ee), albeit with moderate conversion into product (entries 5 and 6).

Table 3. NHC-promoted β-lactone formation using 2-pyridinecarboxaldehydes



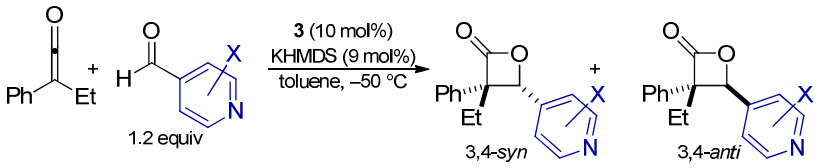
Entry	Ar	R	dr[a] (*syn*:*anti*)	Major product	Yield %[b]	ee %[c] (*syn*,*anti*)
1	Ph	Me	77:23	 **22**	78	88,86
2[d]	Ph	*n*-Bu	82:18	 **23**	62	84,37
3[d]	4-FC_6H_4	Et	82:18	 **24**	73	79,42
4	4-BrC_6H_4	Et	80:20	 **25**	45	80,–
5	Ph	Me	80:20	 **26**	70	86,67
6	Ph	Me	18:82	 **27**	14	–,91

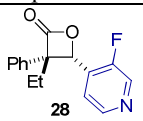
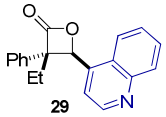
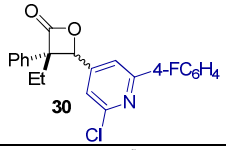
Ketene added dropwise as a solution in toluene. [a]dr determined by ^{1}H NMR analysis of the crude reaction mixture. [b]Isolated yield of separable diastereoisomers. [c]ee determined by HPLC analysis. [d]1.1 equiv of ketene and 1.0 equiv of aldehyde used.

The compatibility of a range of 4-pyridinecarboxaldehyde derivatives of increasing complexity with the methodology was next investigated (Table 4). The use of 3-fluoro-4-pyridinecarboxaldehyde resulted in a switch in diastereoselectivity compared with the parent 4-pyridinecarboxaldehyde, giving moderate diastereocontrol in favour of *syn*-stereoisomer **28** (*syn*:*anti* 63:37, entry 1). 4-Quinolinecarboxaldehyde gave *anti* β-lactone **29** with excellent diastereoselectivity (3:97 *syn*:*anti*) and promising

enantioselectivity (82% ee *anti*) in 57% yield (entry 2). The use of a complex 3,5-disubstituted-4-pyridinecarboxaldehyde gave β-lactone **30** with no diastereocontrol, providing readily separable *syn* and *anti*-lactones (50:50 dr) in good yield and moderate enantioselectivity (70% combined yield, 76% ee *syn* , 74% ee *anti*, entry 3).

Table 4. NHC-promoted β-lactone formation using 4-pyridinecarboxaldehyde derivatives



Entry	dr[a] (*syn*:*anti*)	Major product	Yield %[b]	ee %[c] (*syn*,*anti*)
1	63:37	 **28**	31	37,64
2[d]	3:97	 **29**	57	–,82
3[d]	50:50	 **30**	70	76,74

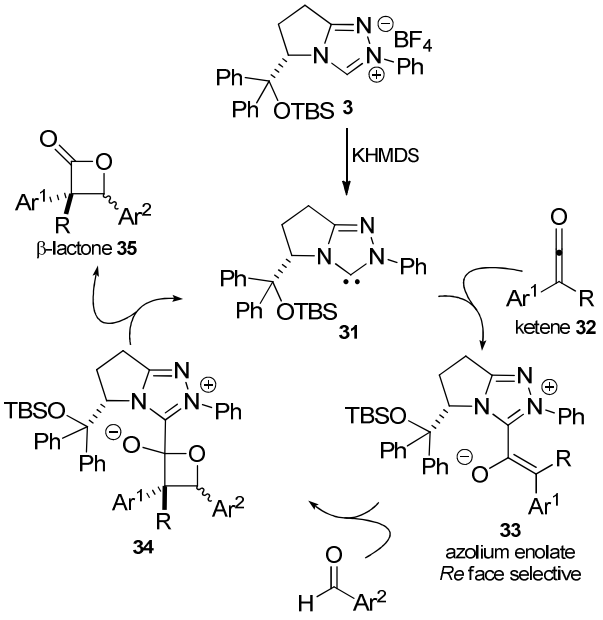
Ketene added dropwise as a solution in toluene. [a]dr determined by ^{1}H NMR analysis of the crude reaction mixture. [b]Isolated yield of separable diastereoisomers. [c]ee determined by HPLC analysis. [d]1.1 equiv of ketene and 1.0 equiv of aldehyde used.

Postulated Reaction Mechanism

While Kerrigan favours Lewis base addition to the aldehyde as the initial step in the phosphine-catalysed β-lactone synthesis from ketenes and benzaldehydes, in this NHC-mediated process, concurrent with the ideas of Ye, we propose initiation through NHC addition to the ketene (Scheme 4). Addition of *in situ* generated NHC **31** to ketene **32** *anti*- to the aryl unit generates azolium enolate intermediate **33**. Subsequent concerted but asynchronous formal [2+2] cycloaddition with electron

deficient benzaldehydes or 2- and 4-pyridinecarboxaldehydes yields zwitterionic intermediate **34**, with subsequent catalyst regeneration and β-lactone formation. The consistency of configuration at the *C*(3) position of all the major diastereoisomeric β-lactone products observed herein is consistent with favourable reaction upon the *Re*-face addition of the azolium enolate **33**. However, given the obvious subtle interplay between steric and electronic factors within the aldehyde component that leads to diastereocontrol in these processes, a full rationale for the differing observed *syn*- or *anti*-selectivities with change in the aldehyde unit is at best speculative.

Scheme 4. Proposed mechanism

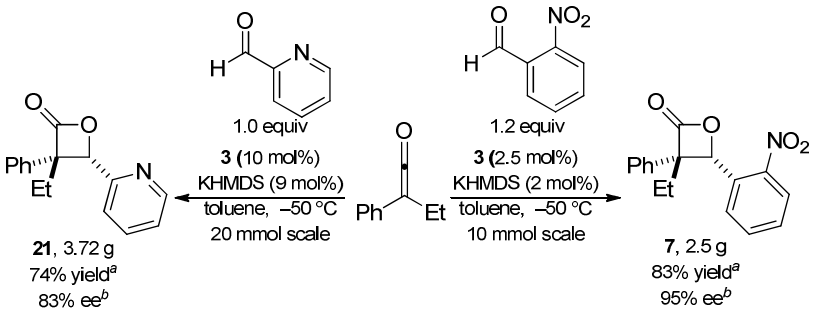


Scale up and derivatisation procedures

To demonstrate the synthetic utility of this methodology, this reaction of ethylphenylkene with 2-nitrobenzaldehyde could be conveniently carried out on a preparative scale with reduced NHC loadings (2.5 mol%), providing >2.5g of β-lactone **7** as a single diastereoisomer after purification and in high ee (83% yield, 95%

ee), which could be recrystallised to enantiopurity. Using higher precatalyst **3** loading of 10 mol%, 2-pyridyl β-lactone **21** could also be obtained as a single diastereoisomer on a >3.5g scale after purification (74% yield, 82:18 dr *syn*:*anti*) and in good enantioselectivity for the major *syn* β-lactone (83% ee).

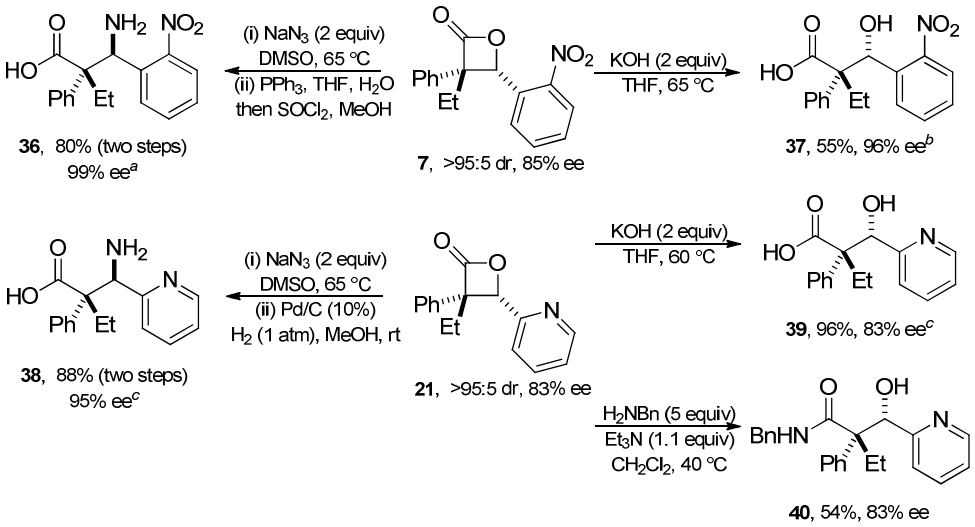
Scheme 5. Scale up of NHC-catalysed reactions with 2-nitrobenzaldehyde and 2-pyridinecarboxaldehyde



[a]Combined isolated yield of separable diastereoisomers. [b]ee determined by HPLC analysis.

Functionalisation of β-lactones **7** and **21** was subsequently achieved through ring opening with either azide or hydroxide to give the corresponding α,α-disubstituted β-amino- and β-hydroxy acid derivatives **36**-**39** as single diastereoisomers without loss of enantiopurity (Scheme 6).[13,34] Alternatively, **21** could be treated with benzylamine to generate β-hydroxy acid amide **40** as single diastereoisomer.

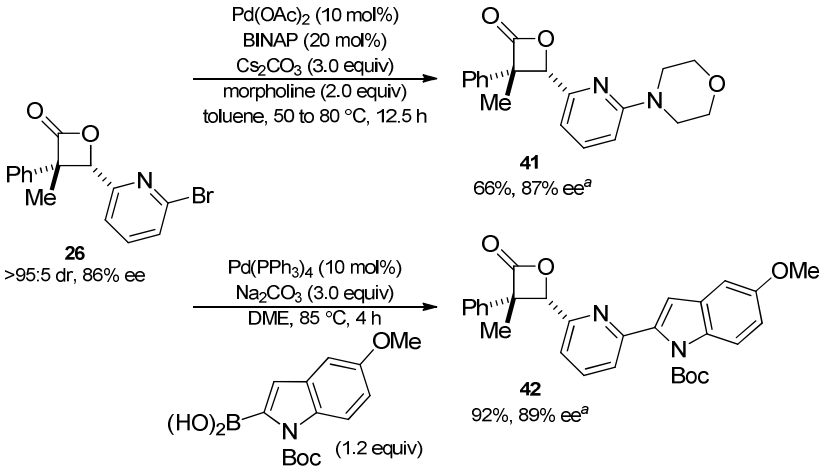
Scheme 6. Derivatisation *via* ring-opening of β-lactones



[a]ee determned by HPLC analysis *via* conversion into NBn, OBn derivative. [b]ee determined by HPLC analysis *via* conversion into OBn ester. [c]ee determined by HPLC analysis *via* conversion into Me ester.

Finally, further complexity within the pyridyl substituted β-lactone series could be obtained *via* palladium cross coupling of β-lactone **26** bearing a bromine substituent (Scheme 7). Both Buchwald-Hartwig[35] and Suzuki[36] couplings of **26** with morpholine and indole **43** respectively provided highly complex β-lactone frameworks **41** and **42** in good yield (66% and 92% yield respectively) and with no erosion of enantiopurity.

Scheme 7. Functionalisation of β-lactones by cross-coupling



[a]ee determined by HPLC analysis.

Conclusion: In summary, an efficient and scalable methodology for the stereocontrolled formation of β-lactones catalyzed by chiral NHCs has been developed. The reaction of a range of disubstituted ketenes with either 2-nitrobenzaldehyde or a variety of 2- and 4-pyridinecarboxaldehydes proceeds with generally excellent levels of enantio- and diastero-selectivity. Importantly, this methodology expands the scope of the formal [2+2] cycloaddition between ketenes and aldehydes to heteroaromatic aldehydes for the first time, allowing access to highly functionalised novel structural architectures. Notably, no competing benzoin or significant formation of ketene dimerisation products were observed under the reaction conditions, with the β-lactones readily transformed into useful synthetic building blocks. Further studies focusing upon the generation and reaction of azolium enolates in NHC-mediated catalysis are underway, alongside mechanistic and kinetic investigations to advance our understanding of the reaction dynamics in these systems.

Experimental

General: All reactions were performed in flame dried glassware using anhydrous solvents. The required aldehydes where purified by Kugelrohr distillation under reduced pressure prior to use. All other reagents were obtained from commercial sources and were used without further purification. Room temperature (rt) refers to 20–25 °C, with temperatures between 0 °C and −50 °C obtained using an immersion cooler. ^{1}H NMR spectra were acquired at either 300, 400, or 500 MHz, ^{13}C{^{1}H} NMR spectra were acquired at either 75, 100, or 125 MHz, and ^{19}F{^{1}H} NMR spectra were acquired at 376 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 ^{1}H COSY and 2D ^{1}H NOESY where necessary. Infra-red spectra were recorded as thin films on either NaCl plates or KBr discs. Mass spectrometry (*m/z*) data were acquired using either electrospray ionisation (ESI), electron impact (EI), atmostpheric solids analysis probe (ASAP), or nanospray ionisation (NSI) using a TOF mass analyser. Optical rotations were recorded with a path length of 1 dm and concentrations, *c*, are quoted in g/100 mL. All chiral HPLC traces were compared with an authentic racemic trace prepared using racemic **3**.

General procedure for the preparation of ketenes: A flame dried two-neck round bottom flask separated by a sintered adaptor to a second two-neck round bottom flask under an argon atmosphere is charged with anhydrous Et_2O and the appropriate acid chloride (1 equiv) before being cooled to 0 °C. Et_3N (1.1 equiv) is added dropwise over 30 min and the reaction stirred overnight at 0 °C. The solution was warmed to rt and filtered through the sintered adaptor into the second flask and concentrated. The

crude oil was transferred *via* cannula into a flame dried Kugelrohr flask and purified by distillation.

Ethylphenylketene: Prepared according to the general procedure from 2-phenylbutanoyl chloride (3.00 g, 16.4 mmol) and Et_3N (2.52 mL, 18.1 mmol) in Et_2O (45 mL). The crude oil was purified *via* Kugelrohr distillation 80–90 °C (5 mbar) {lit 70 °C (0.5 torr)}[37] to give ethylphenylketene (1.40 g, 60%) as light yellow oil that is stable for up to two months in the freezer under an argon atmosphere. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 1.24 (3H, t, *J* 7.4, CH_2CH_3), 2.44 (2H, q, *J* 7.4, CH_2CH_3), 7.02–7.10 (3H, m, Ar*H*), 7.28–7.35 (2H, m, Ar*H*).

Methylphenylketene: Prepared according to the general procedure from 2-phenylpropanoyl chloride (4.05 g, 24.0 mmol) and Et_3N (3.34 mL, 24.0 mmol) in Et_2O (50 mL). The crude oil was purified *via* Kugelrohr distillation 60–80 °C (5 mbar) {lit 50 °C, (4 torr)}[37] to give methylphenylketene (1.44 g, 45%) as yellow/orange oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.92 (3H, s, CH_3), 6.93–6.95 (2H, m, Ar*H*), 6.97–7.01 (1H, m, Ar*H*), 7.21–7.25 (2H, m, Ar*H*).

Butylphenylketene: Prepared according to the general procedure from 2-phenylhexanoyl chloride (3.00 g, 14.2 mmol) and Me_2EtN (1.70 mL, 15.7 mmol) in Et_2O (45 mL). The crude oil was purified *via* Kugelrohr distillation 110–120 °C (5 mbar) to give butylphenylketene (1.26 g, 51%) as yellow/orange oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 0.87 (3H, t, *J* 7.2, *n*Bu*H*), 1.30–1.53 (4H, m, *n*Bu*H*), 2.32 (2H, t, *J* 7.4, *n*Bu*H*), 6.93–7.01 (3H, m, Ar*H*), 7.19–7.25 (2H, m, Ar*H*).

Isobutylphenylketene: Prepared according to the general procedure from 4-methyl-2-phenylpentanoyl chloride (3.80 g, 18.0 mmol) and Me_2EtN (2.15 mL, 20.0 mmol) in Et_2O (45 mL). The crude oil was purified *via* Kugelrohr distillation 110–117 °C (5 mbar) {lit 37–46 °C, (0.8 torr)}[38] to give isobutylphenylketene (1.75 g, 56%) as yellow/orange oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 0.92 (6H, d, *J* 6.6, CH(CH_3)$_2$), 1.66–1.83 (1H, m, C*H*(CH_3)$_2$), 2.19 (2H, d, *J* 7.0, CH_2CH(CH_3)$_2$), 6.95–7.01, (3H, m, Ar*H*), 7.17–7.25 (2H, m, Ar*H*).

Ethyl-4-flourophenylketene: Prepared according to the general procedure from 2-(4-fluorophenyl)butanoyl chloride (2.70 g, 13.5 mmol) and $EtMe_2N$ (1.60 mL, 14.8 mmol) in Et_2O (40 mL). The crude oil was purified *via* Kugelrohr distillation 104–110 °C (7 mbar) to give ethyl-4-flourophenylketene (1.21 g, 55%) as yellow/orange oil. ν_{max} (thin film)/cm^{-1} 2100; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 1.13 (3H, t, *J* 7.4, CH_2CH_3), 2.33 (2H, q, *J* 7.4, CH_2CH_3), 6.87–7.97 (4H, m, Ar*H*); ^{13}C{^{1}H} NMR (75 MHz $CDCl_3$): δ_C 12.9, 17.5, 41.1, 116.1 (d, *J* 21.7), 125.5 (d, *J* 7.6), 128.5 (d, *J* 3.1), 160.5 (d, *J* 243.4), 205.7.

Ethyl-4-chlorophenylketene: Prepared according to the general procedure from 2-(4-chlorophenyl)butanoyl chloride (763 mg, 3.51 mmol) and Et_3N (0.49 mL, 3.51 mmol) in Et_2O (20 mL). The crude oil was purified *via* Kugelrohr distillation 125–135 °C (7 mbar) to give ethyl-4-chlorophenylketene (0.37 g, 56%) as yellow/orange oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 1.34 (3H, t, *J* 7.4, CH_2CH_3), 2.53 (2H, q, *J* 7.4, CH_2CH_3), 7.05–7.09 (2H, m, Ar*H*), 7.37–7.42 (2H, m, Ar*H*).

Ethyl-4-bromophenylketene: Prepared according to the general procedure from 2-(4-

bromophenyl)butanoyl chloride (5.00 g, 19.1 mmol) and Et_2MeN (2.30 mL, 21.0 mmol) in Et_2O (45 mL). The crude oil was purified *via* Kugelrohr distillation 180 °C (7 mbar) to give ethyl-4-bromophenylketene (1.21 g, 28%) as yellow/orange oil. ν_{max} (thin film)/cm^{-1} 2100; ^1H NMR (300 MHz, $CDCl_3$) δ_H 1.13 (3H, t, *J* 7.4, CH_2CH_3), 2.33 (2H, q, *J* 7.4, CH_2CH_3), 6.87–7.97 (4H, m, Ar*H*); $^{13}C\{^1H\}$ NMR (75 MHz $CDCl_3$): δ_C 11.7, 15.9, 40.7, 116.2, 124.4, 130.9, 131.0, 203.2.

Ethyl-4-tolylketene: Prepared according to the general procedure from 2-(*p*-tolyl)butanoyl chloride (2.16 g, 11.0 mmol) and Et_3N (1.53 mL, 11.0 mmol) in Et_2O (40 mL). The crude oil was purified *via* Kugelrohr distillation 110–120 °C (7 mbar) {lit 68–72 °C, (0.2 torr)}[19] to give ethyl-4-tolylketene (0.92 g, 52%) as yellow/orange oil. ^1H NMR (300 MHz, $CDCl_3$) δ_H 1.29 (3H, t, *J* 7.4, CH_2CH_3), 2.40 (3H, s, $ArCH_3$), 2.50 (2H, q, *J* 7.4, CH_2CH_3), 7.02 (2H, d, *J* 8.1, Ar*H*), 7.21 (2H, d, *J* 8.1, Ar*H*).

Ethyl-4-methoxyphenylketene: Prepared according to the general procedure from 2-(4-methoxyphenyl)butanoyl chloride (3.00 g, 14.1 mmol) and Et_3N (3.93 mL, 28.2 mmol) in Et_2O (45 mL). The crude oil was purified *via* Kugelrohr distillation 140–150 °C (3 mbar) to give ethyl-4-methoxyphenylketene (1.19 g, 48%) as yellow/orange oil. ν_{max} (thin film)/cm^{-1} 2096; ^1H NMR (300 MHz, $CDCl_3$) δ_H 1.21 (3H, t, *J* 7.4, CH_2CH_3), 2.41 (2H, q, *J* 7.4, CH_2CH_3), 3.79 (3H, s, $ArCH_3$), 6.86–6.91 (2H, m, Ar*H*), 6.95–6.99 (2H, m, Ar*H*).

Isopropyl-3-thionylketene: Prepared according to a literature procedure[39] from 3-methyl-2-(thiophen-3-yl)butanoyl chloride (2.27 g, 11.2 mmol, 1 equiv) and Me_2EtN (5.46 mL, 50.4 mmol, 4.5 equiv) in THF (30 mL) at 0 °C for 10 min then rt for 4.5 h. The crude oil was purified *via* Kugelrohr distillation 85–90 °C (3 mbar) {lit 71–73 °C}[39] to give isopropyl-3-thionylketene (1.09 g, 59%) as yellow/orange oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 1.25 (6H, d, *J* 6.7, $CH(CH_3)_2$), 2.77 (1H, hep, *J* 6.7, $CH(CH_3)_2$), 6.79–6.82 (2H, m, Ar*H*), 7.33–7.35 (1H, m, Ar*H*).

General procedure for NHC catalysed [2+2] cycloadditions: To a flame dried Schlenk flask under an argon atmosphere was added NHC precursor **3** (0.1 equiv), KHMDS (0.5 M in toluene, 0.09 equiv) and toluene (to give 0.025 M NHC **3**) and the mixture stirred for 15 min. The solution was cooled to –50 °C before the required aldehyde (1.2 equiv) was added followed by dropwise addition of a solution of the required ketene (1.0 equiv) in toluene (0.17 M) over 30 min. The solution was stirred at rt for the time stated before being opened to air and stirred for 30 min. The solution was concentrated *in vacuo* and the crude product purified by silica gel chromatography.

3-Methyl-4-(2-nitrophenyl)-3-phenyloxetan-2-one ***11***: Prepared according to the general procedure from NHC precursor **3** (57.0 mg, 0.10 mmol), KHMDS (0.18 mL, 0.09 mmol), methylphenylketene (132 mg, 1.00 mmol) and 2-nitrobenzaldehyde (181 mg, 1.20 mmol) in toluene (10 mL) at –50 °C for 3.5 h. The crude product (dr 43:57 *syn*:*anti*) was purified by silica gel chromatography (95:5 petrol:Et_2O) to give *syn*-**11** (88 mg, 30%) as colourless solid and *anti*-**11** (103 mg, 35% yield) as colourless solid. ***syn*-11:** mp 68–70 °C; $[\alpha]_D^{20}$ –61 (*c* 0.15, $CHCl_3$); Chiral HPLC analysis Chiralpak

OJ-H (5% IPA:hexane, flow rate 1.0 mL min^{-1}, 220 nm) t_R major (*S*,*R*): 32.0 min, t_R minor (*R*,*S*): 36.2 min, 90% ee; ν_{max} (KBr)/cm^{-1} 2925, 1834 (C=O), 1527, 1341, 1351 1246, 1133, 945, 911, 866, 790, 745, 699; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 2.20 (3H, s, C*H*$_3$), 6.22 (1H, s, C*H*-lactone), 7.00–7.09 (5H, m, Ar*H*), 7.31–7.35 (1H, m, Ar*H*NO_2) 7.55 (1H, td, *J* 7.5, 1.1, Ar*H*NO_2), 7.62 (1H, d, *J* 7.7, Ar*H*NO_2), 7.96 (1H, dd, *J* 8.2, 1.2, Ar*H*NO_2); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ_c 22.4, 67.8, 82.1, 124.9, 126.6, 126.7, 128.0, 128.2, 128.5, 129.2, 132.8, 134.2, 134.4, 146.3, 173.0; HRMS (ASAP) $C_{16}H_{14}O_4N$ $[M+H]^+$ requires 284.0917; found 284.0912 (–1.9 ppm). ***anti*-11:** mp 128–130 °C; $[\alpha]_D^{20}$ –41 (*c* 0.3, $CHCl_3$); Chiral HPLC analysis Chiralpak AS-H (5% IPA:hexane, flow rate 1.0 mL min^{-1}, 220 nm) t_R major (*S*,*S*): 22.5 min, t_R minor (*R*,*R*): 30.4 min, 90% ee; ν_{max} (KBr)/cm^{-1} 2982, 1836 (C=O), 1613, 1578, 1526, 1443, 1342, 1125, 1085, 861, 790, 737, 725, 630; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.34 (3H, s, C*H*$_3$), 6.13 (1H, s, C*H*-lactone), 7.37–7.56 (5H, m, Ar*H*), 7.60–7.64 (1H, m, Ar*H*NO_2), 7.84 (1H, td, *J* 7.6, 0.9, Ar*H*NO_2), 7.95 (1H, d, *J* 7.8, Ar*H*NO_2), 8.25 (1H, dd, *J* 8.2, 1.0, Ar*H*NO_2); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ_c 15.5, 65.9, 82.0, 125.5, 126.1, 128.3, 128.5, 129.1, 129.8, 132.3, 134.9, 137.6, 146.8, 173.0; HRMS (ASAP) $C_{16}H_{14}O_4N$ $[M+H]^+$ requires 284.0904; found 284.0912 (+2.8 ppm).

(3S,4R)-3-Ethyl-4-(2-nitrophenyl)-3-phenyloxetan-2-one ***7***: Prepared according to the general procedure from NHC precursor **3** (28.5 mg, 0.05 mmol), KHMDS (0.09 mL, 0.045 mmol), ethylphenylketene (73.1 mg, 0.50 mmol) and 2-nitrobenzaldehyde (91 mg, 0.60 mmol) in toluene (10 mL) at –50 °C for 3.5 h. The crude product (dr 93:7 *syn*:*anti*) was purified by silica gel chromatography (95:5 petrol:Et_2O) to give *syn*-**7** (157 mg, 83%) as off white solid. mp 58–62 °C [(±) *syn*-**7** mp 86 °C]; $[\alpha]_D^{20}$ –44 (*c*

0.45, $CHCl_3$); Chiral HPLC analysis Chiralpak OJ-H (5% IPA:hexane, flow rate 0.5 mL min^{-1}, 220 nm) t_R major: (*S*,*R*) 43.7 min, t_R minor: (*R*,*S*) 51.1 min, 93% ee; ν_{max} (KBr)/cm^{-1} 3094, 1768 (C=O), 1646, 1513, 1452, 1377, 1214, 1124, 971, 883, 851, 778, 738; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.09 (3H, t, *J* 7.4, CH_2CH_3), 2.51–2.59 (2H, m, CH_2CH_3), 6.19 (1H, s, C*H*lactone), 6.94–7.02 (5H, m, Ar*H*), 7.20–7.27 (1H, m, Ar*H*NO_2), 7.38–7.48 (2H, m, Ar*H*NO_2), 7.90 (1H, dd, *J* 8.2, 1.2, Ar*H*NO_2); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ_c 9.5, 29.4, 73.1, 79.4, 124.8, 126.9, 127.9, 128.3, 128.6, 129.1, 134.1, 146.6, 172.2; HRMS (EI) $C_{17}H_{16}O_4N$ $[M+H]^+$ requires 298.1074; found 298.1078 (+1.4 ppm).

(3S,4R)-3-Butyl-4-(2-nitrophenyl)-3-phenyloxetan-2-one ***12***: Prepared according to the general procedure from NHC precursor **3** (57.0 mg, 0.10 mmol), KHMDS (0.18 mL, 0.09 mmol), butylphenylketene (174 mg, 1.00 mmol) and 2-nitrobenzaldehyde (181 mg, 1.20 mmol) in toluene (10 mL) at −50 °C for 3.5 h. The crude product (dr 94:6 *syn*:*anti*) was purified by silica gel chromatography (95:5 petrol:Et_2O) to give *syn*-**12** (240 mg, 74%) as off white solid. mp 64–66 °C; $[\alpha]_D^{20}$ −20 (*c* 0.60, $CHCl_3$); ν_{max} (KBr)/cm^{-1} 2958, 1828 (C=O), 1527, 1346, 1117, 918, 790, 744, 701; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 0.93 (3H, t, *J* 7.3, *n*BuCH_3), 1.24–1.50 (3H, m, *n*Bu*H*), 1.66–1.81 (1H, m, *n*Bu*H*), 2.56 (2H, dd, *J* 9.3, 7.3, *n*Bu*H*), 6.25 (1H, s, C*H*-lactone), 7.00–7.09 (5H, m, Ar*H*), 7.28–7.33 (1H, m, Ar*H*NO_2), 7.45–7.53 (2H, m, Ar*H*NO_2), 7.97 (1H, dd, *J* 8.2, 1.0, Ar*H*NO_2); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ_c 13.9, 22.9, 27.0, 36.1, 72.4, 79.7, 124.7, 126.7, 127.8, 128.2, 128.5, 129.0, 132.8, 134.0, 134.1, 134.1, 146.5, 172.2; HRMS (ASAP) $C_{19}H_{20}O_4N$ $[M+H]^+$ requires 326.1387; found 326.1381 (–1.8 ppm). *syn*-**12** was ring opened with NaN_3 and converted into its

benzyl ester to allow chiral HPLC analysis: Chiral HPLC analysis Chiralpak AD-H (5% IPA:hexane, flow rate 1.0 mL min^{-1}, 220 nm) t_R minor: 4.9 min, t_R major: 6.4 min, 89% ee.

(3S,4R)-3-Isobutyl-4-(2-nitrophenyl)-3-phenyloxetan-2-one ***13***: Prepared according to the general procedure from NHC precursor **3** (57.0 mg, 0.10 mmol), KHMDS (0.18 mL, 0.09 mmol), *iso*-butylphenylketene (167 mg, 1.00 mmol) and 2-nitrobenzaldehyde (181 mg, 1.20 mmol) in toluene (10 mL) at −50 °C for 6 h. The crude product (dr 94:6 *syn*:*anti*) was purified by silica gel chromatography(95:5 petrol:Et_2O) to give *syn*-**13** (95 mg, 30%) as off white solid. mp 78–80 °C; $[\alpha]_D^{20}$ 0.0 (*c* 0.3, $CHCl_3$); Chiral HPLC analysis Chiralpak OJ-H (5% IPA:hexane, flow rate 1.0 mL min^{-1}, 220 nm) t_R: 10.6 min, t_R: 12.3 min, <10% ee; ν_{max} (KBr)/cm^{-1} 2958, 1819 (C=O), 1613, 1582, 1521, 1448, 1341, 1243, 1118, 974, 904, 788, 842, 706, 642, 534; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 0.82 (3H, d, *J* 6.7, *i*-BuCH_3), 1.06 (3H, d, *J* 6.7, *i*-BuCH_3), 1.90 (1H, hep, *J* 6.6, *i*-Bu*H*) 2.44 (1H, dd, *J* 14.6, 6.4, *i*-BuCH_2), 2.65 (1H, dd, *J* 14.6, 6.4, *i*-BuCH_2), 6.20 (1H, s, C*H*-lactone), 7.00–7.11 (5H, m, Ar*H*), 7.26–7.34 (1H, m, Ar*H*NO_2), 7.41–7.46 (2H, m, Ar*H*NO_2), 7.97 (1H, dt, *J* 8.1, 0.7, Ar*H*NO_2); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ_c 23.8, 23.9, 25.4, 45.3, 72.2, 80.1, 124.7, 126.7, 127.7, 128.2, 128.5, 129.0, 132.6, 134.0, 134.3, 146.8, 172.0; HRMS (ASAP) $C_{19}H_{20}O_4N$ $[M+H]^+$ requires 326.1387; found 326.1382 (−1.5 ppm).

(3S,4R)-3-Ethyl-3-(4-fluorophenyl)-4-(2-nitrophenyl)oxetan-2-one ***14***: Prepared according to the general procedure from NHC precursor **3** (57.0 mg, 0.10 mmol), KHMDS (0.18 mL, 0.09 mmol), ethyl-4-flourophenylketene (211 mg, 1.20 mmol) and 2-nitrobenzaldehyde (151 mg, 1.00 mmol) in toluene (10 mL) at −50 °C for 3 h.

The crude product (dr 93:7 *syn*:*anti*) was purified by silica gel chromatography (95:5 petrol:Et_2O) to give *syn*-**14** (216 mg, 69%) as colourless solid. mp 102–104 °C; $[\alpha]_D^{20}$ –19 (*c* 0.85, $CHCl_3$); Chiral HPLC analysis Chiralpak AS-H (5% IPA:hexane, flow rate 1.0 mL min^{-1}, 220 nm) t_R minor (*R*,*S*): 11.1 min, t_R major (*S*,*R*): 12.3 min, 85% ee; ν_{max} (KBr)/cm^{-1} 2971, 1831 (C=O), 1614, 1605, 1522, 1319, 1353, 1310, 1299, 1225, 1167, 1144, 1118, 1017, 949, 894, 859, 816, 787, 745, 682, 654, 609, 536, 506; ^1H NMR (400 MHz, $CDCl_3$) δ_H 1.15 (3H, t, *J* 7.4, CH_2CH_3), 2.53–2.68 (2H, m, CH_2CH_3), 6.23 (1H, s, C*H*-lactone), 6.74–7.81 (2H, m, 4-FAr*H*), 7.00–7.07 (2H, m, 4-FAr*H*), 7.33–7.38 (1H, m, Ar*H*NO_2), 7.53 (2H, dd, *J* 1.0, 4.9, Ar*H*NO_2), 8.00 (1H, d, *J* 8.1, Ar*H*NO_2); $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ_F –114; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ_c 9.5, 29.6, 72.4, 79.5, 115.6 (d, *J* 21.4), 125.0 128.2, 128.7 (d, *J* 8.2), 129.4, 129.7 (d *J* 3.1) 132.7, 134.3, 146.6, 162.1 (d, *J*, 248), 172.0; HRMS (ASAP) $C_{17}H_{15}FO_4N$ $[M+H]^+$ requires 316.0980; found 316.0974 (–1.8 ppm).

(3S,4R)-3-(4-Chlorophenyl)-3-ethyl-4-(2-nitrophenyl)oxetan-2-one ***15***: Prepared according to the general procedure from NHC precursor **3** (57.0 mg, 0.10 mmol), KHMDS (0.18 mL, 0.09 mmol), ethyl-4-chlorophenylketene (181 mg, 1.00 mmol) and 2-nitrobenzaldehyde (181 mg, 1.20 mmol) in toluene (10 mL) at –50 °C for 3 h h. The crude product (dr 93:7 *syn*:*anti*) was purified by silica gel chromatography (95:5 petrol:Et_2O) to give *syn*-**15** (262mg, 79%) as off white solid. mp 78–80 °C; $[\alpha]_D^{20}$ –15 (*c* 0.5, $CHCl_3$); Chiral HPLC analysis Chiralpak AS-H (5% IPA:hexane, flow rate 0.5 mL min^{-1}, 220 nm) t_R minor (*R*,*S*): 22.5 min, t_R major (*S*,*R*): 24.9 min, 86% ee; ν_{max} (KBr)/cm^{-1} 2975, 1822 (C=O), 1614, 1525, 1497, 1343, 1250, 1130, 1014, 939, 900, 860, 840, 792, 745, 685; ^1H NMR (300 MHz, $CDCl_3$) δ_H 1.14 (3H, t, *J* 7.4, CH_2CH_3),

2.52–2.67 (2H, m, CH_2CH$_3$), 6.22 (1H, s, C*H*-lactone), 6.97–7.08 (4H, m, 4-ClAr*H*), 7.33–7.41 (1H, m, Ar*H*NO$_2$), 7.50–7.55 (2H, m, Ar*H*NO$_2$), 7.98–8.04 (1H, m, Ar*H*NO$_2$); ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) δ_c 9.4, 29.6, 72.4, 79.3, 125.0, 128.2, 128.3, 128.9, 129.5, 132.5 (2×C), 134.0, 134.4, 146.7, 171.7; HRMS (ASAP) $C_{17}H_{15}ClO_4N$ $[M+H]^+$ requires 332.0684; found 332.0681 (–0.9 ppm).

(3S,4R)-3-(4-Bromophenyl)-3-ethyl-4-(2-nitrophenyl)oxetan-2-one ***16***: Prepared according to the general procedure from NHC precursor **3** (57.0 mg, 0.10 mmol), KHMDS (0.18 mL, 0.09 mmol), ethyl-4-bromophenylketene (225 mg, 1.00 mmol) and 2-nitrobenzaldehyde (181 mg, 1.20 mmol) in toluene (10 mL) at –50 °C for 3 h. The crude product (dr 94:6 *syn*:*anti*) was purified by silica gel chromatography (95:5 petrol:Et$_2$O) to give *syn*-**16** (257mg, 68%) as pale brown solid. mp 102–104 °C; $[\alpha]_D^{20}$ –14 (*c* 0.5, CHCl$_3$); Chiral HPLC analysis Chiralpak AS-H (5% IPA:hexane, flow rate 0.2 mL min^{-1}, 220 nm) t_R minor (*R*,*S*): 56.8 min, t_R major (*S*,*R*): 61.7 min, 92% ee; ν_{max} (KBr)/cm^{-1} 2974, 1821 (C=O), 1613, 1526, 1494, 1342, 1249, 1129, 1077, 1011, 957, 938, 899, 860, 839, 791, 744, 721, 652, 517; ^{1}H NMR (300 MHz, CDCl$_3$) δ_H 1.14 (3H, t, *J* 7.4, CH$_2$CH_3), 2.52–2.66 (2H, m, CH_2CH$_3$), 6.22 (1H, s, C*H*-lactone), 6.91–6.96 (2H, m, 4-BrAr*H*), 7.19–7.23 (2H, m, 4-BrAr*H*), 7.34–7.41 (1H, m, Ar*H*NO$_2$), 7.50–7.55 (2H, m, Ar*H*NO$_2$), 8.00–8.04 (1H, m, Ar*H*NO$_2$); ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) δ_c 9.4, 29.6, 72.5, 79.3, 122.2, 125.0, 128.2, 128.6, 129.5, 131.8, 132.5, 133.1, 134.5, 146.7, 171.7; HRMS (ASAP) $C_{17}H_{15}BrO_4N$ $[M+H]^+$ requires 376.0184; found 376.0176 (–0.8 ppm).

(3S,4R)-3-Ethyl-4-(2-nitrophenyl)-3-(p-tolyl)oxetan-2-one ***17***: Prepared according to the general procedure from NHC precursor **3** (57.0 mg, 0.10 mmol), KHMDS (0.18 mL, 0.09 mmol), ethyl-4-tolylketene (167 mg, 1.00 mmol) and 2-nitrobenzaldehyde (181 mg, 1.20 mmol) in toluene (10 mL) at −50 °C for 3 h. The crude product (dr 90:10 *syn*:*anti*) was purified by silica gel chromatography (95:5 petrol:Et_2O) to give *syn*-**17** (162 mg, 52%) as off white solid. mp 100–102 °C; $[\alpha]_D^{20}$ −39 (*c* 0.25, $CHCl_3$); Chiral HPLC analysis Chiralpak AD-H (5% IPA:hexane, flow rate 1.0 mL min^{-1}, 220 nm) t_R minor (*R*,*S*): 9.6 min, t_R major (*S*,*R*): 10.5 min, 83% ee; ν_{max} (KBr)/cm^{-1} 2975, 1825 (C=O), 1612, 1526, 1341, 1236, 1134, 1104, 951, 937, 890, 858, 837, 742, 722, 697, 520; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 1.14 (3H, t, *J* 7.4, CH_2CH_3), 2.14 (3H, s, $ArCH_3$), 2.52–2.66 (2H, m, CH_2CH_3), 6.23 (1H, s, C*H*-lactone), 6.82–6.93 (4H, m, 4-tolylAr*H*), 7.31 (1H, ddd, *J* 8.5, 6.8, 1.8, Ar*H*NO_2), 7.47–7.55 (2H, m, Ar*H*NO_2), 7.98 (1H, dd, *J* 8.3, 1.1, Ar*H*NO_2); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ_c 9.5, 21.0, 29.5, 72.7, 79.6, 124.8, 126.7, 128.3, 129.1, 129.3, 130.7, 133.0, 134.2, 137.6, 146.5, 172.4; HRMS (ASAP) $C_{18}H_{18}O_4N$ $[M+H]^+$ requires 312.1230; found 312.1226 (−1.4 ppm).

(3S,4R)-3-Ethyl-3-(4-methoxyphenyl)-4-(2-nitrophenyl)oxetan-2-one ***18***: Prepared according to the general procedure from NHC precursor **3** (57.0 mg, 0.10 mmol), KHMDS (0.18 mL, 0.09 mmol), ethyl-4-methoxyphenylketene (211 mg, 1.20 mmol) and 2-nitrobenzaldehyde (151 mg, 1.00 mmol) in toluene (10 mL) at −50 °C for 3 h. The crude product (dr 86:14 *syn*:*anti*) was purified by silica gel chromatography (90:10 petrol:Et_2O) to give *syn*-**18** (247 mg, 75%) as off white solid. mp 58–64 °C; $[\alpha]_D^{20}$ −57 (*c* 0.25, $CHCl_3$); Chiral HPLC analysis Chiralpak AS-H (10% IPA:hexane, flow rate 0.8 mL min^{-1}, 220 nm) t_R major (*S*, *R*): 18.5 min, t_R minor (*R*,*S*): 20.4 min,

86% ee; ν_{max} (KBr)/cm^{-1} 2974, 1828 (C=O), 1612, 1578, 1527, 1465, 1300, 1254, 1185, 1109, 945, 895, 837, 791, 742, 699, 686 ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 1.13 (3H, t, *J* 7.4, CH_2CH_3), 2.51–2.64 (2H, m, CH_2CH_3), 3.63 (3H, s, $ArOCH_3$), 6.21 (1H, s, C*H*-lactone), 6.57 (2H, d, *J* 8.9, 4-MeOAr*H*), 6.93 (2H, d, *J* 8.9, 4-MeOAr*H*), 7.31 (1H, ddd, *J* 8.6, 6.7, 2.1, $ArHNO_2$), 7.47–7.55 (2H, m , $ArHNO_2$), 7.96 (1H, dd, *J* 8.3, 0.9, $ArHNO_2$); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ_c 9.4, 29.4, 55.1, 72.3, 79.7, 113.9, 124.8, 125.7, 128.0, 128.2, 129.0, 133.0, 134.2, 146.4, 158.9, 172.4; HRMS (ASAP) $C_{18}H_{18}O_5N$ $[M+H]^+$ requires 328.1179; found 328.1175 (–1.8 ppm).

3-Isopropyl-4-(2-nitrophenyl)-3-(thiophen-3-yl)oxetan-2-one ***19***: Prepared according to the general procedure from NHC precursor **3** (57.0 mg, 0.10 mmol), KHMDS (0.18 mL, 0.09 mmol), isopropyl-3-thionylketene (180 mg, 1.00 mmol) and 2-nitrobenzaldehyde (181 mg, 1.20 mmol) in toluene (10 mL) at 0 °C to rt over 12 h. The crude product (dr 45:55 *syn*:*anti*) was purified by silica gel chromatography (97:3 petrol:Et_2O) to give *syn*-**19** (73 mg, 23%) as pale brown solid and *anti*-**19** (38 mg, 12%) as off white solid. ***syn*-19:** mp 114 °C; $[\alpha]_D^{20}$ –24 (*c* 0.15, $CHCl_3$); Chiral HPLC analysis Chiralpak OJ-H (2% IPA:hexane, flow rate 0.5 mL min^{-1}, 220 nm) t_R major (*S*,*R*): 44.0 min, t_R minor (*R*,*S*): 49.8 min, 58% ee; ν_{max} (KBr)/cm^{-1} 2978, 1825 (C=O), 1613, 1577, 1522, 1342, 1244, 953, 896, 857, 784, 744, 705, 688, 622; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 0.96 (3H, d, *J* 6.8, *i*-PrCH_3), 1.45 (3H, d, *J* 6.8, *i*-PrCH_3), 2.87 (1H, hep, *J* 6.8, *i*-Pr*H*), 6.37 (1H, s, C*H*-lactone), 6.56 (1H, dd, *J* 4.9, 1.5, thiopheneAr*H*), 6.97–7.01 (2H, m, thiopheneAr*H*), 7.30–7.38 (1H, m, $ArHNO_2$), 7.50 (2H, d, *J* 3.9, $ArHNO_2$), 8.01 (1H, dt, *J* 8.1, 0.8, $ArHNO_2$); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ_c 18.4, 19.0, 32.8, 74.5, 76.9, 123.0, 124.7, 125.2, 126.7, 128.3, 129.1, 133.2, 134.2,

135.0, 146.6, 171.2; HRMS (ASAP) $C_{16}H_{16}O_4NS$ $[M+H]^+$ requires 318.0795; found 318.0791 (–1.1 ppm); ***anti*-19:** mp 138–142 °C; $[\alpha]_D^{20}$ +40 (*c* 0.1, $CHCl_3$); Chiral HPLC analysis Chiralpak OJ-H (2% IPA:hexane, flow rate 1.0 mL min^{-1}, 220 nm) t_R major (*S*,*S*): 28.8 min, t_R minor (*R*,*R*): 43.2 min, 92% ee; ν_{max} (KBr)/cm^{-1} 2974, 1818 (C=O), 1613, 1535, 1469, 1389, 1344, 1261, 1227, 1192, 1143, 1121, 995, 955, 902, 883, 863, 831, 790, 744, 710, 686, 638; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 0.41 (3H, d, *J* 6.7, *i*-PrC*H*$_3$), 0.93 (3H, d, *J* 6.8, *i*-PrC*H*$_3$), 2.19 (1H, hep, *J* 6.7, *i*-Pr*H*) 6.32 (1H, s, C*H*-lactone), 7.40 (1H, dd, *J* 5.1, 3.0, thiopheneAr*H*), 7.46 (1H, dd, *J* 5.1, 1.3, thiopheneAr*H*), 7.61-7.68 (2H, m, thiopheneAr*H* and Ar*H*NO_2), 7.82 (1H, tdd, *J* 7.9, 1.5, 0.4, Ar*H*NO_2), 7.93 (1H, dd, *J* 8.0, 1.3, Ar*H*NO_2), 8.22 (1H, dd, *J* 8.2, 1.3, Ar*H*NO_2); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ_c 16.8, 18.2, 29.3, 71.9, 79.0, 124.4, 125.5, 125.6, 128.5, 129.8, 130.1, 131.8, 133.8, 134.2, 148.3, 171.8; HRMS (ASAP) $C_{16}H_{16}O_4NS$ $[M+H]^+$ requires 318.0795; found 318.0788 (–2.1 ppm).

3-Ethyl-3-phenyl-4-(pyridin-4-yl)oxetan-2-one ***20***: Prepared according to the general procedure from NHC precursor **3** (57.0 mg, 0.10 mmol), KHMDS (0.18 mL, 0.09 mmol), ethylphenylketene (175 mg, 1.2 mmol) and 4-pyridinecarboxaldehyde (94 μL, 1.0 mmol) in toluene (20 mL) at –50 °C for 2 h. The crude product (dr 17:83, *syn*:*anti*) was purified by silica gel chromatography (50:50 petrol:Et_2O) to give *anti*-**20** (174 mg, 67%) as colourless solid and *syn*-**20** (21 mg, 8% yield) as colourless solid. ***anti*-20:** mp 74–82 °C; $[\alpha]_D^{20}$ +18.0 (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.08 (3H, t, *J* 7.4, CH_2CH_3), 2.30–2.37 (1H, m, $CH_AH_BCH_3$), 2.38–2.45 (1H, m, $CH_AH_BCH_3$), 5.51 (1H, s, C*H*(Ar)), 6.97–6.98 (2H, m, Ph*H*-4, Py*H*-5), 7.02–7.03 (2H, d, *J* 6.0, Ph*H*), 7.08-7.15 (3H, m, Ph*H*), 8.41 (1H, d, *J* 4.9, Py*H*-6); ^{13}C{^{1}H} NMR

(125 MHz, $CDCl_3$) δ_c 9.4, 31.3, 72.1, 81.2, 121.5, 126.9, 127.9, 128.8, 133.7, 144.6, 149.4, 171.3; Chiral HPLC analysis Chiralpak AS-H (10% IPA:hexane, flow rate 1.0 mL min^{-1}, 254 nm, 30 °C) t_R major (*S,S*): 8.61 min, t_R minor (*R,R*): 12.0 min, 78% ee; ν_{max} (ATR)/cm^{-1} 2974, 1825 (C=O), 1599, 1414, 1107, 1086, 957, 907, 827; HRMS (ESI) $C_{16}H_{16}O_2N$ $[M+H]^+$ requires 254.1176; found 254.1178; ***syn*-20:** mp 66–70 °C; $[\alpha]_D^{20}$ 0.0 (*c* 0.01, $CHCl_3$); Chiral HPLC analysis Chiralpak AS-H (5% IPA:hexane, flow rate 1.0 mL min^{-1}, 254 nm) t_R major (*S,R*): 15.5 min, t_R minor (*R,S*): 18.1 min, 91% ee; ν_{max} (ATR)/cm^{-1} 2974, 1829 (C=O), 1603, 1418, 1242, 1098, 947, 901; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 0.69 (3H, t, *J* 7.4, CH_2CH_3), 1.45–1.53 (1H, m, $CH_AH_BCH_3$), 1.64–1.71 (1H, m, $CH_AH_BCH_3$), 5.63 (1H, s, C*H*(Ar)), 7.37–7.48 (7H, m, Ph*H*, Py*H*-3,4,5), 8.74 (1H, d, *J* 5.8, Py*H*-6); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ_c 8.5, 27.5, 69.1, 81.2, 120.7, 126.3, 128.3, 129.3, 136.8, 144.1, 150.2, 171.0; HRMS (ESI) $C_{16}H_{16}O_2N$ $[M+H]^+$ requires 254.1176; found 254.1178.

3-Ethyl-3-phenyl-4-(pyridin-2-yl)oxetan-2-one ***21***: Prepared according to the general procedure from NHC precursor **3** (57.0 mg, 0.10 mmol), KHMDS (0.18 mL, 0.09 mmol), ethylphenylketene (146 mg, 1.00 mmol) and 2-pyridinecarboxaldehyde (114 μL, 1.20 mmol) in toluene (20 mL) at −50 °C for 3 h. The crude product (dr 74:26, *syn*:*anti*) was purified by silica gel chromatography (95:5 to 90:10 petrol:EtOAc) to give *syn*-**21** (140 mg, 55%) as pale brown solid and *anti*-**21** (38 mg, 15% yield) as pale brown oil. ***syn*-21:** mp 72–76 °C; $[\alpha]_D^{20}$ −63.7 (*c* 0.51, $CHCl_3$); Chiral HPLC analysis Chiralpak AD-H (5% IPA:hexane, flow rate 1.0 mL min^{-1}, 220 nm) t_R minor (*R,R*): 8.6 min, t_R major (*S,S*): 9.3 min, 82% ee; ν_{max} (ATR)/cm^{-1}1819 (C=O), 1591, 1453, 1105, 1094, 955, 893; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 1.07 (3H, t, *J* 7.4,

CH_2CH_3), 2.28–2.35 (1H, m, $CH_AH_BCH_3$), 2.37–2.44 (1H, m, $CH_AH_BCH_3$), 5.71 (1H, s, C*H*(Ar)), 7.00–7.09 (7H, m, Ph*H*, Py*H*-3,5), 7.41 (1H, td, *J* 7.7, 1.5, Py*H*-4), 8.46 (1H, dd, *J* 4.8, 0.6, Py*H*-6); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ_c 9.3, 31.7, 71.8, 82.5, 121.4, 123.3, 127.0, 127.3, 128.3, 134.6, 136.6, 148.8, 155.5, 172.1; HRMS (ESI) $C_{16}H_{16}O_2N$ $[M+H]^+$ requires 254.1176; found 254.1176; ***anti*-21:** $[\alpha]_D^{20}$ 0.0 (*c* 0.26, $CHCl_3$); Chiral HPLC analysis Chiralpak AS-H (2% IPA:hexane, flow rate 1.0 mL min^{-1}, 220 nm) t_R major (*S*,*R*): 8.82 min, t_R minor (*R*,*S*): 10.4 min, 47% ee; ν_{max} (ATR)/cm^{-1} 2974, 1822 (C=O), 1591, 1437, 1110, 1088, 959, 914, 764; ^1H NMR (500 MHz, $CDCl_3$) δ_H 0.64 (3H, t, *J* 7.4, CH_2CH_3), 1.52–1.59 (1H, m, $CH_AH_BCH_3$), 1.61-1.68 (1H, m, $CH_AH_BCH_3$), 5.77 (1H, s, C*H*(Ar)), 7.31–7.36 (2H, m, Ph*H*-4, Py*H*-5), 7.45 (2H, t, *J* 7.7, Ph*H*), 7.59 (1H, d, *J* 7.8, Py*H*-3), 7.64 (1H, d, *J* 7.3, Ph*H*), 7.83 (1H, td, *J* 7.7, 1.4, Py*H*-4), 8.70 (1H, d, *J* 4.8, Py*H*-6); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ_c 8.5, 28.0, 69.1, 82.2, 120.7, 123.3, 126.9, 127.8, 128.9, 137.0, 137.5, 149.7, 155.5, 171.9; HRMS (ESI) $C_{16}H_{16}O_2N$ $[M+H]^+$ requires 254.1176; found 254.1179.

3-Methyl-3-phenyl-4-(pyridin-2-yl)oxetan-2-one ***22***: Prepared according to the general procedure from NHC precursor **3** (57.0 mg, 0.10 mmol), KHMDS (0.18 mL, 0.09 mmol), methylphenylketene (132 mg, 1.00 mmol) and 2-pyridinecarboxaldehyde (114 μL, 1.20 mmol) in toluene (20 mL) at −50 °C for 3 h. The crude product (dr 77:23 *syn:anti*) was purified by silica gel chromatography (95:5 to 90:10 petrol:EtOAc) to give *syn*-**22** (144 mg, 60%) as colourless solid and *anti*-**22** (42 mg, 18%) as colourless oil. ***syn*-22:** mp 94–98 °C; $[\alpha]_D^{20}$ −37.1 (*c* 0.49, $CHCl_3$); Chiral HPLC analysis Chiralpak AD-H (2% IPA:hexane, flow rate 1.0 mL min^{-1}, 220 nm) t_R minor (*R*,*R*): 15.0 min, t_R major (*S*,*S*): 17.2 min, 88% ee; ν_{max} (ATR)/cm^{-1} 1821 (C=O), 1591, 1453,

1257, 1099, 952, 754; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 2.00 (3H, s, C*H*$_3$), 5.68 (1H, s, C*H*(Ar)), 7.02–7.10 (7H, m, Ph*H*, Py*H*-3,5), 7.43 (1H, td, *J* 7.7, 1.4, Py*H*-4), 8.44 (1H, dd, *J* 5.1, 1.3, Py*H*-6); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ_c 24.7, 66.9, 84.3, 121.0, 123.2, 126.6, 127.4, 128.3, 135.8, 136.5, 148.9, 155.3, 172.7; HRMS $C_{15}H_{14}O_2N$ (ESI) $[M+H]^+$ requires 240.1019; found 240.1022; ***anti*-22:** $[\alpha]_D^{20}$ –21.6 (*c* 0.26, $CHCl_3$); Chiral HPLC analysis Chiralpak AS-H (2% IPA:hexane, flow rate 1.0 mL min^{-1}, 220 nm) t_R major (*S*,*R*): 11.6 min, t_R minor (*R*,*S*): 13.3 min, 86% ee; ν_{max} (ATR)/cm^{-1} 1828 (C=O), 1591, 1437, 1140, 1086, 995, 961, 768; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 1.24 (3H, s, C*H*$_3$), 5.80 (1H, s, C*H*(Ar)), 7.31–7.36 (2H, m, Ph*H*-4, Py*H*-5), 7.45 (2H, t, *J* 7.7, Ph*H*), 7.58 (1H, d, *J* 7.8, Py*H*-3), 7.64–7.65 (2H, m, Ph*H*), 7.83 (1H, td, *J* 7.7, 1.5, Py*H*-4), 8.71 (1H, d, *J* 4.7, Py*H*-6); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ_c 21.4, 65.1, 81.9, 120.4, 123.3, 126.0, 127.9, 129.2, 137.1, 139.7, 149.8, 155.5, 172.6; HRMS (ESI) $C_{15}H_{14}O_2N$ $[M+H]^+$ requires 240.1019; found 240.1022.

3-Butyl-3-phenyl-4-(pyridin-2-yl)oxetan-2-one ***23***: Prepared according to the general procedure from NHC precursor **3** (57.0 mg, 0.10 mmol), KHMDS (0.18 mL, 0.09 mmol) butylphenylketene (174 mg, 1.00 mmol) and 2-pyridinecarboxaldehyde (114 μL, 1.20 mmol) in toluene (20 mL) at –50 °C for 3 h. The crude product (dr 82:18, *syn*:*anti*) was purified by silica gel chromatography (95:5 to 90:10 petrol:EtOAc) to give *syn*-**23** (128 mg, 45%) as colourless solid and *anti*-**23** (47 mg, 17%) as colourless oil. ***syn*-23:** $[\alpha]_D^{20}$ –41.7 (*c* 0.36, $CHCl_3$); Chiral HPLC analysis Chiralpak AS-H (2% IPA:hexane, flow rate 1.0 mL min^{-1}, 220 nm) t_R major (*S*,*S*): 8.5 min, t_R minor (*R*,*R*): 12.0 min, 84% ee; ν_{max} (ATR)/cm^{-1} 2959, 1825 (C=O), 1591, 1439, 1259, 1109, 930, 761; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 0.87 (3H, t, *J* 7.2, C*H*$_3$), 1.15–1.43 (3H, m, *n*-

Bu*H*), 1.57–1.71 (1H, m, *n*-Bu*H*), 2.21–2.38 (2H, m, *n*-Bu*H*), 5.70 (1H, s, C*H*(Ar)), 6.98–7.11 (7H, m, Ph*H*, Py*H*-3,4,5), 7.40 (1H, td, *J* 7.8, 1.7, Py*H*-4), 8.46 (1H, ddd, *J* 4.8, 1.6, 0.9, Py*H*-6); $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) δ_c 13.9, 22.8, 26.9, 38.4, 71.2, 82.7, 121.3, 123.3, 127.0, 127.3, 128.3, 134.9, 136.5, 148.9, 155.5, 172.2; HRMS (ESI) $C_{18}H_{20}NO_2$ [M+H$^+$ requires 282.1494; found 282.1492; ***anti*-23:** $[\alpha]_D^{20}$ +2.4 (*c* 0.21, $CHCl_3$); Chiral HPLC analysis Chiralpak OD-H (1% IPA:hexane, flow rate 1.0 mL min^{-1}, 220 nm) t_R major (*S*,*R*): 6.8 min, t_R minor (*R*,*S*): 9.5 min, 37% ee; ν_{max} (ATR)/cm^{-1} 2957, 1825 (C=O), 1589, 1437, 1259, 1109, 1090, 997, 934, 775; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 0.61 (3H, s, CH_3), 0.75–1.03 (3H, m, *n*-Bu*H*), 1.14–1.23 (1H, m, *n*-Bu*H*), 1.48–1.57 (2H, m, *n*-Bu*H*), 5.76 (1H, s, C*H*(Ar)), 7.31–7.36 (2H, m, Ph*H*-4, Py*H*-5), 7.44 (2H, t, *J* 7.7, Ph*H*), 7.58 (1H, d, *J* 7.8, Py*H*-3), 7.63 (2H, d, *J* 7.9, Ph*H*), 7.83 (1H, td, *J* 7.7, 1.5, Py*H*-4), 8.71 (1H, d, *J* 4.7, Py*H*-6); $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) δ_c 13.7, 22.6, 26.0, 34.3, 68.7, 82.2, 120.8, 123.4, 126.8, 127.8, 128.9, 137.0, 138.0, 149.7, 155.5, 172.0; HRMS (ESI) $C_{18}H_{20}NO_2$ [M+H]$^+$ requires 282.1494; found 282.1493.

3-Ethyl-3-(4-fluorophenyl)-4-(pyridin-2-yl)oxetan-2-one ***24***: Prepared according to the general procedure from NHC precursor **3** (57.0 mg, 0.10 mmol), KHMDS (0.18 mL, 0.09 mmol), ethylphenylketene (164 mg, 1.00 mmol) and 2-pyridinecarboxaldehyde (114 μL, 1.20 mmol) in toluene (20 mL) at −50 °C for 3 h. The crude product (dr 82:18, *syn*:*anti*) was purified by silica gel chromatography (90:10 to 80:20 petrol:EtOAc) to give *syn*-**24** (159 mg, 59%) as colourless solid and *anti*-**24** (38 mg, 14%) as colourless solid. ***syn*-24:** mp 82–84 °C; $[\alpha]_D^{20}$ −57.8 (*c* 0.71, $CHCl_3$); Chiral HPLC analysis Chiralpak AS-H (2% IPA:hexane, flow rate 1.0 mL

min^{-1}, 220 nm) t_R major (*S,S*): 9.9 min, t_R minor (*R,R*): 13.5 min, 79% ee; ν_{max} (ATR)/cm^{-1}1819 (C=O), 1512, 1438, 1229, 1113, 897, 840, 795, 767; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 1.05 (3H, t, *J* 7.4, C*H*$_3$), 2.21–2.33 (1H, m, C*H*$_A$H$_B$CH$_3$), 2.33-2.45 (1H, m, CH$_A$*H*$_B$CH$_3$), 5.68 (1H, s, C*H*(Ar)), 6.71–6.79 (2H, m, Ph*H*-3,5), 6.97–7.09 (4H, m, Ph*H*-2,6, Py*H*-3,5), 7.45 (1H, td, *J* 7.8, 1.7, Py*H*-4), 8.46 (1H, ddd, *J* 4.8, 1.6, 0.6, Py*H*-6); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ_c 9.3, 31.8, 71.1, 82.3, 115.2 (d, *J* 21.4), 121.2, 123.4, 128.8 (d, *J* 8.1), 130.4 (d, *J* 3.0), 136.7, 148.9, 155.4, 161.8 (d, *J* 246), 171.9; HRMS (ESI) $C_{16}H_{15}O_2NF$ $[M+H]^+$ requires 272.1081; found 272.1086; ***anti*-24:** mp 82–84 °C; $[\alpha]_D^{20}$ 0.0 (*c* 0.26, $CHCl_3$); Chiral HPLC analysis Chiralpak AS-H (2% IPA:hexane, flow rate 1.0 mL min^{-1}, 220 nm) t_R major (*S,R*): 9.51 min, t_R minor (*R,S*): 10.4 min, 42% ee; ν_{max} (ATR)/cm^{-1} 1827 (C=O), 1591, 1508, 1437, 1219, 1113, 1088, 961, 917, 838; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 0.63 (3H, t, *J* 7.4, C*H*$_3$), 1.45–1.56 (1H, m, C*H*$_A$H$_B$CH$_3$), 1.57–1.68 (1H, m, CH$_A$*H*$_B$CH$_3$), 5.72 (1H, s, C*H*(Ar)), 7.09–7.17 (2H, m, Ph*H*-3,5), 7.30–7.34 (1H, m, Py*H*-5), 7.55–7.65 (3H, m, Py*H*-3, Ph*H*-2,6), 7.82 (1H, td, *J* 7.7, 1.7, Py*H*-4), 8.67–8.70 (1H, m, Py*H*-6); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ_c 8.4, 28.1, 68.4, 82.1, 115.8 (d, *J* 21.5), 120.6, 123.4, 128.7 (d, *J* 8.1), 133.2 (d, *J* 3.1), 137.1, 149.7, 155.3, 162.4 (d, *J* 246), 171.6; HRMS (ESI) $C_{16}H_{15}O_2NF$ $[M+H]^+$ requires 272.1081; found 272.1086.

(3S,4S)-3-(4-Bromophenyl)-3-ethyl-4-(pyridin-2-yl)oxetan-2-one ***25***: Prepared according to the general procedure from NHC precursor **3** (15.0 mg, 0.026 mmol), KHMDS (47 μL, 0.024 mmol), ethyl-4-bromophenylketene (59 mg, 0.26 mmol) and 2-pyridinecarboxaldehyde (30 μL, 0.32 mmol) in toluene (5 mL) at −50 °C for 3 h. The crude product (dr 80:20, *syn*:*anti*) was purified by silica gel chromatography

(95:5 to 90:10 petrol:EtOAc) to give *syn*-**25** (39 mg, 45%) as colourless solid. $[\alpha]_D^{20}$ –40 (*c* 0.09, $CHCl_3$); Chiral HPLC analysis Chiralpak AD-H (2% IPA:hexane, flow rate 1.0 mL min^{-1}, 220 nm) t_R minor (*R*,*R*): 14.1 min, t_R major (*S*,*S*): 15.8 min, 80% ee; ν_{max} (ATR)/cm^{-1} 2974, 1819 (C=O), 1589, 1489, 1115, 1099, 1076, 1009, 943, 901, 843, 824; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 1.06 (3H, t, *J* 7.4, CH_3), 2.21–2.32 (1H, m, CH_AH$_B$CH$_3$), 2.33–2.44 (1H, m, CH$_A$$H_BCH_3$), 5.69 (1H, s, C*H*(Ar)), 6.89–6.94 (2H, m, Ar*H*), 7.05 (1H, d, *J* 7.9, Py*H*-3), 7.10 (1H, ddd, *J* 7.9, 4.9, 0.9, Py*H*-5), 7.18–7.23 (2H, m, Ar*H*), 7.48 (1H, td, *J* 7.9, 1.7, Py*H*-4), 8.47–8.49 (1H, m, Py*H*-6); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ_c 9.3, 31.8, 71.2, 82.2, 121.3, 121.6, 123.5, 128.8, 131.4, 133.8, 136.8, 149.0, 155.3, 171.6; HRMS (ESI) $C_{16}H_{15}O_2NBr$ $[M+H]^+$ requires 332.0281; found 332.0287.

4-(6-Bromopyridin-2-yl)-3-methyl-3-phenyloxetan-2-one ***26***: Prepared according to the general procedure from NHC precursor **3** (57.0 mg, 0.10 mmol), KHMDS (0.18 mL, 0.09 mmol), methylphenylketene (145 mg, 1.10 mmol) and 6-bromo-2-pyridinecarboxaldehyde (186 mg, 1.00 mmol) in toluene (20 mL) at –50 °C for 3 h. The crude product (dr 80:20, *syn*:*anti*) that was purified by silica gel chromatography (5% Et_2O:petrol) to give *syn*-**26** (175 mg, 55%) as colourless solid and *anti*-**26** (47 mg, 15%) as pale yellow oil. ***syn*-26:** mp 112–118 °C; $[\alpha]_D^{20}$ –24.9 (*c* 1.00, $CHCl_3$); Chiral HPLC analysis Chiralpak AS-H (2% IPA:hexane, flow rate 1.0 mL min^{-1}, 220 nm) t_R major (*S*,*S*): 13.2 min, t_R minor (*R*,*R*): 15.9 min, 86% ee; ν_{max} (ATR)/cm^{-1}1811 (C=O), 1557, 1437, 1416, 1260, 1119, 962, 878, 791; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 2.00 (3H, s, CH_3), 5.64 (1H, s, C*H*(Ar)), 7.00 (1H, d, *J* 7.5, Py*H*-3), 7.05–7.09 (3H, m, Ph*H*), 7.11–7.15 (2H, m, *J* 7.2, Ph*H*), 7.22 (1H, d, *J* 7.8, Py*H*-5), 7.28 (1H, t, *J* 7.8,

Py*H*-4); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ_c 24.6, 67.5, 83.3, 119.7, 126.6, 127.6, 127.7, 128.5, 135.4, 138.8, 141.1, 156.9, 172.3; HRMS (ESI) $C_{15}H_{13}O_2NBr$ $[M+H]^+$ requires 318.0124; found 318.0132; ***anti*-26:** $[\alpha]_D^{20}$ +24.0 (*c* 0.20, $CHCl_3$); Chiral HPLC analysis Chiralpak AS-H (2% IPA:hexane, flow rate 1.0 mL min^{-1}, 220 nm) t_R major (*S*,*R*): 12.8 min, t_R minor (*R*,*S*): 16.0 min, 67% ee; ν_{max} (ATR)/cm^{-1} 2974, 1832 (C=O), 1582, 1558, 1437, 1406, 1123, 1082, 986, 972, 781; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 1.28 (3H, s, CH_3), 5.73 (1H, s, C*H*(Ar)), 7.35 (1H, t, *J* 7.4, Ph*H*-4), 7.45 (2H, t, *J* 7.7, Ph*H*), 7.51 (1H, d, *J* 7.9, Py*H*-5), 7.54 (1H, d, *J* 7.6, Py*H*-3), 7.61 (2H, d, *J* 7.5, Ph*H*), 7.69 (1H, t, *J* 7.8, Py*H*-4); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ_c 21.5, 65.5, 81.2, 119.3, 126.0, 127.9, 128.1, 129.2, 139.2, 139.4, 142.3, 156.9, 172.1; HRMS (ESI) $C_{15}H_{13}O_2NBr$ $[M+H]^+$ requires 318.0124; found 318.0129.

(3S,4R)-4-(3-Bromopyridin-2-yl)-3-methyl-3-phenyloxetan-2-one ***27***: Prepared according to the general procedure from NHC precursor **3** (57.0 mg, 0.10 mmol), KHMDS (0.18 mL, 0.09 mmol), methylphenylketene (145 mg, 1.10 mmol) and 3-bromo-2-pyridinecarboxaldehyde (186 mg, 1.00 mmol) in toluene (20 mL) at −50 °C for 3 h. The crude product (dr 18:82 *syn*:*anti*) was purified by silica gel chromatography (80:20 petrol:EtOAc) to give *anti*-**27** (45 mg, 14% yield) as pale brown solid. mp 118−122 °C; $[\alpha]_D^{20}$ +26.5 (*c* 0.50, $CHCl_3$); Chiral HPLC analysis Chiralpak AD-H (2% IPA:hexane, flow rate 1.0 mL min^{-1}, 220 nm, 30 °C) t_R major (*S*,*R*): 19.3 min, t_R minor (*R*,*S*): 21.0 min, 91% ee; ν_{max} (ATR)/cm^{-1} 1819 (C=O), 1427, 1377, 1132, 1090, 959, 700; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.38 (3H, s, CH_3), 6.05 (1H, s, C*H*(Ar)), 7.25 (1H, dd, *J* 8.1, 4.6, Py*H*-5), 7.34–7.40 (1H, m, Ph*H*-4), 7.42–7.47 (2H, m, Ph*H*-3,5), 7.58–7.62 (2H, m, Ph*H*-2,6), 7.95 (1H, dd, *J* 8.1, 1.5,

Py*H*-4), 8.75 (1H, dd, *J* 4.6, 1.5, Py*H*-6); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ_c 17.7, 66.0, 81.0, 120.2, 124.9, 126.1, 128.3, 129.2, 138.8, 140.8, 148.6, 152.6, 172.3; HRMS (ESI) $C_{15}H_{13}O_2NBr$ $[M+H]^+$ requires 318.0124; found 318.0131.

3-Ethyl-4-(3-fluoropyridin-4-yl)-3-phenyloxetan-2-one ***28***: Prepared according to the general procedure from NHC precursor **3** (57.0 mg, 0.10 mmol), KHMDS (0.18 mL, 0.09 mmol), ethylphenylketene (161 mg, 1.10 mmol) and 3-fluoro-4-pyridinecarboxaldehyde (102 μL, 1.00 mmol) in toluene (20 mL) at −50 °C for 3 h. The crude product (dr 63:37 *syn*:*anti*) was purified by silica gel chromatography (90:10 petrol:Et_2O and then 90:10 petrol:EtOAc) to give *syn*-**28** and *anti*-**28** (85 mg, 31%) as colourless oil. ***syn*-28:** $[\alpha]_D^{20}$ +24.0 (*c* 0.03, $CHCl_3$); Chiral HPLC analysis Chiralpak IC (2% IPA:hexane, flow rate 1.0 mL min^{-1}, 254 nm) t_R minor (*R*,*R*): 15.2 min, t_R major (*S,S*): 16.1 min, 37% ee; ν_{max} (ATR)/cm^{-1} (*syn* and *anti*); 2974, 1830 (C=O), 1609, 1568, 1493, 1449, 1416, 1250, 1103, 1053, 959, 905, 914, 841, 756; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.09 (3H, t, *J* 7.4, C*H*$_3$), 2.35–2.51 (2H, m, C*H*$_2$CH$_3$), 5.80 (1H, s, C*H*(Ar)), 7.03–7.17 (6H, m, Ph*H*, Py*H*-5), 8.19 (1H, d, *J* 4.7, Py*H*-6), 8.29 (1H, s, Py*H*-2); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ_c 9.4, 30.3, 72.6, 76.0 (d, *J* 3.5), 121.3, 126.3, 128.3, 128.9, 132.5 (d, *J* 11.1), 133.5, 137.2 (d, *J* 22.9), 145.8 (d, *J* 5.0), 151.5 (d, *J* 235), 170.9; HRMS (ESI) $C_{16}H_{15}O_2NF$ $[M+H]^+$ requires 272.1081; found 272.1086; ***anti*-28:** $[\alpha]_D^{20}$ +20.0 (*c* 0.03, $CHCl_3$); Chiral HPLC analysis Chiralpak AS-H (2% IPA:hexane, flow rate 1.0 mL min^{-1}, 220 nm) t_R major (*S*,*R*): 8.82 min, t_R minor (*R,S*): 10.4 min, 64% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 0.70 (3H, t, *J* 7.4, C*H*$_3$), 1.56–1.65 (1H, m, C*H*$_A$H$_B$CH$_3$), 1.68–1.77 (1H, m, CH$_A$*H*$_B$CH$_3$), 5.87 (1H, s, C*H*(Ar)), 7.39 (1H, tt, *J* 7.2, 1.3, Ph*H*-4), 7.44–7.48 (2H, m, Ph*H*), 7.51–7.54

(2H, m, Ph*H*), 7.57 (1H, t, *J* 5.5, Py*H*-5), 8.58–8.60 (2H, m, Py*H*-2,6); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ_c 8.4, 26.9, 69.9, 77.00 (d, *J* 2.7), 122.0, 126.5 (d, *J* 3.5), 128.4, 129.2, 131.8 (d, *J* 11.4), 136.4, 138.1 (d, *J* 22.8), 146.7 (d, *J* 4.9), 156.6 (d, *J* 256), 170.7; HRMS (ESI) $C_{16}H_{15}O_2NF$ $[M+H]^+$ requires 272.1081; found 272.1085.

(3S,4S)-3-Ethyl-3-phenyl-4-(quinolin-4-yl)oxetan-2-one ***29***: Prepared according to the general procedure from NHC precursor **3** (57.0 mg, 0.10 mmol), KHMDS (0.18 mL, 0.09 mmol), ethylphenylketene (175 mg, 1.20 mmol) and 4-quinolinecarboxaldehyde (157 mg, 1.00 mmol, 1.0 equiv) in toluene (20 mL) at −50 °C for 3 h. The crude product (dr 3:97 *syn*:*anti*) was purified by silica gel chromatography (85:15 petrol:EtOAc) to give *anti*-**29** (172 mg, 57% yield) as pale yellow solid. mp 121−126 °C; $[\alpha]_D^{20}$ +157.2 (*c* 0.46, $CHCl_3$); Chiral HPLC analysis Chiralpak AD-H (5% IPA:hexane, flow rate 1.0 mL min^{-1}, 254 nm) t_R major (*S*,*S*): 12.3 min, t_R minor (*R*,*R*): 17.5 min, 82% ee; ν_{max} (ATR)/cm^{-1} 2976, 1827 (C=O), 1595, 1508, 1246, 1107, 1042, 899, 760; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 0.73 (3H, t, *J* 7.4, CH_3), 1.51−1.58 (1H, m, CH_AH$_B$CH$_3$), 1.64−1.71 (1H, m, CH$_A$$H_BCH_3$), 6.05 (1H, s, C*H*(Ar)), 7.43−7.50 (3H, m, Ar*H*), 7.51−7.57 (4H, m, Ar*H*), 7.65 (1H, d, *J* 4.4, Qu*H*-7), 7.73−7.78 (1H, m, Qu*H*-8), 8.20 (1H, d, *J* 8.4, Qu*H*-5), 9.01 (1H, d, *J* 4.3, Qu*H*-6); $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) δ_c 8.6, 23.6, 69.8, 81.2, 118.2, 122.7, 124.9, 126.6, 127.3, 128.6, 129.6, 129.8, 130.8, 135.6, 140.6, 148.0, 150.4, 171.5; HRMS (ESI) $C_{20}H_{18}O_2N$ $[M+H]^+$ requires 304.1332; found 304.1337.

4-(2-Chloro-6-(4-fluorophenyl)pyridin-4-yl)-3-ethyl-3-phenyloxetan-2-one ***30***: Prepared according to the general procedure from NHC precursor **3** (28.5 mg, 0.05 mmol), KHMDS (90 μL, 0.045 mmol), ethylphenylketene (80.0 mg, 0.55 mmol) and

2-chloro-6-(4-fluorophenyl)isonicotinaldehyde (118 mg, 0.50 mmol) in toluene (10 mL) at −50 °C for 3 h. The crude product (dr 50:50 *syn*:*anti*) was purified by silica gel chromatography (95:5 petrol:Et_2O) to give *syn*-**30** (83 mg, 44%) as colourless solid and *anti*-**30** (50 mg, 26%) as colourless oil. ***syn*-30:** mp 114–118 °C; $[\alpha]_D^{20}$ +15.9 (*c* 0.15, $CHCl_3$); Chiral HPLC analysis Chiralpak AS-H (2% IPA:hexane, flow rate 1.0 mL min^{-1}, 254 nm) t_R major (*S*,*R*): 9.56 min, t_R minor (*R*,*S*): 12.0 min, 76% ee; ν_{max} (ATR)/cm^{-1} 1823 (C=O), 1603, 1549, 1514, 1412, 1323, 1159, 1109, 827, 760; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 0.75 (3H, t, *J* 7.4, CH_3), 1.52–1.64 (1H, m, CH_AH$_B$CH$_3$), 1.70–1.82 (1H, m, CH$_A$$H_BCH_3$), 5.63 (1H, s, C*H*(Ar)), 7.15–7.23 (2H, m, *p*-FPh*H*-3,5), 7.32 (1H, br. s, Py*H*-3), 7.38–7.53 (5H, m, Ph*H*), 7.68 (1H, br. s, Py*H*-5), 8.02–8.09 (2H, m, *p*-FPh*H*-2,6); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ_c 8.6, 27.5, 69.5, 80.9, 115.2, 116.1 (d, *J* 22), 119.1, 126.2, 128.5, 129.2 (d, *J* 8.6), 129.4, 133.3 (d, *J* 3.1), 136.5, 148.1, 152.2, 157.9, 164.3 (d, *J* 251), 170.5; HRMS (ESI) $C_{22}H_{18}O_2NFCl$ $[M+H]^+$ requires 382.1005; found 382.1009; ***anti*-30:** $[\alpha]_D^{20}$ −11.2 (*c* 0.30, $CHCl_3$); Chiral HPLC analysis Chiralpak AS-H (2% IPA:hexane, flow rate 1.0 mL min^{-1}, 254 nm) t_R major (*S*,*S*): 11.3 min, t_R minor (*R*,*R*): 14.9 min, 74% ee; ν_{max} (ATR)/cm^{-1} 2974, 1825 (C=O), 1603, 1459, 1512, 1450, 1231, 1206, 1099, 902, 832; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 1.10 (3H, t, *J* 7.4, CH_3), 2.31–2.51 (2H, m, CH_2CH$_3$), 5.51 (1H, s, C*H*(Ar)), 6.99 (1H, d, *J* 0.7, Py*H*-3), 7.02–7.21 (8H, s, Ar*H*), 7.71–7.78 (2H, m, *p*-FPh*H*-2,6); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ_c 9.4, 31.0, 72.5, 80.5, 115.8, 116.1 (d, *J* 9.1), 120.2, 126.8, 128.3, 128.9 (d, *J* 8.7), 129.1, 133.4, 148.2, 151. 5, 157.1, 166.7 (d, *J* 250), 171.0; HRMS (ESI) $C_{22}H_{18}O_2NFCl$ $[M+H]^+$ requires 382.1005; found 382.1009.

(S)-2-((S)-Amino(2-nitrophenyl)methyl)-2-phenylbutanoic acid ***36***: According to a literature procedure,[13] sodium azide (219 mg, 3.36 mmol, 2.0 equiv) was added to a solution of *syn*-**7** (500 mg, 1.68 mmol, 1.0 equiv) in DMSO (5 mL) in a screw top vial and the mixture heated at 65 ºC for 42 h. The solution was cooled to rt, diluted with $NaHCO_3$ (20mL) and extracted with EtOAc (20 mL). The aqueous phase was acidified with 2 M HCl (50mL) and extracted with EtOAc (3×20 mL). The combined organics were washed with brine (20 mL) and water (20 mL) before being dried over Na_2SO_4 and concentrated to give (*S*)-2-((*S*)-azido(2-nitrophenyl)methyl)-2-phenylbutanoic acid as light brown solid; (564 mg, 99%); mp 156–160 °C; $[\alpha]_D^{20}$ +386 (*c* 0.25, $CHCl_3$); ν_{max} (KBr)/cm^{-1} 2975, 2104 (N_3), 1707 (C=O), 1613, 1528, 1360, 1253, 1227, 1141, 1143, 1121, 857, 783, 831, 698, 744, 677; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 1.10 (3H, t, *J* 7.4, CH_3), 2.10–2.22 (1H, m, CH_AH$_B$CH$_3$), 2.55–2.67 (1H, m, CH$_A$$H_BCH_3$), 6.32 (1H, s, C$HN_3$), 6.42 (1H, dd, *J* 7.9, 1.2, Ar*H*), 6.92–6.98 (2H, m, Ar*H*), 7.18–7.35 (5H, m, Ar*H*), 7.67 (1H, dd, *J* 8.1, 1.4, Ar*H*); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ_c 9.5, 27.6, 60.6, 60.6, 123.9, 127.9, 128.2, 128.8, 129.1, 130.5, 131.1, 131.6, 136.5, 151.2, 178.9; HRMS (EI) $C_{17}H_{15}O_4N_4$ $[M-H]^-$ requires 339.1099; found 339.1093 (–1.7 ppm).

Next, PPh_3 (84 mg, 0.31 mmol, 1.08 equiv) was added to a solution of(*S*)-2-((*S*)-azido(2-nitrophenyl)methyl)-2-phenylbutanoic acid (100 mg, 0.29 mmol, 1.00 equiv) in THF (4 mL) and water (1 mL) in a screw top vial and stirred vigorously for 6 h. The mixture was concentrated before being diluted with methanol and cooled to 0 °C in a screw cap vial. $SOCl_2$ (0.06 mL, 0.30 mmol, 1.0 equiv) was added dropwise and the vial heated at 65 °C for 12 h. The reaction was concentration and the resulting solid was triturated with cold $CHCl_3$ to give (*S*,*S*)-**36** as off white solid; (75 mg, 81%

yield); mp 188–194 °C dec.; $[\alpha]_D^{20}$ +213 (*c* 0.15 MeOH); ν_{max} (KBr)/cm^{-1} 3417, 2800, 1684 (C=O), 1602, 1531, 1496, 1352, 1220, 1195, 857, 713, 603; ^{1}H NMR (300 MHz, $MeOD_3$) δ_H 0.73 (3H, t, *J* 7.1, C*H*$_3$), 1.80–1.99 (2H, m, C*H*$_2$CH$_3$), 5.88 (1H, s, C*H*NH$_2$), 7.12–7.19 (2H, m, Ar*H*), 7.32–7.41 (3H, m, Ar*H*), 7.50–7.55 (1H, m, Ar*H*), 7.59–7.74 (2H, m, Ar*H*), 7.94 (1H, dd, *J* 7.9, 1.5, Ar*H*); ^{13}C{^{1}H} NMR (75 MHz, MeOD) δ_c 9.9, 28.2, 54.9, 59.9, 126.5, 129.0, 129.1, 129.6, 130.1, 130.3, 131.8, 134.4, 137.4, 151.7, 176.2; HRMS (EI) $C_{17}H_{17}O_4N_2$ $[M-H]^-$ requires 313.1194; found 313.1186 (–2.5 ppm).

(*S*,*S*)-**36** was derivatised into its dibenzyl compound to allow chiral HPLC analysis. Benzylbromide (25 μL, 0.21mmol, 2.2 equiv) and DIEPA (0.37 μL, 0.19 mmol, 2.2 equiv) were added to a solution of (*S*,*S*)-**36** (30 mg, 0.10 mmol, 1.0 equiv) in DMF (2 mL) and stirred at rt for 12 h. The reaction was diluted with Et_2O, washed with 2 M HCl and water (×2) before being dried over Na_2SO_4 and concentrated. The crude product was purified by silica gel chromatography (90:10 petrol:Et_2O) to give (*S*)-benzyl 2-((*S*)-(benzylamino)(2-nitrophenyl)methyl)-2-phenylbutanoate (16 mg, 34%) as pale yellow oil; $[\alpha]_D^{20}$ +269 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralpak OD-H (1% IPA:hexane, flow rate 1.0 mL min^{-1}, 220 nm) t_R minor (*R,R*): 15.7 min, t_R major (*S,S*): 19.2 min, 99% ee; ν_{max} (KBr)/cm^{-1}3031, 1730 (C=O), 1646, 1603, 1529, 1496, 1454, 1357, 1218, 1108, 1029, 856, 739, 698; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 0.64 (3H, t, *J* 7.3, C*H*$_3$), 1.78–1.87 (1H, m, C*H*$_A$H$_B$CH$_3$), 2.33–2.41 (1H, m, CH$_A$*H*$_B$CH$_3$), 3.45 (1H, d, *J* 13.4, OC*H*$_A$H$_B$Ph), 3.60 (1H, d, *J* 13.4, OCH$_A$*H*$_B$Ph), 5.00 (1H, d, *J* 12.3, NC*H*$_A$H$_B$Ph), 5.08 (1H, d, *J*, 12.3, NCH$_A$*H*$_B$Ph), 5.30 (1H, s, C*H*NHBn), 6.75 (1H, d, *J* 8.0, Ar*H*), 6.91 (2H, dd, *J* 8.1, 1.4, Ar*H*), 7.11–7.24 (15H, m, Ar*H*), 7.64 (1H, dd, *J* 8.1, 1.4, Ar*H*); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ_c 9.7, 28.7, 51.8, 58.6, 61.6, 66.7,

124.0, 127.0, 127.3, 127.8, 128.0, 128.2, 128.3, 128.5, 128.6, 128.7, 130.1, 131.3, 135.5, 135.6, 139.0, 140.5, 152.6, 173.8; HRMS (EI) $C_{31}H_{31}O_4N_2$ $[M+H]^+$ requires 495.2278; found 495.2271 (–1.5 ppm).

(S)-2-((R)-Hydroxy(2-nitrophenyl)methyl)-2-phenylbutanoic acid ***37***: According to a literature procedure,[13] 1 M KOH (1.35 mL, 1.35 mmol, 2.0 equiv) was added to a solution of *syn*-**7** (200 mg, 0.67 mmol, 1.0 equiv) in THF (4 mL) in a screw cap vial and heated at 65 °C for 5 h. The solution was cooled to rt, diluted with $NaHCO_3$ and extracted with Et_2O. The aqueous layer was slowly acidified with 2 M HCl and extracted with EtOAc (×3). The combined organics were dried over Na_2SO_4 and concentrated to give (*S*,*R*)-**37** as off white solid; (116 mg, 55%); mp 140–148 °C; $[\alpha]_D^{20}$ –406 (*c* 0.05 MeOH); ν_{max} (KBr)/cm^{-1} 3438, 1705 (C=O), 1528, 1355, 1223, 1037, 943, 857; ^{1}H NMR (400 MHz, MeOD) δ_H 0.84 (3H, t, *J* 7.4, C*H*$_3$), 1.79 (2H, q, *J* 7.5, C*H*$_2$CH$_3$), 6.14 (1H, s, C*H*OH), 6.37 (1H, dd, *J* 8.0, 1.2, Ar*H*), 7.05–7.14 (3H, m, Ar*H*), 7.16–7.26 (3H, m, Ar*H*), 7.28–7.33 (1H, m, Ar*H*), 7.65 (1H, dd, *J* 8.1, 1.1, Ar*H*); ^{13}C{^{1}H} NMR (100 MHz, MeOD) δ_c 9.5, 26.7, 49.0, 63.1, 72.0, 123.7, 127.8, 128.0, 129.2, 131.8, 131.9, 132.2, 135.5, 136.8, 151.4, 177.7; HRMS (EI) $C_{17}H_{16}O_5N$ $[M–H]^–$ requires 314.1034; found 314.1029 (–1.6 ppm).

(*S*,*R*)-**37** was derivatised into its benzyl ester to allow chiral HPLC analysis. Benzylbromide (50 μL, 0.37 mmol, 1.2 equiv) and DIEPA (80 μL, 0.37 mmol, 1.2 equiv) were added to a solution of (*S*,*R*)-**37** (98 mg, 0.31 mmol, 1.0 equiv) in DMF (2 mL) and stirred at rt for 12 h. The reaction was diluted with Et_2O, washed with 2 M HCl and water (×2) before being dried over Na_2SO_4 and concentrated. The crude product was purified by silica gel chromatography (80:20 petrol:Et_2O) to give (*S*)-

benzyl 2-((*R*)-hydroxy(2-nitrophenyl)methyl)-2-phenylbutanoate (79 mg, 63%) as orange oil. $[\alpha]_D^{20}$ −807 (*c* 0.3, $CHCl_3$); Chiral HPLC analysis Chiralpak AD-H (5% IPA:hexane, flow rate 1.0 mL min^{-1}, 220 nm) t_R minor (*S,R*): 22.8 min, t_R major (*S,R*): 34.1 min, 96% ee; ν_{max} (KBr)/cm^{-1} 3527, 2975, 1714 (C=O), 1607, 1527, 1447, 1355, 1216, 1125, 1039, 990, 912, 856, 785, 738, 699; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 0.83 (3H, t, *J* 7.3, C*H*$_3$), 1.63–1.75 (1H, m, C*H*$_A$H$_B$CH$_3$), 1.89–2.01 (1H, m, CH$_A$*H*$_B$CH$_3$), 3.87 (1H, d, *J* 4.0, CHO*H*), 5.23 (2H, s, OC*H*$_2$Ph), 6.20 (1H, d, *J* 4.0, C*H*OH), 6.37 (1H, dd, *J* 8.3, 1.1, Ar*H*), 6.83–6.90 (2H, m, Ar*H*), 7.04–7.09 (1H, m, Ar*H*), 7.14–7.21 (2H, m, Ar*H*), 7.23–7.34 (7H, m, Ar*H*), 7.63 (1H, dd, *J* 8.3, 1.1, Ar*H*); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ_c; 9.2, 26.3, 61.3, 67.2, 69.8, 123.0, 127.3, 127.5, 128.3, 128.5, 128.6, 128.6, 129.4, 131.1, 131.1, 132.5, 135.3, 136.6, 149.8, 175.7; HRMS (EI) $C_{24}H_{24}O_5N$ $[M+H]^+$ requires 406.1649; found 406.1650 (+0.2 ppm).

(S)-2-((R)-Amino(pyridin-2-yl)methyl)-2-phenylbutanoic acid ***38***: Based upon a literature procedure,[13] *syn*-**21** (100 mg, 0.39 mmol, 1 equiv) and NaN_3 (51 mg, 0.78 mmol, 2 equiv) in DMSO (1.25 mL) were heated at 65 °C in a sealed screw cap vial for 48 h. The reaction mixture was cooled to rt, diluted with $NaHCO_3$ (5 mL) and washed with EtOAc (5 mL). The aqueous phase was acidified to pH 3 with 1 M HCl before being extracted with EtOAc (3×10 mL). The combined organics were dried over $MgSO_4$ and concentrated before the resulting solid was triturated with Et_2O to give (*S*)-2-((*R*)-azido(pyridin-2-yl)methyl)-2-phenylbutanoic acid (103 mg, 88%) as white solid. mp 138 ºC dec. (Et_2O); $[\alpha]_D^{20}$ +167.1 (*c* 0.70 in $CHCl_3$); ν_{max} (film) 2104 (CN_3), 1699 (C=O), 1599; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 0.99 (3H, t, *J* 7.4, C*H*$_3$), 2.22–2.34 (1H, m, C*H*$_A$H$_B$CH$_3$), 2.37–2.53 (1H, m, CH$_A$*H*$_B$CH$_3$), 5.44 (1H, s, C*H*N_3),

6.84 (1H, d, *J* 7.92, C(5)-py*H*), 7.09–7.24 (5H, m, Ar*H*), 7.29–7.36 (1H, m, Ar*H*), 7.63 (1H, td, *J* 7.8, 1.7, C(4)-py*H*), 8.75 (1H, d, *J* 5.2, C(2)-py*H*); $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) δ_C: 9.6, 28.9, 61.7, 71.2, 124.1, 124.5, 127.4, 127.7, 129.2, 137.2, 138.3, 147.6, 156.1, 173.5; HRMS (NSI^+) $C_{16}H_{17}O_2N_4$ $[M+H]^+$ requires 297.1346; found 297.1346 (+0.0 ppm).

Based upon a literature procedure,[34] (*S*)-2-((*R*)-azido(pyridin-2-yl)methyl)-2-phenylbutanoic acid (103 mg, 0.35 mmol, 1 equiv) and Pd/C (10% w/w, 37 mg, 35 μmol, 10 mol%) were placed under an atmosphere of N_2 before MeOH (6 mL) was added. The solution was placed under an atmosphere of H_2 using a balloon and stirred at rt for 3 h. The reaction mixture was filtered through a pad of Celite®, washing with MeOH, before being concentrated to give (*S*,*R*)-**38** (95 mg, 100%) as white solid. mp 112–115 ºC dec.; $[\alpha]_D^{20}$ −12.6 (*c* 0.54 in $CHCl_3$); ν_{max} (film) 3364 (br. N-H), 1591 (br. C=O), 1572; ^1H NMR (300 MHz, $CDCl_3$) δ_H: 0.78 (3H, t, *J* 7.1, C*H*$_3$), 1.57–1.85 (2H, m, C*H*$_2$CH$_3$), 4.84 (1H, s, C*H*NH$_2$), 6.13 (1H, d, *J* 7.6, C(5)-py*H*), 7.05–7.35 (8H,m, Ar*H*), 8.38 (2H, br. s, N*H*$_2$), 8.49 (1H, d, *J* 4.2, C(2)-py*H*); $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) δ_C: 9.8, 24.0, 58.1, 60.9, 123.2, 124.1, 127.0, 128.2, 129.1, 135.9, 140.6, 148.2, 154.5, 178.0; HRMS (NSI^+) $C_{16}H_{19}O_2N_2$ $[M+H]^+$ requires 271.1442; found 271.1441 (+0.4 ppm).

(*S*,*R*)-**38** was derivatised into its methyl ester to allow chiral HPLC analysis. (*S*,*R*)-**38** (95 mg, 0.35 mmol, 1 equiv) was dissolved in MeOH (1.75 mL) under an inert atmosphere of nitrogen. (Trimethylsilyl)diazomethane (0.6 M in hexanes, 0.65 mL, 0.39 mmol, 1.1 equiv) was added dropwise and the resulting solution was stirred at rt for 3 h in the absence of light. The reaction was quenched with $NaHCO_3$, diluted with H_2O and extracted with Et_2O (×3). The combined organics were washed with brine, dried over $MgSO_4$, and concentrated. The crude product was purified by silica gel

chromatography (95:5 CH_2Cl_2:MeOH) to give (*S*)-methyl 2-((*R*)-amino(pyridin-2-yl)methyl)-2-phenylbutanoate (47 mg, 47%) as orange oil. $[\alpha]_D^{20}$ −25.0 (*c* 0.58 in $CHCl_3$); Chiral HPLC analysis, Chiralpak AD-H (5% IPA:hexane, flow rate 1 mL min^{-1}, 254 nm, 30 ºC) t_R (minor): 30.4 min, t_R (major): 34.3 min, 95% ee; ν_{max} (film) 1724 (C=O), 1589, 1570; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 0.65 (3H, t, *J* 7.4, $CH_AH_BCH_3$), 1.65–1.77 (1H, m, $CH_AH_BCH_3$), 1.91–2.03 (1H, m, $CH_AH_BCH_3$), 2.50 (2H, br. s, NH_2), 3.69 (3H, s, OCH_3), 4.59 (1H, s, $CHNH_2$), 6.96 (1H, br. d, *J* 8.0, C(5)-py*H*), 7.01–7.29 (6H, m, Ar*H*), 7.46 (1H, td, *J* 7.6, 1.9, C(4)-py*H*), 8.42–8.46 (1H, m, C(2)-py*H*); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ_C: 9.9, 29.0, 51.9, 61.7, 63.0, 122.6, 123.9, 127.0, 128.2, 128.4, 135.9, 139.7, 148.9, 159.7, 174.6; HRMS (NSI^+) $C_{17}H_{21}N_2O_2$ $[M+H]^+$ requires 285.1598; found 285.1601 (+1.2 ppm).

(S)-2-((S)-Hydroxy(pyridin-2-yl)methyl)-2-phenylbutanoic acid ***39***: Based upon a literature procedure,[13] *syn*-**21** (100 mg, 0.39 mmol, 1 equiv), 1 M KOH (0.79 mL, 0.79 mmol, 2 equiv) and THF (1.3 mL) were heated at 60 °C in a screw cap vial for 16 h. The solution was cooled to rt before being concentrated. The resulting oil was dissolved in EtOAc (5 mL) and acidified to pH 3 with 1 M HCl. The layers were separated and the aqueous extracted with EtOAc (2×5 mL) before the combined organics were washed with brine, dried over $MgSO_4$, and concentrated to give (*S*,*S*)-**39** (102 mg, 96%) as pale yellow solid. mp 48–50 ºC; $[\alpha]_D^{20}$ −99.6 (*c* 1.12 in $CHCl_3$); ν_{max} (film) 3439 (br. O-H), 1699 (C=O), 1601; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 1.00 (3H, t, *J* 7.4, CH_3), 1.99–2.16 (1H, m, $CH_AH_BCH_3$), 2.21–2.39 (1H, m. $CH_AH_BCH_3$), 5.51 (1H, s, C*H*OH), 6.71 (1H, d, *J* 7.8, C(5)-py*H*), 7.01–7.09 (2H, m, Ar*H*), 7.11–7.20 (4H, m, Ar*H*), 7.48 (1H, td, *J* 7.8, 1.6, C(4)-py*H*), 8.45 (1H, *br*. d, *J* 4.9,

C(2)-py*H*), 9.06 (1H, br. s, COO*H*); $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) δ_C: 9.7, 28.4, 61.8, 77.2, 123.2, 124.2, 127.0, 127.6, 129.1, 137.5, 137.6, 146.0, 158.5, 177.4; HRMS (NSI^+) $C_{16}H_{18}NO_3$ $[M+H]^+$ requires 272.1281; found 272.1284 (+1.0 ppm).

(*S*,*S*)-**39** was derivatised into its methyl ester to allow chiral HPLC analysis. (*S*,*S*)-**39** (108 mg, 0.39 mmol, 1 equiv) was dissolved in MeOH (2 mL) in under an inert atmosphere of nitrogen and cooled to 0 °C. (Trimethylsilyl)diazomethane (0.6 M in hexanes, 0.83 mL, 0.5 mmol, 1.3 equiv) was added dropwise and the resulting solution was stirred at rt for 3 h in the absence of light. The reaction was quenched with $NaHCO_3$, diluted with H_2O and extracted with Et_2O (×3). The combined organics were washed with brine, dried over $MgSO_4$, and concentrated to give (*S*)-methyl 2-((*S*)-hydroxy(pyridin-2-yl)methyl)-2-phenylbutanoate (52 mg, 47%) as pale yellow solid. mp 96–98 ºC (Et_2O); $[\alpha]_D^{20}$ −161.9 (*c* 0.80 in $CHCl_3$); Chiral HPLC analysis, Chiralpak AD-H (5% IPA:hexane, flow rate 1 mL min^{-1}, 254 nm, 30 ºC) t_R (major): 14.3 min, t_R (minor): 20.2 min, 83% ee; ν_{max} (film) 1728 (C=O), 1591, 1570, 1499; ^1H NMR (300 MHz, $CDCl_3$) δ_H: 1.02 (3H, t, *J* 7.4, $CH_AH_BCH_3$), 2.00–2.12 (1H, m, $CH_AH_BCH_3$), 2.17-2.29 (1H, m, $CH_AH_BCH_3$), 3.78 (3H, s, OCH_3), 5.45 (1H, s, C*H*OH), 6.64 (1H, d, *J* 7.9, C(5)-py*H*), 6.94–6.99 (2H, m, Ar*H*), 7.08 (1H, ddd, *J* 7.5, 4.9, 1.2, Ar*H*), 7.14–7.23 (3H, m, Ar*H*), 7.40 (1H, td, *J* 7.8, 1.8, C(4)-py*H*), 8.33–8.38 (1H, m, C(2)-py*H*); $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) δ_C: 9.8, 26.7, 52.3, 61.5, 76.3, 122.6, 122.7, 127.1, 127.4, 128.8, 135.5, 137.3, 147.5, 158.5, 176.1; HRMS (NSI^+) $C_{17}H_{20}NO_3$ $[M+H]^+$ requires 286.1438; found 286.1439 (+0.5 ppm).

(S)-N-Benzyl-2-((S)-hydroxy(pyridin-2-yl)methyl)-2-phenylbutanamide ***40***: *syn*-**21** (100 mg, 0.039 mmol, 1 equiv) was dissolved in anhydrous CH_2Cl_2 (1.7 mL) in a screw cap vial under a N_2 atmosphere. Benzylamine (0.22 mL, 1.97 mmol, 5 equiv)

and triethylamine (60 μL, 0.43 mmol, 1.1 equiv) were added and the solution was heated at 40 °C for 16 h. The reaction mixture was cooled to rt before being diluted with CH_2Cl_2 and washed with NH_4Cl (×2) and then brine. The organic layer was dried over $MgSO_4$ and concentrated. The crude product was purified by silica gel chromatography (99:1 CH_2Cl_2:MeOH) to give (*S*,*S*)-**40** (72 mg, 54%) as white solid. mp 157–158 ºC (CH_2Cl_2); $[\alpha]_D^{20}$ −152.4 (*c* 0.97 in $CHCl_3$); Chiral HPLC analysis, Chiralpak AD-H (5% IPA:hexane, flow rate 1 mL min^{-1}, 254 nm, 30 ºC) t_R (minor): 37.2 min, t_R (major): 48.7 min, 83% ee; ν_{max} (film) 3302 (N-H), 1616 (C=O), 1589, 1545; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 1.20 (3H, t, *J* 7.4, C*H*$_3$), 1.88–2.00 (1H, m, C*H*$_A$H$_B$CH$_3$), 2.32–2.44 (1H, m, CH$_A$*H*$_B$CH$_3$), 4.56 (2H, d, *J* 5.8, C*H*$_2$Ph), 4.76 (1H, br. s, O*H*), 5.59 (1H, s, C*H*OH), 6.00 (1H, br. t, *J* 5.7, N*H*), 6.60 (1H, d, *J* 8.0, C(5)-py*H*), 7.01–7.12 (3H, m, Ar*H*), 7.14–7.42 (9H, m, Ar*H*), 8.38–8.42 (1H, m, C(2)-py*H*); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ_C: 9.6, 27.6, 44.0, 60.7, 76.1, 122.3, 122.7, 127.4, 127.6, 127.7, 128.0, 128.8, 129.3, 135.4, 138.1, 138.2, 147.3, 159.3, 176.2; HRMS (NSI^+) $C_{23}H_{25}N_2O_2$ $[M+H]^+$ requires 361.1911; found 361.1914 (+1.0 ppm).

(3S,4S)-3-Methyl-4-(6-morpholinopyridin-2-yl)-3-phenyloxetan-2-one ***41***: $Pd(OAc)_2$ (7.0 mg, 0.031 mmol, 0.10 equiv), (±)-BINAP (39.1 mg, 0.063 mmol, 0.20 equiv) and Cs_2CO_3 (307 mg, 0.942 mmol, 3.0 equiv) were added to an oven dried vial and suspended in anhydrous toluene (4 mL) under an atmosphere of argon. The suspension was stirred for 20 min before *syn*-**26** (100mg, 0.314 mmol, 1.00 equiv, 86% ee, >95:5 dr) and morpholine (54 μL, 0.629 mmol, 2.00 equiv) were added. The reaction was heated at 50 °C for 8.5 h then 80 °C for 4 h. The suspension was cooled to rt, filtered through Celite® and concentrated. The crude product was purified by silica gel chromatography (80:20 petrol:Et_2O) to give (*S*,*S*)-**41** (67 mg, 66%) as

colourless solid. mp 80–82 °C; $[\alpha]_D^{20}$ −177.5 (*c* 0.48, $CHCl_3$); Chiral HPLC analysis Chiralpak AS-H (5% IPA:hexane, flow rate 1.0 mL min^{-1}, 254 nm) t_R major (*S,S*): 25.4 min, t_R minor (*R,R*): 31.0 min, 87% *ee*; ν_{max} (ATR)/cm^{-1} 2961, 2365, 1817 (C=O), 1593, 1558, 1473, 1437, 1260, 1244, 1113, 1103, 976, 966, 912, 878, 764; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 1.97 (3H, s, C*H*$_3$), 3.34 (4H, t, *J* 4.8, morphC*H*$_2$-3,5), 3.74 (4H, t, *J* 4.8, morphC*H*$_2$-2,6), 5.43 (1H, s, C*H*(Ar)), 6.35 (1H, d, *J* 8.5, Py*H*-5), 6.53 (1H, d, *J* 7.3, Py*H*-3), 7.05–7.12 (5H, m, Ph*H*), 7.26–7.31 (1H, m, Py*H*-4); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ_c 25.3, 45.5, 66.8, 84.2, 106.5, 111.4, 126.5, 127.2, 128.1, 136.7, 137.9, 153.0, 158.6, 173.3; HRMS (ESI) $C_{19}H_{21}O_3N_2$ $[M+H]^+$ requires 325.1547; found 325.1552.

Tert-butyl 5-methoxy-2-(6-((2S,3S)-3-methyl-4-oxo-3-phenyloxetan-2-yl)pyridin-2-yl)-1H-indole-1-carboxylate ***42***: $Pd(PPh_3)_4$ (36.3 mg, 0.031 mmol, 0.10 equiv), *syn*-**26** (100 mg, 0.314 mmol, 1.00 equiv, 86% ee, >95:5 dr) and (1-(*tert*-butoxycarbonyl)-5-methoxy-1*H*-indol-2-yl)boronic acid (110 mg, 0.377 mmol, 1.20 equiv) were added to an oven dried vial and suspended in DME (5 mL) under an atmosphere of argon. 2 M Na_2CO_3 (0.47 mL, 0.377 mmol, 3.0 equiv) was added and the reaction heated at 85 °C for 4 h. The solution was cooled to rt before being diluted with EtOAc and washed with water. The organic phase was dried over $MgSO_4$ and concentrated. The crude product was purified by silica gel chromatography (90:10 petrol:EtOAc) to give (*S,S*)-**42** (140 mg, 92%) as pale yellow oil. $[\alpha]_D^{20}$ −263.6 (*c* 0.39, $CHCl_3$); Chiral HPLC analysis Chiralpak AD-H (5% IPA:hexane, flow rate 1.0 mL min^{-1}, 254 nm) t_R major (*S,S*): 13.7 min, t_R minor (*R,R*): 20.6 min, 89% ee; ν_{max} (ATR)/cm^{-1} 2976, 1830 (C=O), 1732 (C=O), 1593, 1574, 1454, 1369, 1319, 1219, 1159, 1121, 1099, 1059, 1032, 984, 905, 849, 804, 760; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.39 (9H, s, OC(C*H*$_3$)$_3$), 1.99 (3H,

s, CCH_3), 3.88 (3H, s, OCH_3), 5.72 (1H, s, CH(Ar)), 6.60 (1H, s, Ind$H$-3), 6.97–7.01 (2H, m, HetArH), 7.06 (1H, d, J 2.6, HetArH), 7.08–7.16 (5H, m, PhH), 7.23 (1H, dd, J 7.8, 0.8, HetArH), 7.47 (1H, t, J 7.8, HetArH), 8.05 (1H, d, J 9.1, PyH-3); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ_c 25.1, 27.9, 55.8, 67.0, 83.7, 84.5, 103.4, 111.5, 114.2, 116.2, 119.5, 123.2, 126.8, 127.5, 128.4, 129.7, 132.4, 135.9, 136.3, 139.4, 150.0, 152.5, 154.8, 156.2, 172.8; HRMS (ESI) $C_{29}H_{29}O_5N_2$ $[M+H]^+$ requires 485.2071; found 485.2068.

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Supporting Information

^1H and $^{13}C\{^1H\}$ NMR spectra and HPLC trances of all β-lactones and derivatisation products. X-ray crystal structures and CIF files for *syn*-**7** and *syn*-**21**. This material is available free of charge *via* the Internet at http://pubs.acs.org.

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(25) β-Lactones **8-10** derived from 2-halobenzaldehydes proved difficult to purify to homogeneity and were therefore isolated after ring-opening with KOH followed by esterification to give isolable β-hydroxyacids in 25-36% yield over three steps.

(26) Employing 2-tolylbenzaldehyde under the optimised conditions gave only ketene dimerisation and return of the aldehyde, consistent with the requirement for an electron-withdrawing 2-substituent within the aldehyde to facilitate β-lactone formation.

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(33) The relative and absolute configuration within **21**, **25** and **27** were determined by X-ray crystallography. Crystallographic data for **21**, **25** and **27** has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 923189, 923190 and 923191.

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