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NHC-Promoted Asymmetric β-Lactone Formation from Arylalkylketenes and Electron-Deficient Benzaldehydes or Pyridinecarboxaldehydes

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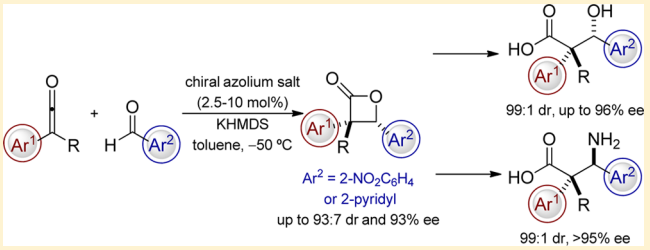
Supporting Information

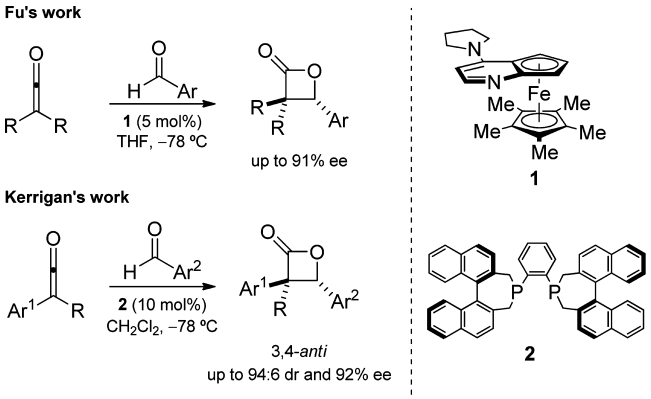
ABSTRACT: A chiral NHC catalyzes the asymmetric formal [2 + 2] cycloaddition of alkylarylketenes with both electron-deficient benzaldehydes and 2- and 4-pyridinecarboxaldehydes to generate stereodefined β-lactones. In the benzaldehyde series, optimal product diastereo- and enantiocontrol is observed 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 multigram quantities of the β-lactone products to be prepared. Derivatization 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 a versatile starting material in complex molecule[1] and building block synthesis[1b,2] and a monomer 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 utilized 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 monosubstituted 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 the 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

Scheme 1. Previous Lewis Base Promoted Asymmetric β-Lactone Formation from Disubstituted Ketenes and Benzaldehydes



anti-β-lactones with high diastereo- and enantiocontrol (up to 94:6 dr and 92% ee).[14]

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-chlorophenyl)ketene is a necessary substrate constraint for high diastereoselectivity in the latter process, with 4-chlorobenzal-

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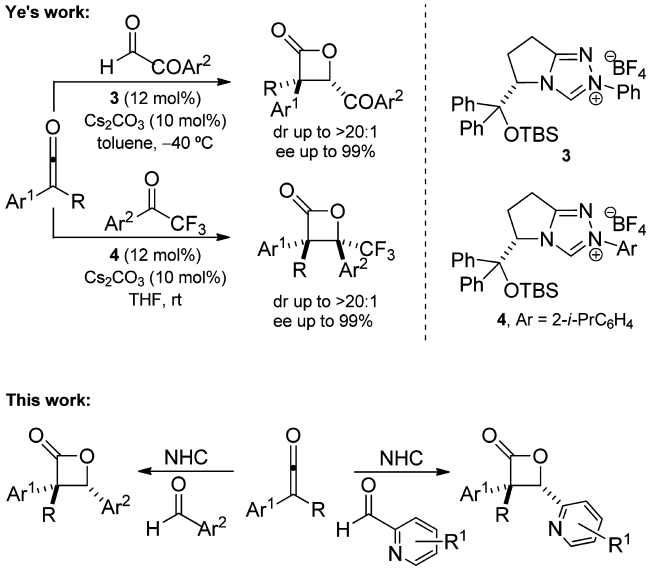
Scheme 2. Previous and Proposed Asymmetric β-Lactone Formation from Disubstituted Ketenes and Aldehydes Using NHCs

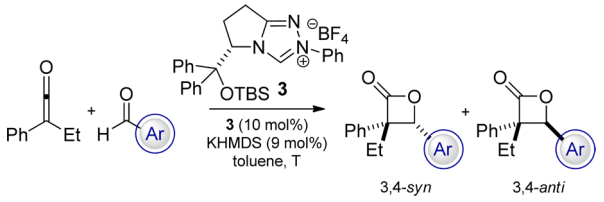


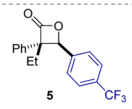
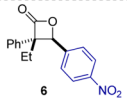
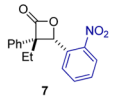
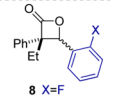
dehyde proving inactive to β-lactone formation in this study. Building upon these precedents and our interest in NHC-mediated asymmetric processes,[17] we now report the development of an alternative and scalable NHC-promoted asymmetric β-lactone synthesis from alkylarylketenes and both benzaldehydes bearing electron-withdrawing substituents and pyridinecarboxaldehydes. Furthermore, derivatization 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.

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 dimerization processes,[19] at the outset of our investigations these were recognized as possible competitive reaction manifolds. NHC precatalyst **3** was chosen for our studies, given its precedent to participate in enantioselective cycloaddition processes using ketenes, despite its moderate reactivity in benzoin reactions.[20] Initial studies employed ethylphenylketene and triazolium precatalyst **3** with a range of substituted benzaldehydes (Table 1). While benzaldehyde gave no β-lactone products (giving only ketene dimer), promising reactivity was observed with electron-deficient benzaldehydes utilizing dropwise ketene addition to minimize dimerization. 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 the 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 and 7). Interestingly, lowering the reaction temperature below −50 °C had a detrimental effect on product

Table 1. Initial Screening of Benzaldehydes for NHC-Promoted β-Lactone Synthesis[h]



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

[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 derivatization. [h]Unless stated, the ketene was added dropwise as a solution in toluene.

ee (entry 8), postulated to be due to a competitive KHMDS-catalyzed racemic pathway at this temperature.[23] The absolute and relative configurations within **7** were 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]

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). First, 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 isobutyl 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 isopropyl(3-thiophene)ketene

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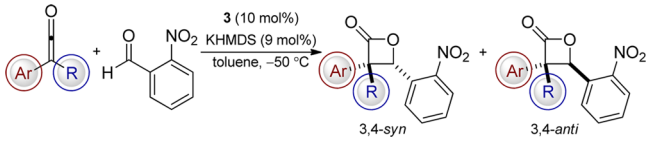
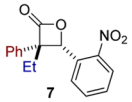
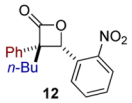
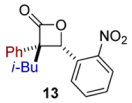
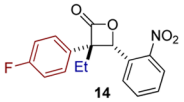
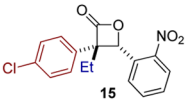
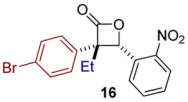
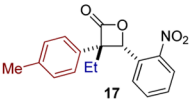
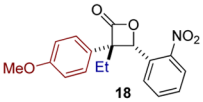
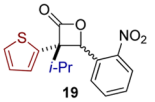
Table 2. Reaction Scope and Limitations Employing 2-Nitrobenzaldehyde[g]



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	–	–	–	–

[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 opening with NaN_3. [f]1.2 equiv of ketene and 1.0 equiv of aldehyde used. [g]The ketene was added dropwise as a solution in toluene.

gave *β*-lactone **19** with poor dr, although the *anti* diastereoisomer was formed in high ee (entry 10). The NHC-catalyzed reaction of either ethyl(2-tolyl)- or ethyl(1-naphthyl)ketene 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]

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 both to their use in asymmetric catalysis[28] and their appearance in biologically relevant molecules.[29] Although a number of methods have previously been developed to prepare these

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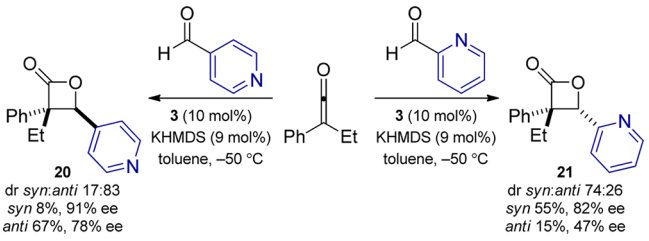
motifs,[30] enantiomerically enriched pyridyl substituted β-lactones, to the best of our knowledge, are unreported.[31]

While both furfural and 3-pyridinecarboxaldehyde gave the corresponding β-lactone products with unsatisfactory levels of conversion (<10%), 2- and 4-pyridinecarboxaldehyde both proved to be efficient coupling partners with ethylphenylketene (Scheme 3). Notably, 2-pyridinecarboxaldehyde preferentially

Scheme 3. Initial Reactivity Employing 2- and 4-Pyridinecarboxaldehydes



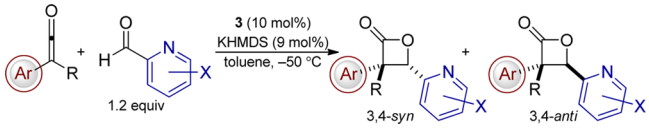
gave the *syn* diastereoisomer **21** (74:26 *syn*:*anti*), while 4-pyridinecarboxaldehyde preferentially gave the *anti* diastereoisomer **20** (17:83 *syn*:*anti*), consistent with the differences in *syn*:*anti* product distributions previously observed using 2- and 4-nitrobenzaldehydes.[32] The absolute 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.

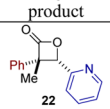
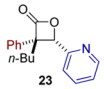
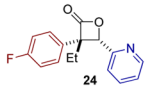
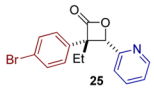
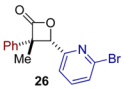
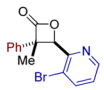
Subsequent studies probed the generality of this process through variation of the alkylarylketene and through the effect of substitution within the 2-pyridinecarboxaldehyde (Table 3).[33] Using 2-pyridinecarboxaldehyde, variation of either the aryl unit within the ketene or the alkyl chain length had 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).

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 in comparison with the parent 4-pyridinecarboxaldehyde, giving moderate diastereocontrol in favor 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).

Postulated Reaction Mechanism. While Kerrigan favors Lewis base addition to the aldehyde as the initial step in the phosphine-catalyzed β-lactone synthesis from ketenes and benzaldehydes, in this NHC-mediated process, concurrent with the ideas of Ye, we propose initiation through NHC

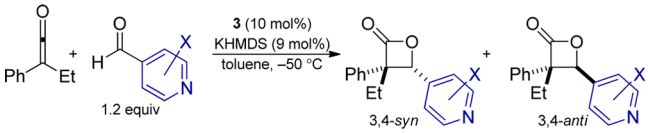
Table 3. NHC-Promoted β-Lactone Formation Using 2-Pyridinecarboxaldehydes[e]

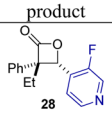
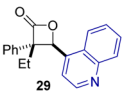
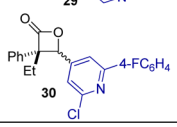


Entry	Ar	R	dr[a] (*syn*:*anti*)	Major product	Yield %[b]	ee %[c] (*syn*,*anti*)
1	Ph	Me	77:23	 **22**	78	88,86
2[d]	Ph	*n*-Bu	82:18	 **23**	62	84,37
3[d]	4-FC_6H_4	Et	82:18	 **24**	73	79,42
4	4-BrC_6H_4	Et	80:20	 **25**	45	80,–
5	Ph	Me	80:20	 **26**	70	86,67
6	Ph	Me	18:82	 **27**	14	–,91

[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. [e]The ketene was added dropwise as a solution in toluene.

Table 4. NHC-Promoted β-Lactone Formation Using 4-Pyridinecarboxaldehyde Derivatives[e]



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

[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. [e]The ketene was added dropwise as a solution in toluene.

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

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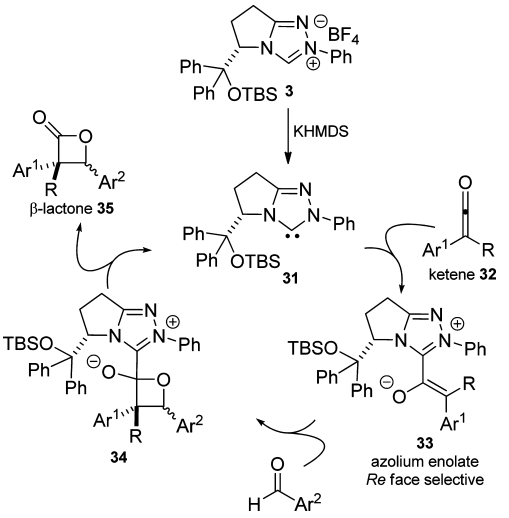
Scheme 4. Proposed Mechanism

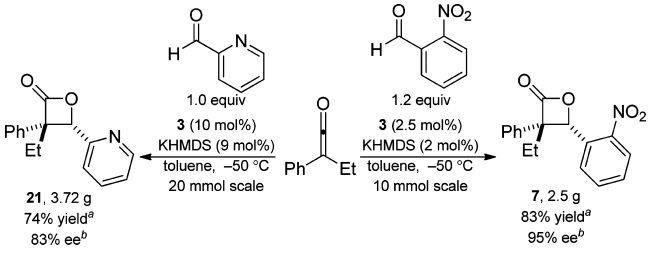


regeneration and β-lactone formation. The consistency of the configuration at the C(3) position of all the major diastereoisomeric β-lactone products observed herein is congruent with a favorable reaction upon the *Re*-face addition of the azolium enolate **33**. However, given the obvious subtle interplay 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.

Scaleup and Derivatization Procedures. To demonstrate the synthetic utility of this methodology, the reaction of ethylphenylketene with 2-nitrobenzaldehyde could be conveniently carried out on a preparative scale with reduced NHC loadings (2.5 mol %), providing >2.5 g of β-lactone **7** as a single diastereoisomer after purification in high ee (83% yield, 95% ee), which could be recrystallized to enantiopurity. Using a higher precatalyst **3** loading of 10 mol %, 2-pyridyl β-lactone **21** could also be obtained as a single diastereoisomer on a >3.5 g scale after purification (74% yield, 82:18 dr *syn*:*anti*) and in good enantioselectivity for the major *syn* β-lactone (83% ee) (Scheme 5).

Functionalization 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 the β-hydroxy acid amide **40** as a single diastereoisomer.

Scheme 5. Scaleup of NHC-Catalyzed Reactions with 2-Nitrobenzaldehyde and 2-Pyridinecarboxaldehyde[a]



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

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% yields, respectively) and with no erosion of enantiopurity.

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 diastereoselectivity. 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 functionalized novel structural architectures. Notably, no competing benzoin or significant formation of ketene dimerization products was 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 SECTION

General Considerations. All reactions were performed in flame-dried glassware using anhydrous solvents. The required aldehydes were 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 refers to 20–25 °C, with temperatures between 0 and −50 °C obtained using an immersion cooler. ^{1}H NMR spectra were acquired at 300, 400, or 500 MHz, ^{13}C{^{1}H} NMR spectra were acquired at 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. Infrared spectra were recorded as thin films on either NaCl plates or KBr disks. Mass spectrometry (*m*/*z*) data were acquired using electrospray ionization (ESI), electron impact (EI), atmospheric solids analysis probe (ASAP), or nanospray ionization (NSI) using a TOF mass analyzer. Optical rotations were recorded with a path length of 1 dm, and concentrations, *c*, are quoted in g/100 mL. All chiral 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 was charged with anhydrous Et_2O and the appropriate acid chloride (1 equiv) before being cooled to 0 °C. Et_3N (1.1 equiv) was added dropwise over 30 min, and the reaction mixture was stirred overnight at 0 °C. The solution was warmed to room temperature 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.[37] 70 °C (0.5 Torr)} to

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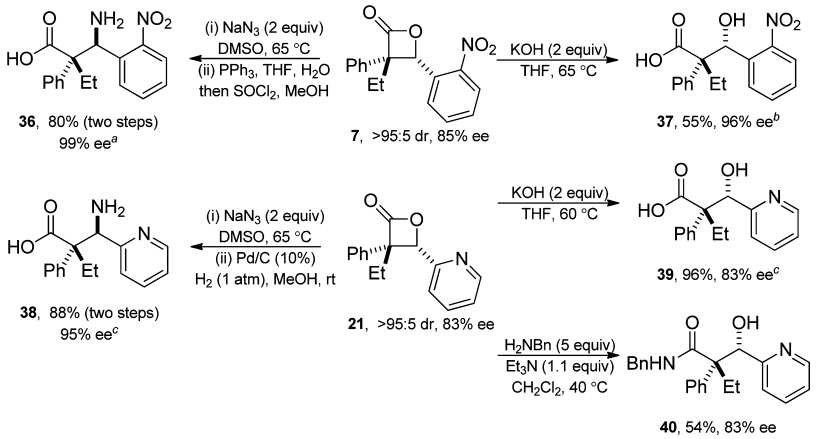
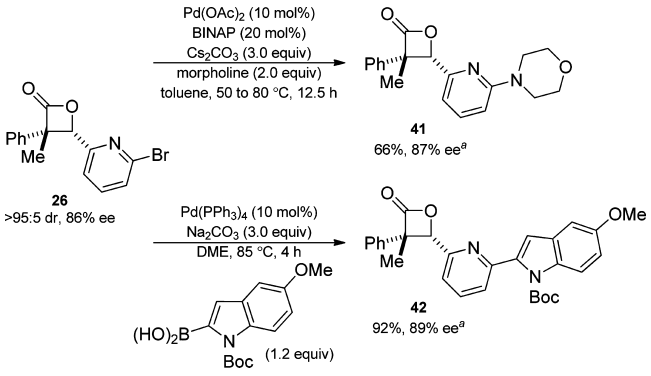
Scheme 6. Derivatization via Ring Opening of β-Lactones



[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.

Scheme 7. Functionalization of β-Lactones by Cross-Coupling



[a]ee determined by HPLC analysis.

give ethylphenylketene (1.40 g, 60%) as a light yellow oil that is stable for up to 2 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 at 60−80 °C (5 mbar) {lit.[37] 50 °C (4 Torr)} to give methylphenylketene (1.44 g, 45%) as a 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 at 110−120 °C (5 mbar) to give butylphenylketene (1.26 g, 51%) as a 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 at 110−117 °C (5 mbar) {lit.[38] 37−46 °C (0.8 Torr)} to give isobutylphenylketene (1.75 g, 56%) as a 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, $CH(CH_3)_2$), 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-fluorophenyl)ketene. 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 at 104−110 °C (7 mbar) to give ethyl(4-fluorophenyl)ketene (1.21 g, 55%) as a 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-chlorophenyl)ketene. 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 at 125−135 °C (7 mbar) to give ethyl(4-chlorophenyl)ketene (0.37 g, 56%) as a 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-bromophenyl)ketene. 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 at 180 °C (7 mbar) to give ethyl(4-bromophenyl)ketene (1.21 g, 28%) as a 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 11.7, 15.9, 40.7, 116.2, 124.4, 130.9, 131.0, 203.2.

Ethyl(4-tolyl)ketene. 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 at 110−120 °C (7 mbar) {lit.[19] 68−72 °C (0.2 Torr)} to give ethyl(4-tolyl)ketene (0.92 g, 52%) as a yellow-orange oil: ^{1}H 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-methoxyphenyl)ketene. 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 at 140−150 °C (3 mbar) to give ethyl(4-methoxyphenyl)ketene (1.19 g, 48%) as a yellow-orange oil: ν_{max} (thin film)/cm^{-1} 2096; ^{1}H 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-thionyl)ketene. 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 and then room temperature for 4.5 h. The crude oil was purified via Kugelrohr distillation at 85−90 °C

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(3 mbar) {lit.[39] 71−73 °C} to give isopropyl(3-thionyl)ketene (1.09 g, 59%) as a 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-Catalyzed [2 + 2] Cycloadditions. To a flame-dried Schlenk flask under an argon atmosphere were 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 was 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 room temperature 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 petroleum ether/Et_2O) to give *syn*-**11** (88 mg, 30%) as a colorless solid and *anti*-**11** (103 mg, 35% yield) as a colorless 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, CH_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, CH_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 petroleum ether/Et_2O) to give *syn*-**7** (157 mg, 83%) as an 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{^{1}H} 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 petroleum ether/Et_2O) to give *syn*-**12** (240 mg, 74%) as an 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{^{1}H} 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), isobutylphenylketene (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 petroleum ether/Et_2O) to give *syn*-**13** (95 mg, 30%) as an 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{^{1}H} 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-fluorophenyl)ketene (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 petroleum ether/Et_2O) to give *syn*-**14** (216 mg, 69%) as a colorless 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; ^{1}H 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{^{1}H} NMR (376 MHz, $CDCl_3$) δ_F −114; ^{13}C{^{1}H} 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-chlorophenyl)ketene (181 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 93:7 *syn*:*anti*) was purified by silica gel chromatography (95/5 petroleum ether/Et_2O) to give *syn*-**15** (262 mg, 79%) as an 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; ^{1}H

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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); $^{13}C\{^1H\}$ 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-bromophenyl)ketene (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 petroleum ether/Et_2O) to give *syn*-**16** (257 mg, 68%) as a 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; ^1H NMR (300 MHz, $CDCl_3$) δ_H 1.14 (3H, t, J = 7.4, CH_2CH_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); $^{13}C\{^1H\}$ 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-tolyl)ketene (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 petroleum ether/Et_2O) to give *syn*-**17** (162 mg, 52%) as an 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; ^1H 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-methoxyphenyl)ketene (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 petroleum ether/Et_2O) to give *syn*-**18** (247 mg, 75%) as an 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; ^1H 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, Ar*H*NO_2), 7.47−7.55 (2H, m, Ar*H*NO_2), 7.96 (1H, dd, J = 8.3, 0.9, Ar*H*NO_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-thionyl)ketene (180 mg, 1.00 mmol), and 2-nitrobenzaldehyde (181 mg, 1.20 mmol) in toluene (10 mL) at 0 °C to room temperature over 12 h. The crude product (dr 45:55 *syn*:*anti*) was purified by silica gel chromatography (97/3 petroleum ether/Et_2O) to give *syn*-**19** (73 mg, 23%) as a pale brown solid and *anti*-**19** (38 mg, 12%) as an 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; ^1H 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, Ar*H*NO_2), 7.50 (2H, d, J = 3.9, Ar*H*NO_2), 8.01 (1H, dt, J = 8.1, 0.8, Ar*H*NO_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; ^1H NMR (300 MHz, $CDCl_3$) δ_H 0.41 (3H, d, J = 6.7, *i*-PrCH_3), 0.93 (3H, d, J = 6.8, *i*-PrCH_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); $^{13}C\{^1H\}$ 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 petroleum ether/Et_2O) to give *anti*-**20** (174 mg, 67%) as a colorless solid and *syn*-**20** (21 mg, 8% yield) as a colorless solid. ***anti*-20**: mp 74−82 °C; $[\alpha]_D^{20}$ = +18.0 (*c* 1.00, $CHCl_3$); ^1H 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); $^{13}C\{^1H\}$ 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; ^1H 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,

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syn:*anti*) was purified by silica gel chromatography (95/5 to 90/10 petroleum ether/EtOAc) to give *syn*-**21** (140 mg, 55%) as a pale brown solid and *anti*-**21** (38 mg, 15% yield) as apale 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; ^{1}H 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 petroleum ether/EtOAc) to give *syn*-**22** (144 mg, 60%) as a colorless solid and *anti*-**22** (42 mg, 18%) as a colorless 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, CH_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); $^{13}C\{^1H\}$ 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, CH_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); $^{13}C\{^1H\}$ 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 petroleum ether/EtOAc) to give *syn*-**23** (128 mg, 45%) as a colorless solid and *anti*-**23** (47 mg, 17%) as a colorless 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, CH_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); $^{13}C\{^1H\}$ 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); $^{13}C\{^1H\}$ 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 petroleum ether/EtOAc) to give *syn*-**24** (159 mg, 59%) as a colorless solid and *anti*-**24** (38 mg, 14%) as aq colorless 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, CH_3), 2.21−2.33 (1H, m, $CH_AH_BCH_3$), 2.33−2.45 (1H, m, $CH_AH_BCH_3$), 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); $^{13}C\{^1H\}$ 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, CH_3), 1.45−1.56 (1H, m, $CH_AH_BCH_3$), 1.57−1.68 (1H, m, $CH_AH_BCH_3$), 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); $^{13}C\{^1H\}$ 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-bromophenyl)ketene (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 petroleum ether/EtOAc) to give *syn*-**25** (39 mg, 45%) as a colorless 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, $CH_AH_BCH_3$), 2.33−2.44 (1H, m, $CH_AH_BCH_3$), 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); $^{13}C\{^1H\}$ 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**

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(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*) was purified by silica gel chromatography (5% Et_2O/petroleum ether) to give *syn*-**26** (175 mg, 55%) as a colorless solid and *anti*-**26** (47 mg, 15%) as a 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; ^1H 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); $^{13}C\{^1H\}$ 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; ^1H 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); $^{13}C\{^1H\}$ 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 petroleum ether/EtOAc) to give *anti*-**27** (45 mg, 14% yield) as a 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; ^1H 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); $^{13}C\{^1H\}$ 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 petroleum ether/Et_2O and then 90/10 petroleum ether/EtOAc) to give *syn*-**28** and *anti*-**28** (85 mg, 31%) as a colorless 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; ^1H NMR (400 MHz, $CDCl_3$) δ_H 1.09 (3H, t, *J* = 7.4, CH_3), 2.35−2.51 (2H, m, CH_2CH_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); $^{13}C\{^1H\}$ 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; ^1H NMR (400 MHz, $CDCl_3$) δ_H 0.70 (3H, t, *J* = 7.4, CH_3), 1.56−1.65 (1H, m, $CH_AH_BCH_3$), 1.68−1.77 (1H, m, $CH_AH_BCH_3$), 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); $^{13}C\{^1H\}$ 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 petroleum ether/EtOAc) to give *anti*-**29** (172 mg, 57% yield) as a 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; ^1H NMR (500 MHz, $CDCl_3$) δ_H 0.73 (3H, t, *J* = 7.4, CH_3), 1.51−1.58 (1H, m, $CH_AH_BCH_3$), 1.64−1.71 (1H, m, $CH_AH_BCH_3$), 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); $^{13}C\{^1H\}$ 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 petroleum ether/Et_2O) to give *syn*-**30** (83 mg, 44%) as a colorless solid and *anti*-**30** (50 mg, 26%) as a colorless 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; ^1H NMR (300 MHz, $CDCl_3$) δ_H 0.75 (3H, t, *J* = 7.4, CH_3), 1.52−1.64 (1H, m, $CH_AH_BCH_3$), 1.70−1.82 (1H, m, $CH_AH_BCH_3$), 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); $^{13}C\{^1H\}$ 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; ^1H 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); $^{13}C\{^1H\}$ 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] NaN_3 (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 to 65 °C for 42 h. The solution was cooled to room temperature, diluted with $NaHCO_3$ (20 mL), and extracted with EtOAc (20 mL). The aqueous phase was acidified with 2 M HCl (50 mL) 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 a light brown solid (564

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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, $CH_AH_BCH_3$), 2.55−2.67 (1H, m, $CH_AH_BCH_3$), 6.32 (1H, s, CHN_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*); $^{13}C\{^1H\}$ 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 the mixture was 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 mixture was concentrated, and the resulting solid was triturated with cold $CHCl_3$ to give (*S*,*S*)-**36** as an 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, CH_3), 1.80−1.99 (2H, m, CH_2CH_3), 5.88 (1H, s, $CHNH_2$), 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*); $^{13}C\{^1H\}$ 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 derivatized into its dibenzyl compound to allow chiral HPLC analysis. Benzyl bromide (25 μL, 0.21 mmol, 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 room temperature for 12 h. The reaction mixture was diluted with Et_2O and 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 petroleum ether/Et_2O) to give (*S*)-benzyl 2-((*S*)-(benzylamino)(2-nitrophenyl)methyl)-2-phenylbutanoate (16 mg, 34%) as a 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, CH_3), 1.78−1.87 (1H, m, $CH_AH_BCH_3$), 2.33−2.41 (1H, m, $CH_AH_BCH_3$), 3.45 (1H, d, *J* = 13.4, OCH_AH_BPh), 3.60 (1H, d, *J* = 13.4, OCH_AH_BPh), 5.00 (1H, d, *J* = 12.3, NCH_AH_BPh), 5.08 (1H, d, *J*, 12.3, NCH_AH_BPh), 5.30 (1H, s, $CHNHBn$), 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*); $^{13}C\{^1H\}$ 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 to 65 °C for 5 h. The solution was cooled to room temperature, 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 an 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, CH_3), 1.79 (2H, q, *J* = 7.5, CH_2CH_3), 6.14 (1H, s, $CHOH$), 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*); $^{13}C\{^1H\}$ 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 derivatized into its benzyl ester to allow chiral HPLC analysis. Benzyl bromide (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 the mixture was stirred at room temperature for 12 h. The reaction mixture was diluted with Et_2O and 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 petroleum ether/Et_2O) to give (*S*)-benzyl 2-((*R*)-hydroxy(2-nitrophenyl)methyl)-2-phenylbutanoate (79 mg, 63%) as an 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, CH_3), 1.63−1.75 (1H, m, $CH_AH_BCH_3$), 1.89−2.01 (1H, m, $CH_AH_BCH_3$), 3.87 (1H, d, *J* = 4.0, $CHOH$), 5.23 (2H, s, OCH_2Ph), 6.20 (1H, d, *J* = 4.0, $CHOH$), 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*); $^{13}C\{^1H\}$ 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). According to 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 room temperature, 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 a white solid: mp 138 °C dec (Et_2O); $[\alpha]_D^{20}$ = +167.1 (*c* 0.70, $CHCl_3$); 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, CH_3), 2.22−2.34 (1H, m, $CH_AH_BCH_3$), 2.37−2.53 (1H, m, $CH_AH_BCH_3$), 5.44 (1H, s, CHN_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*); $^{13}C\{^1H\}$ 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).

According to 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 room temperature 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 a white solid: mp 112−115 °C dec; $[\alpha]_D^{20}$ = −12.6 (*c* 0.54, $CHCl_3$); ν_{max} (film) 3364 (br, N−H), 1591 (br, C═O), 1572; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 0.78 (3H, t, *J* = 7.1, CH_3), 1.57−1.85 (2H, m, CH_2CH_3), 4.84 (1H, s, $CHNH_2$), 6.13 (1H, d, *J* = 7.6, C(5)-py*H*), 7.05−7.35 (8H, m, Ar*H*), 8.38 (2H, br s, NH_2), 8.49 (1H, d, *J* = 4.2, C(2)-py*H*); $^{13}C\{^1H\}$ 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 derivatized 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 room temperature for 3 h in the absence of light. The reaction mixture 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

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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 an 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 °C) t_R (minor) 30.4 min, t_R (major) 34.3 min, 95% ee; ν_{max} (film) 1724 (C═O), 1589, 1570; ^1H 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*); $^{13}C\{^1H\}$ 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). According to 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 room temperature 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 layer was 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 a pale yellow solid: mp 48−50 °C; $[\alpha]_D^{20} = -99.6$ (*c* 1.12, $CHCl_3$); ν_{max} (film) 3439 (br, O−H), 1699 (C═O), 1601; ^1H 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*); $^{13}C\{^1H\}$ 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 derivatized 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) 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 room temperature for 3 h in the absence of light. The reaction mixture 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 a pale yellow solid: mp 96−98 °C (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 °C) 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*); $^{13}C\{^1H\}$ 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 to 40 °C for 16 h. The reaction mixture was cooled to room temperature 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 a white solid: mp 157−158 °C (CH_2Cl_2); $[\alpha]_D^{20} = -152.4$ (*c* 0.97, $CHCl_3$); chiral HPLC analysis Chiralpak AD-H (5% IPA/hexane, flow rate 1 mL min^{-1}, 254 nm, 30 °C) 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; ^1H NMR (300 MHz, $CDCl_3$) δ_H 1.20 (3H, t, *J* = 7.4, CH_3), 1.88−2.00 (1H, m, $CH_AH_BCH_3$), 2.32−2.44 (1H, m, $CH_AH_BCH_3$), 4.56 (2H, d, *J* = 5.8, CH_2Ph), 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*); $^{13}C\{^1H\}$ 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).

(3*S*,4*S*)-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** (100 mg, 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 mixture was heated to 50 °C for 8.5 h then to 80 °C for 4 h. The suspension was cooled to room temperature, filtered through Celite, and concentrated. The crude product was purified by silica gel chromatography (80/20 petroleum ether/Et_2O) to give (*S*,*S*)-**41** (67 mg, 66%) as a colorless 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; ^1H NMR (300 MHz, $CDCl_3$) δ_H 1.97 (3H, s, CH_3), 3.34 (4H, t, *J* = 4.8, morphCH_2-3,5), 3.74 (4H, t, *J* = 4.8, morphCH_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); $^{13}C\{^1H\}$ 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-((2*S*,3*S*)-3-methyl-4-oxo-3-phenyloxetan-2-yl)pyridin-2-yl)-1*H*-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. Na_2CO_3 (2 M; 0.47 mL, 0.377 mmol, 3.0 equiv) was added, and the reaction mixture was heated to 85 °C for 4 h. The solution was cooled to room temperature 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 petroleum ether/EtOAc) to give (*S*,*S*)-**42** (140 mg, 92%) as a 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; ^1H NMR (400 MHz, $CDCl_3$) δ_H 1.39 (9H, s, OC(CH_3)$_3$), 1.99 (3H, s, CCH_3), 3.88 (3H, s, OCH_3), 5.72 (1H, s, C*H*(Ar)), 6.60 (1H, s, Ind*H*-3), 6.97−7.01 (2H, m, HetAr*H*), 7.06 (1H, d, *J* = 2.6, HetAr*H*), 7.08−7.16 (5H, m, Ph*H*), 7.23 (1H, dd, *J* = 7.8, 0.8, HetAr*H*), 7.47 (1H, t, *J* = 7.8, HetAr*H*), 8.05 (1H, d, *J* = 9.1, Py*H*-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.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Figures giving ^1H and $^{13}C\{^1H\}$ NMR spectra and HPLC trances of all β-lactones and derivatization products and CIF files giving X-ray crystallographic data for *syn*-**7** and *syn*-**21**, **25**, and **27**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) (a) Taunton, J.; Collins, J. L.; Schreiber, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 10412−10422. (b) Wan, Z.; Nelson, S. G. *J. Am. Chem. Soc.* **2000**, *122*, 10470−10471. (c) Nelson, S. G.; Cheung, W. S.; Kassick, A. J.; Hilfiker, M. A. *J. Am. Chem. Soc.* **2002**, *124*, 13654−13655. (d) Wang, Y. C.; Tennyson, R. L.; Romo, D. *Heterocycles* **2004**, *64*, 605−658. (e) Shen, X.; Wasmuth, A. S.; Zhao, J.; Zhu, C.; Nelson, S. G. *J. Am. Chem. Soc.* **2006**, *128*, 7438−7439.

(2) (a) Nelson, S. G.; Spencer, K. L. *Angew. Chem., Int. Ed.* **2000**, *39*, 1323−1325. (b) Nelson, S. G.; Wan, Z.; Stan, M. A. *J. Org. Chem.* **2002**, *67*, 4680−4683.

(3) (a) Abe, H.; Matsubara, I.; Doi, Y. *Macromolecules* **1995**, *28*, 844−853. (b) Leboucher-Durand, M.-A.; Langlois, V.; Guerin, P. *Polym. Bull. (Berlin)* **1996**, *36*, 35−41.

(4) Pommier, A.; Pons, J. M. *Synthesis* **1995**, 729−744.

(5) (a) Pommier, A.; Pons, J. M. *Synthesis* **1993**, 441−459. (b) Yang, H. W.; Romo, D. *Tetrahedron* **1999**, *55*, 6403−6434. (c) Schneider, C. *Angew. Chem., Int. Ed.* **2002**, *41*, 744−746. (d) Orr, R. K.; Calter, M. A. *Tetrahedron* **2003**, *59*, 3545−3565.

(6) (a) Case-Green, S. C.; Davies, S. G.; Hedgecock, C. J. R. *Synlett* **1991**, 781−782. (b) Case-Green, S. C.; Davies, S. G.; Hedgecock, C. J. R. *Synlett* **1991**, 779−780. (c) Buttero, P.; Montrasio, D. *Molecules* **2001**, *6*, 13−20.

(7) (a) Tamai, Y.; Yoshiwara, H.; Someya, M.; Fukumoto, J.; Miyano, S. *J. Chem. Soc., Chem. Commun.* **1994**, 2281−2282. (b) Dymock, B. W.; Kocienski, P. J.; Pons, J.-M. *Chem. Commun.* **1996**, 1053−1054. (c) Forslund, R. E.; Cain, J.; Colyer, J.; Doyle, M. P. *Adv. Synth. Catal.* **2005**, *347*, 87−92. (d) Gnanadesikan, V.; Corey, E. J. *Org. Lett.* **2006**, *8*, 4943−4945. (e) Kull, T.; Peters, R. *Adv. Synth. Catal.* **2007**, *349*, 1647−1652.

(8) Staudinger, H.; Bereza, S. *Liebigs Ann. Chem.* **1911**, 243−247.

(9) (a) Wynberg, H.; Staring, E. G. J. *J. Am. Chem. Soc.* **1982**, *104*, 166−168. (b) Wynberg, H.; Staring, E. G. J. *J. Org. Chem.* **1985**, *50*, 1977−1979.

(10) (a) Nelson, S. G.; Peelen, T. J.; Wan, Z. *J. Am. Chem. Soc.* **1999**, *121*, 9742−9743. (b) Zhu, C.; Shen, X.; Nelson, S. G. *J. Am. Chem. Soc.* **2004**, *126*, 5352−5353.

(11) (a) Tennyson, R.; Romo, D. *J. Org. Chem.* **2000**, *65*, 7248−7252. (b) Cortez, G. S.; Tennyson, R. L.; Romo, D. *J. Am. Chem. Soc.* **2001**, *123*, 7945−7946. (c) Oh, S. H.; Cortez, G. S.; Romo, D. *J. Org. Chem.* **2005**, *70*, 2835−2838. (d) Henry-Riyad, H.; Lee, C.; Purohit, V. C.; Romo, D. *Org. Lett.* **2006**, *8*, 4363−4366. (e) Purohit, V. C.; Richardson, R. D.; Smith, J. W.; Romo, D. *J. Org. Chem.* **2006**, *71*, 4549−4558. (f) Leverett, C. A.; Purohit, V. C.; Romo, D. *Angew. Chem., Int. Ed.* **2010**, *49*, 9479−9483. (g) Morris, K. A.; Arendt, K. M.; Oh, S. H.; Romo, D. *Org. Lett.* **2010**, *12*, 3764−3767.

(12) Calter, M. A.; Tretyak, O. A.; Flaschenriem, C. *Org. Lett.* **2005**, *7*, 1809−1812.

(13) Wilson, J. E.; Fu, G. C. *Angew. Chem., Int. Ed.* **2004**, *43*, 6358−6360.

(14) Mondal, M.; Ibrahim, A. A.; Wheeler, K. A.; Kerrigan, N. J. *Org. Lett.* **2010**, *12*, 1664−1667.

(15) Wang, X.-N.; Shao, P.-L.; Lv, H.; Ye, S. *Org. Lett.* **2009**, *11*, 4029−4031.

(16) He, L.; Lv, H.; Zhang, Y.-R.; Ye, S. *J. Org. Chem.* **2008**, *73*, 8101−8103.

(17) (a) Duguet, N.; Campbell, C. D.; Slawin, A. M. Z.; Smith, A. D. *Org. Biomol. Chem.* **2008**, *6*, 1108−1113. (b) Douglas, J.; Ling, K. B.; Concellón, C.; Churchill, G.; Slawin, A. M. Z.; Smith, A. D. *Eur. J. Org. Chem.* **2010**, *2010*, 5863−5869.

(18) (a) Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev.* **2007**, *107*, 5606−5655. (b) Moore, J. L.; Rovis, T. *Top. Curr. Chem.* **2009**, *291*, 77−144. (c) Campbell, C. D.; Ling, K. B.; Smith, A. D. In *N-Heterocyclic Carbenes in Transition Metal Catalysis and Organocatalysis*; Cazin, C. S. J., Ed.; Springer: Netherlands: 2011, p 263−297.

(19) Lv, H.; Zhang, Y.-R.; Huang, X.-L.; Ye, S. *Adv. Synth. Catal.* **2008**, *350*, 2715−2718.

(20) Enders, D.; Han, J. *Tetrahedron: Asymmetry* **2008**, *19*, 1367−1371.

(21) The relative configuration of the *syn*:*anti* β-lactone diastereoisomers was assigned using nOe spectroscopic analysis.

(22) The relative and absolute configuration within **6** was proven by chemical correlation to Kerrigan's work.[14] The configuration within **5** was assigned by analogy.

(23) (a) Sereda, O.; Wilhelm, R. *Synlett* **2007**, *2007*, 3032−3036. (b) Tabassum, S.; Sereda, O.; Reddy, P. V. G.; Wilhelm, R. *Org. Biomol. Chem.* **2009**, *7*, 4009−4016.

(24) The relative and absolute configurations within **7** were determined by X-ray crystallography. Crystallographic data for **7** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 854302.

(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-hydroxy acids in 25−36% yields over three steps.

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

(27) DiRocco, D. A.; Oberg, K. M.; Dalton, D. M.; Rovis, T. *J. Am. Chem. Soc.* **2009**, *131*, 10872−10874.

(28) (a) Desimoni, G.; Faita, G.; Quadrelli, P. *Chem. Rev.* **2003**, *103*, 3119−3154. (b) Shaw, S. A.; Aleman, P.; Vedejs, E. *J. Am. Chem. Soc.* **2003**, *125*, 13368−13369. (c) Chelucci, G.; Murineddu, G.; Pinna, G. A. *Tetrahedron: Asymmetry* **2004**, *15*, 1373−1389. (d) Fu, G. C. *Acc. Chem. Res.* **2004**, *37*, 542−547. (e) Kwong, H. L.; Yeung, H. L.; Yeung, C. T.; Lee, W. S.; Lee, C. S.; Wong, W. L. *Coord. Chem. Rev.* **2007**, *251*, 2188−2222.

(29) O'Hagen, D. *Nat. Prod. Rep.* **1997**, *14*, 637−651.

(30) Brody, F.; Ruby, P. R. In *Chemistry of Heterocyclic Compounds: Pyridine and its Derivatives*; Wiley: Hoboken, NJ, 2008; Vol. *14*, pp 99−589.

(31) Mulzer, J.; Zippel, M. *Tetrahedron Lett.* **1980**, *21*, 751−754.

(32) A control experiment resubjecting isolated *syn*-**21** (>95:5 dr) to the reaction conditions for 24 h resulted in no loss of diastereoselectivity.

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

(34) Armstrong, A.; Geldart, S. P.; Jenner, C. R.; Scutt, J. N. *J. Org. Chem.* **2007**, *72*, 8091−8094.

(35) Schlummer, B.; Scholz, U. *Adv. Synth. Catal.* **2004**, *346*, 1599−1626.

(36) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483.

(37) Baigrie, L. M.; Seiklay, H. R.; Tidwell, T. T. *J. Am. Chem. Soc.* **1985**, *107*, 5391−5396.

(38) Hodous, B. L.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 1578−1579.

(39) Wiskur, S. L.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 6176−6177.