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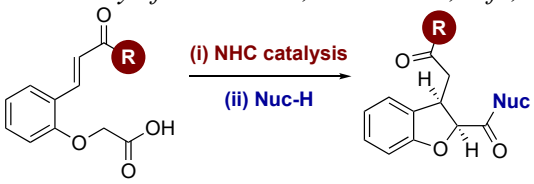

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NHC-Catalysed Enantioselective Intramolecular Formal [4+2] Cycloadditions using Carboxylic Acids as Azolium Enolate Precursors

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ABSTRACT

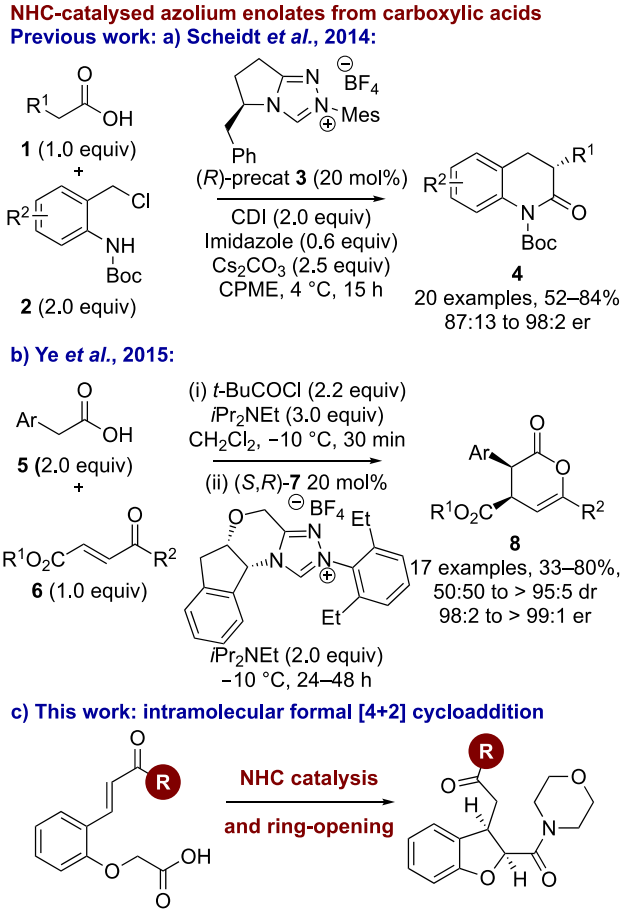
An NHC-catalysed intramolecular formal [4+2] cycloaddition protocol using carboxylic acid starting materials containing a tethered enone is reported. Optimisation studies using a model substrate showed that the use of the Yamaguchi reagent (2,4,6-trichlorobenzoyl chloride) for *in situ* preparation of a mixed anhydride was necessary for effective catalysis, leading to highest product yield and stereoselectivity. Using this protocol, a range of dihydrobenzofurans were accessed in moderate to high yield, and with high to excellent diastereo- and enantioselectivity (up to > 95:5 dr and > 99:1 er). This methodology was extended to the synthesis of *syn*-dihydrochromenone and *syn*-dihydropyranone derivatives in moderate to high yield and with excellent diastereo- and enantioselectivity.

Dedication: This manuscript is dedicated to Professor Steve Davies to celebrate his many outstanding achievements throughout his illustrious career in academia and as an entrepreneur. As a friend, mentor and advisor he has continually been an inspiration.

1. Introduction

Azolium enolates are powerful synthetic intermediates that can undergo a wide range of enantioselective reactions.[1] Such species are readily generated from an NHC through reaction with a variety of substrates, such as disubstituted ketenes,[2] aldehydes in combination with an external oxidant,[3] activated esters,[4] and α-functionalised aldehydes such as enals, α-halo and α-aroyloxy aldehydes.[5] A range of enantioselective reactions have been developed with azolium enolates,[1] however the most common applications involve intermolecular formal [4+2] cycloaddition reactions with reactive Michael acceptors such as enones.[2-5]

Despite their utility, one key remaining challenge in this area is to identify bench stable, readily available and inexpensive azolium enolate precursors. In this regard, carboxylic acids potentially present an ideal profile. While carboxylic acids have been extensively used in Lewis base catalysis using isothiourea-, cinchona alkaloid- and DMAP-derived catalysts for the generation of C1-ammonium enolates through *in situ* formation of an efficient acylating agent such as a mixed anhydride,[6] this concept remains relatively underexplored in NHC-catalysed processes. In this area, only a limited number of publications report the use of carboxylic acids to generate azolium enolate precursors and their use in intermolecular formal [4+2] cycloadditions.[7] A seminal report published in 2014 by Scheidt and coworkers demonstrated the use of carboxylic acids **1** toward the synthesis of dihydroquinolones **4** (Scheme 1a).[7a] *In situ* conversion of the carboxylic acid substrate was achieved using CDI in the presence of imidazole and Cs_2CO_3, with NHC addition, followed by deprotonation providing the azolium enolate. Subsequent enantioselective reaction with an aza-*ortho*-quinone methide, produced *in situ* from an *N*-Boc 2-aminobenzyl chloride derivative **2**, gave heterocycle **4** in excellent yield and stereoselectivity. Building upon this work, in 2015 Ye and coworkers reported the synthesis of *syn*-dihydropyranones **8** with excellent enantioselectivity, by utilising a limited range of arylacetic acids **5** bearing electron donating aryl substituents (2-, 4-, 2,4-$(MeO)_2C_6H_3$, 4-MeC_6H_4) in combination with α,β-unsaturated γ-ketoesters **6** as Michael acceptors (Scheme 1b).[7b] In this process, the use of pivaloyl chloride in the presence of iPr$_2$NEt led to the *in situ* generation of a mixed anhydride as the acylating agent, with subsequent azolium enolate formation and formal [4+2] cycloaddition leading to the observed products. Building upon these precedents, we considered the potential for an NHC-catalysed *intramolecular* formal [4+2] cycloaddition process using carboxylic acids bearing a pendant enone as potential azolium enolate precursors (Scheme 1c). While related processes from carboxylic acids have been developed using tertiary amine Lewis bases,[8] to the best of our knowledge this would represent a new avenue in NHC catalysis. Herein we report the enantioselective NHC-catalysed synthesis of a number of heterocycles using this protocol in good to excellent yields and stereocontrol (up to 94% yield, > 95:5 dr and > 99:1 er).



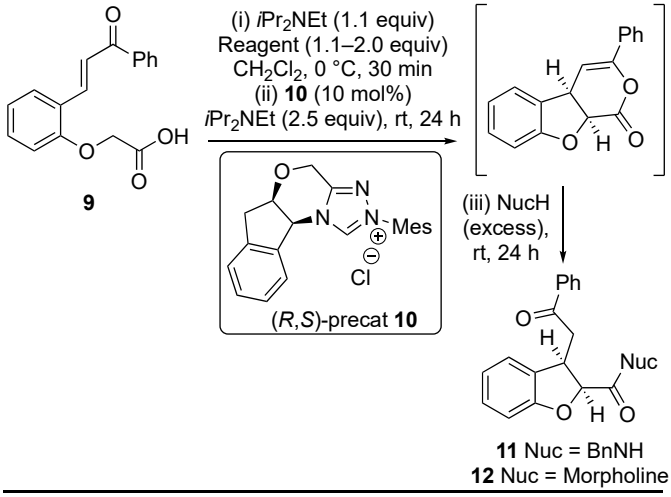
Scheme 1. Carboxylic acids as azolium enolate precursors.

2. Results and Discussion

2.1. Model substrate reaction optimisation

The enantioselective cyclisation of enone-acid **9**, previously investigated using other types of tertiary amine Lewis base catalysts,[8] was chosen as the model system for reaction optimisation.[9] The initial focus aimed to identify the optimal reagent for *in situ* carboxylic acid derivatization in an NHC-catalysed intramolecular cyclisation protocol, with the initial [6,5]-fused dihydropyranone product ring-opened *in situ* using an amine to facilitate isolation (Table 1). A series of reagents (pivaloyl chloride, EDCI, EDCI and HOBt, Mukaiyama reagents,[10] CDI, DCC, HATU) were all tested to facilitate the *in situ* formation of reactive acylating agents from enone-acid **9**. However, in all cases only low product yields (< 15%) were observed (See ESI for details). More encouraging results were obtained using isopropyl chloroformate, with dihydrobenzofuran **11** isolated in 67% yield, > 95:5 dr and > 99:1 er, after addition of benzylamine (Table 1, Entry 1). The (2*S*,3*R*)-configuration within **11** was identified by comparison of both specific rotation value and HPLC analysis to the literature.[8] Disappointingly, attempted repetition led to significant inconsistencies with variable product yields and er observed, indicating that chloroformates were not a reliable reagent for this system. As an alternative, the use of 2,4,6-trichlorobenzoyl chloride (2,4,6-TCBC), widely known as the Yamaguchi reagent,[9] was explored at 0 °C (Table 1, Entries 2–4). Upon addition of benzylamine as the nucleophile, dihydropyranone **11** was obtained in 61% yield, > 95:5 dr and > 99:1 er (Table 1, Entry 2). Changing the nucleophile to morpholine, and decreasing the temperature of the annulation and ring-opening steps to 0 °C, led to formation of dihydropyranone **12** with consistent results (Table 1, Entry 3). Decreasing the reaction time of the ring-opening step to 4 h gave **12** in > 95:5 dr and 97:3 er and improved 94% yield. These conditions were found to be reproducible and were therefore taken forwards as the optimal conditions for this transformation (Table 1, Entry 4).

Table 1. Reaction optimisation



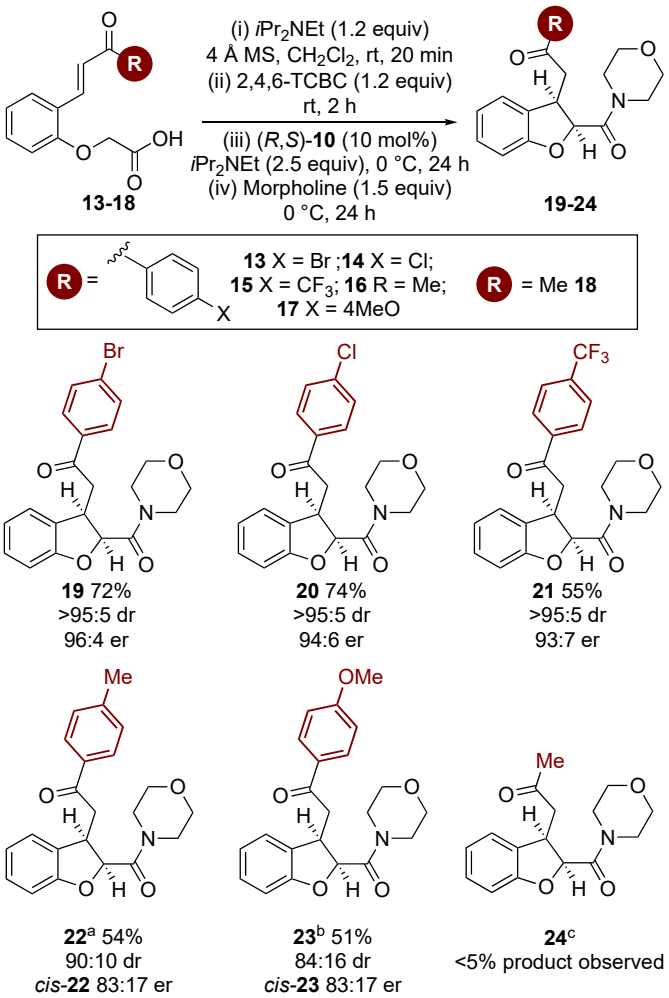
Entry	Reagent (equiv)	NucH (equiv)	Product	dr[a]	Isolated Yield	er[b]
1	Isopropyl chloroformate (2.0)	$BnNH_2$ (excess)	**11**	> 95:5	67%	> 99:1
2	2,4,6-TCBC (1.1)	$BnNH_2$ (1.5)	**11**	> 95:5	61%	> 99:1
3[c]	2,4,6-TCBC (1.1)	Morpholine (1.5)	**12**	> 95:5	73%	97:3
4[d]	2,4,6-TCBC (1.1)	Morpholine (1.5)	**12**	> 95:5	94%	97:3

TCBC = trichlorobenzoyl chloride. [a] Determined by ^{1}H NMR spectroscopic analysis of the crude reaction. [b] Determined by chiral HPLC analysis. [c] (ii) and (iii) at 0 °C for 24h. [d] (ii) at 0 °C for 24h and (iii) at 0 °C for 4h.

2.2. Enone-acid scope and limitations

The scope of this process was examined, with variation of the enone substituent first probed (Table 2). Halogen substituents on the aryl group of the enone were readily incorporated, with dihydrobenzofuran derivative **19** (R = 4-BrC_6H_4) obtained in excellent 72% yield, > 95:5 dr and 96:4 er. Product **20** (R = 4-ClC_6H_4) was prepared in 74% yield and excellent > 95:5 dr and 94:6 er. Similarly, **21** (R = 4-$F_3CC_6H_4$) was formed in excellent > 95:5 dr and 93:7 er, but in reduced but still synthetically useful 55% yield. The lower yield for **21** can be accounted for by the observation of unknown side-products as identified by ^{1}H NMR spectroscopic analysis of the crude reaction product. Interestingly a significant decrease in yield as well as diastereo- and enantiocontrol was observed when electron donating substituents were incorporated on the aromatic group within the enone. For example, when enone-acid **16** (R = 4-MeC_6H_4) was used, **22** was formed in 90:10 dr, with purification giving an inseparable 91:9 mixture of diastereoisomers in 54% yield with 83:17 er for *cis*-**22**. Product **23** (R = 4-$MeOC_6H_4$) was obtained in 84:16 dr and in 51% yield as an inseparable 92:8 mixture of diastereoisomers after purification. Lower enantiocontrol was also observed, with *cis*-**23** obtained in 83:17 er. Finally, applicaiton of an alkyl enone (Me substituent) led to < 5% conversion to product **24** by ^{1}H NMR spectroscopic analysis of the crude reaction product, and was not isolated.

Table 2. Scope: variation of the enone substituent



dr determined by ^{1}H NMR spectroscopic analysis of the crude reaction. er determined by chiral HPLC analysis. Isolated yield. TCBC = trichlorobenzoyl chloride. [a] Isolated as a 91:9 mixture of diastereoisomers. [b] Isolated as a 92:8 mixture of diastereoisomers. [c] Use of 20 mol% precatalyst **10**; **24** could not be isolated.

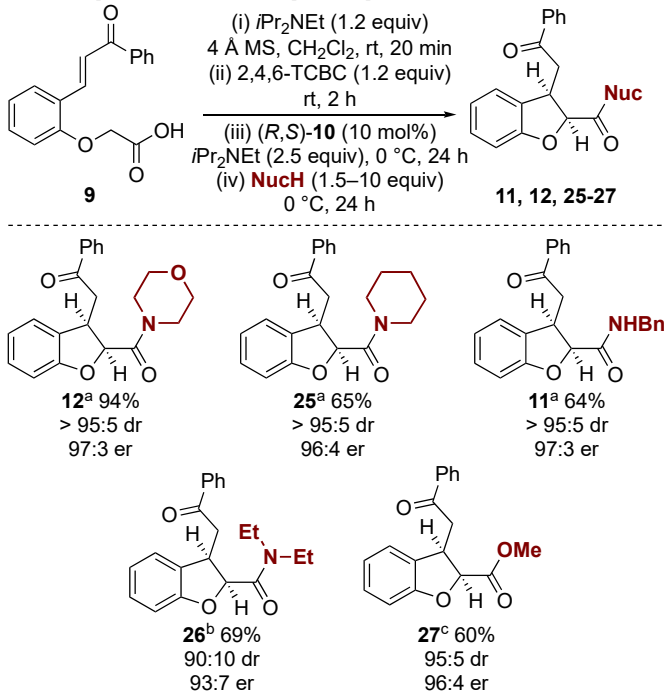
2.3. Nucleophile scope

The scope of this transformation was further evaluated through variation of the nucleophile used to promote ring-opening of the initially formed dihydropyranone product from cyclisation of **9** (Table 3). The use of either piperidine or benzylamine led to similar results, giving **25** and **11,** respectively, in good yield and excellent diastereo- and enantiocontrol. The use of diethylamine gave **26** in 69% yield and excellent 90:10 dr and 93:7 er. The use of MeOH, in combination with catalytic DMAP, led to the formation of methyl ester **27** in 60% yield, 95:5 dr and 96:4 er, with the (2*S*,3*R*)-absolute configuration assigned by comparison with literature HPLC analysis and specific rotation values.[8a]

2.4. Extension to 6-membered ring cyclisation

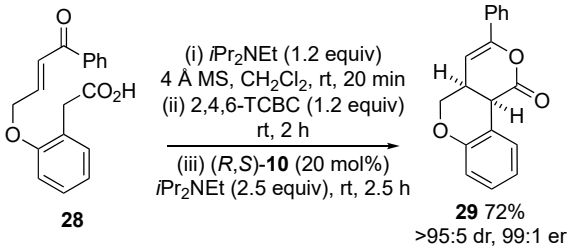
Having demonstrated the viability of this strategy for the preparation of a small range of dihydrobenzofurans, the extension of this protocol toward the formation of 6-membered ring products was investigated (Scheme 2). To date, relatively few reports have been published on organocatalytic intramolecular formal [4+2] cycloadditions for the generation of [6,6]-fused ring systems (through a formal 6-exo-trig Michael addition), with the majority focusing exclusively upon [6,5]-fused ring products (through a formal 5-exo-trig Michael addition).[12] As a test substrate, the cyclisation of enone-acid **28** to prepare chromenone derivative **29** was investigated. Treatment of **28** with 2,4,6-TCBC, followed by precatalyst **10** and *i*Pr$_2$NEt, gave the desired isolable chromenone **29** in 72% yield, > 95:5 dr and 99:1 er (Scheme 2a), with the absolute configuration assigned by comparison to the literature of both specific rotation value and HPLC analysis.[12c] To broaden the scope of this methodology, the cyclisation of the non-benzannulated enone-acid **30**, which was accessed in 4 steps from *tert*-butyl acrylate and buten-1-ol, was investigated. In this case, treatment of **30** with 2,4,6-TCBC, followed by precatalyst **10** and base, gave the desired *cis*-tetrahydropyran derivative **31** in 50% yield, > 95:5 dr and > 99:1 er (Scheme 2b). The relative and absolute configuration within **31** was assigned by analogy to **29**.

Table 3. Scope: variation of the nucleophile component

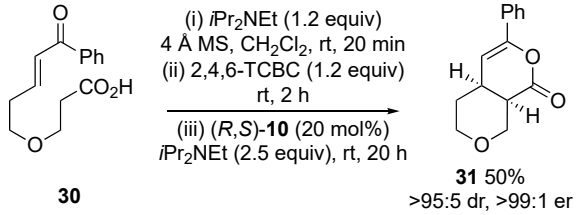


dr determined by ^{1}H NMR spectroscopic analysis of the crude reaction. er determined by chiral HPLC analysis. Isolated yield. TCBC = trichlorobenzoyl chloride. [a] NucH (1.5 equiv). [b] Et$_2$NH (5.0 equiv). [c] MeOH (10 equiv), DMAP (20 mol%); **27** isolated in >95:5 dr.

a) Application to the synthesis of chromenone derivative 29



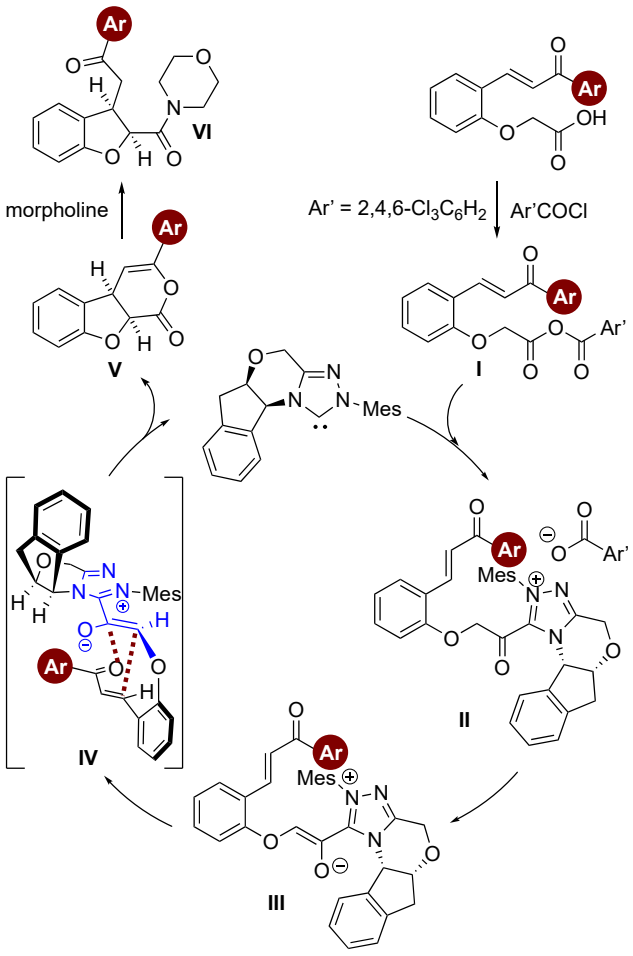
b) Application to the synthesis of pyranone derivative 31



Scheme 2. Extension of protocol for 6-membered ring cyclisations. dr determined by ^{1}H NMR spectroscopic analysis of the crude reaction. er determined by chiral HPLC analysis. Isolated yield. TCBC = trichlorobenzoyl chloride.

2.5. Proposed Mechanism and stereochemical model

A proposed mechanism for the formation of the observed products (illustrated for dihydrobenzofuran formation) involves initial formation of mixed anhydride **I** from the enone-acid and 2,4,6-TCBC, followed by subsequent nucleophilic attack of the NHC catalyst, leading to acyl azolium **II** (Scheme 3). Subsequent deprotonation gives the corresponding azolium enolate **III**, with cyclisation proceeding by either a formal concerted [4+2] cycloaddition[13] or an alternative stepwise Michael addition (5-*exo*-trig) followed by lactonisation (6-*exo*-trig).[7,8] The observed product configuration is consistent with *re*-face addition of the enolate to the *si*-face of the tethered enone. This can be rationalized by the simple stereochemical model **IV**, consistent with the enolate adopting a (*Z*)-configuration and being periplanar to the triazolium ring and orthogonal to the *N*-mesityl group, giving the preferred *cis*-product **V**. Ring-opening of the dihydropyranone by a nucleophile (in this case morpholine) forms the desired 2,3-disubstituted 2,3-dihydrobenzofuran derivative **VI**.



Scheme 3. Proposed mechanism and stereochemical model.

3. Conclusions

In summary, the generation of azolium enolates from enone-acids and an NHC, and their subsequent intramolecular cyclisation with a pendant enone has been demonstrated for the preparation of heterocyclic products. Extensive investigation on a model system showed the optimal reagent to form the reactive mixed anhydride intermediate was 2,4,6-trichlorobenzoyl chloride, leading to *cis*-dihydrobenzofuran products with high diastereo- and enantioselectivity. The scope and limitations of this process has been probed and this method extended to the generation of 6-membered ring pyran and chromenone derivatives with excellent diastereo- and enantiocontrol.

4. Experimental section

Substrates **13** – **18** and **30** were synthesised following literature procedures.[8a,b,12c]**General procedure**: Synthesis of benzofuran derivatives

The appropriate enone-acid (0.20 mmol, 1.0 equiv) and distilled *i*Pr$_2$NEt (0.22 mmol, 1.1 equiv) were stirred at rt for 20 min in anhydrous CH_2Cl_2 (3.0 mL) in a Schlenk flask containing 4 Å molecular sieves. Distilled 2,4,6-trichlorobenzoyl chloride (0.22 mmol, 1.1 equiv) was added and the reaction mixture was stirred at rt for 2 h then cooled down to 0 ºC using an immersion cooler. NHC precatalyst **10** (0.02 mmol, 10 mol%) was added, followed with distilled *i*Pr$_2$NEt (0.50 mmol, 2.5 equiv) and the reaction mixture was stirred at 0 ºC using an immersion cooler for 24 h. The appropriate nucleophile (0.30–2.0 mmol, 1.5–10 equiv) [and when required DMAP (0.04 mmol, 20 mol%)] were added and stirring was carried on at 0 ºC for the required amount of time. The reaction mixture was concentrated under reduced pressure to give the crude product that was purified by flash silica column chromatography to give the desired product.

HPLC traces of enantiomerically enriched compounds were compared with authentic racemic spectra. Authentic racemic samples were prepared using racemic chiral catalyst using the same reaction procedures.

2-((2*S*,3*R*)-2-(Morpholine-4-carbonyl)-2,3-dihydrobenzofuran-3-yl)-1-phenylethan-1-one 12

Following the general procedure, enone-acid **9** (56 mg, 0.20 mmol), distilled *i*Pr$_2$NEt (38 µL, 0.22 mmol) in anhydrous CH_2Cl_2 (3 mL) at rt for 20 min followed by distilled 2,4,6-trichlorobenzoyl chloride (34 µL, 0.22 mmol) at rt for 2 h followed by NHC precatalyst **10** (7.4 mg, 0.02 mmol, 10 mol%) *then* distilled *i*Pr$_2$NEt (88 µL, 0.50 mmol) at 0 ºC for 24 h followed by ring-opening with morpholine (26 µL, 0.30 mmol) at 0 ºC for 4 h gave a crude brown oil (272 mg, > 95:5 dr) that was purified using Biotage® Isolera™ 4 [SNAP Ultra 10 g, 36 mL·min^{-1}, CH_2Cl_2 : Et_2O (95:5 5 CV, 95:5 to 80:20 15 CV, 80:20 10 CV)] to give the title compound (66 mg, 94%, > 95:5 dr) as a yellow oil. $[\alpha]_D^{20}$ +45.5 (*c* 1.03, $CHCl_3$); Chiral HPLC OD-H (92:8 hexane : IPA, flow rate 1.00 mL·min^{-1}, 211 nm, 30 ºC) t_R minor: 47.6 min, t_R major: 73.1 min, 97:3 er; ν_{max} (film) cm^{-1}1676 (C=O ketone), 1647 (N–C=O amide I), 1597, 1479, 1458, 1449, 1231 (Ar–O–R), 1113 (R–O–R); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 3.15 (1H, dd, *J* 18.4, 4.3, C(3)C*H*^{A}H^B), 3.22–3.34 (2H, m, (C*H*^{A}H^B)^1 and (C*H*^{A}H^B)^2), 3.42–3.50 (1H, m, (CH^A*H*^{B})^1), 3.51–3.59 (3H, m, (CH^A*H*^{B})^2 and (C*H*$_2$)^3), 3.65–3.78 (3H, m, C(3)(CH^A*H*^{B}) and (C*H*$_2$)^4), 4.41 (1H, td, *J* 9.1, 4.3, C(3)*H*), 5.68 (1H, d, *J* 8.8, C(2)*H*), 6.86–6.93 (2H, m, Ar*H* × 2), 7.12–7.20 (2H, m, Ar*H* × 2), 7.42–7.49 (2H, m, COArC(3,5)*H*), 7.54–7.61 (1H, m, COArC(4)*H*), 7.90–7.97 (2H, m, COArC(2,6)*H*); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ_C: 40.0 (*C*(3)), 40.7 (C(3)*C*H$_2$), 41.9 ((*C*H$_2$)^1), 46.0 ((CH$_2$)^3), 66.1 ((*C*H$_2$)^4), 66.5 ((CH$_2$)^2), 79.9 (*C*(2)), 110.0 (Ar*C*H), 121.3 (Ar*C*H), 124.0 (Ar*C*H), 128.2 (COAr*C*(2,6)), 128.78 (COAr*C*(3,5)), 128.84 (Ar*C*H), 129.1 (*C*(3a)), 133.6 (COAr*C*(4)), 136.3 (COAr*C*(1)), 159.0 (*C*(7a)), 167.0 (C(2)*C*O), 198.2 (*C*OPh); *m/z* (NSI$^+$) 374 ([M + Na]$^+$, 31%), 352 ([M + H]$^+$, 100%); HRMS (NSI$^+$) $C_{21}H_{22}NO_4$ [M+H]$^+$ found 352.1546 requires 352.1543 (+0.8 ppm). Selected date for minor *trans*-diastereoisomer ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 3.37 (1H, app d, *J* 8.9, C(3)C*H*^{A}H^B), 4.56–4.62 (1H, m, C(3)*H*), 5.15 (1H, d, *J* 5.8, C(2)*H*), 6.81 (1H, app d, *J* 8.0, Ar*H*), 7.36 (1H, app s, Ar*H*), 7.97–7.98 (1H, m, COArC*H*).

1-(4-Bromophenyl)-2-((2*S*,3*R*)-2-(morpholine-4-carbonyl)-2,3-dihydrobenzofuran-3-yl)ethan-1-one 19

Following the general procedure, enone-acid **13** (72 mg, 0.20 mmol), distilled *i*Pr$_2$NEt (38 µL, 0.22 mmol) in anhydrous CH_2Cl_2 (3 mL) at rt for 20 min followed by distilled 2,4,6-trichlorobenzoyl chloride (34 µL, 0.22 mmol) at rt for 2 h followed by NHC precatalyst **10** (7.4 mg, 0.02 mmol, 10 mol%) *then* distilled *i*Pr$_2$NEt (88 µL, 0.50 mmol) at 0 ºC for 24 h followed by ring-opening with morpholine (26 µL, 0.30 mmol) at 0 ºC for 4 h gave a crude brown oil (227 mg, >

95:5 dr) that was purified using Biotage® Isolera™ 4 [SNAP Ultra 10 g, 36 mL·min^{-1}, pentane : EtOAc (100:0 10 CV, 100:0 to 50:50 20 CV, 50:50 15 CV)] to give the title compound (62 mg, 72%, > 95:5 dr) as a dark orange oil. $[\alpha]_D^{20}$ +25.7 (*c* 0.69, $CHCl_3$); Chiral HPLC AS-H (98:2 hexane : IPA, flow rate 1.00 mL·min^{-1}, 211 nm, 40 ºC) t_R minor: 47.3 min, t_R major: 74.2 min, 96:4 er; ν_{max} (film) cm^{-1} 1680 (C=O ketone), 1647 (N–C=O amide I), 1585, 1479, 1458, 1233, 1113, 1070; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 3.07 (1H, dd, *J* 18.4, 4.2, C(3)C*H*^{A}H^B), 3.25 (1H, ddd, *J* 13.4, 6.8, 3.1, (C*H*^{A}H^B)^1), 3.37 (1H, ddd, *J* 11.4, 6.3, 3.1, (C*H*^{A}H^B)^2), 3.46–3.61 (4H, m, (CH^A*H*^{B})^1, (CH^A*H*^{B})^2 and (C*H*$_2$)^3), 3.66–3.77 (3H, m, C(3)CH^A*H*^{B} and (C*H*$_2$)^4), 4.37 (1H, td, *J* 9.1, 4.2, C(3)*H*), 5.65 (1H, d, *J* 8.6, C(3)*H*), 6.87–6.93 (2H, m, Ar*H* × 2), 7.13–7.20 (2H, m, Ar*H* × 2), 7.58–7.63 (2H, m, COArC(3,5)*H*), 7.77–7.82 (2H, m, COArC(2,6)*H*); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ_C: 40.0 (*C*(3)), 40.7 (C(3)*C*H$_2$), 42.0 ((*C*H$_2$)^1), 46.0 ((*C*H$_2$)^3), 66.2 ((*C*H$_2$)^4), 66.5 ((*C*H$_2$)^2), 79.8 (*C*(3)), 110.1 (Ar*C*H), 121.4 (Ar*C*H), 124.0 (Ar*C*H), 128.90 (*C*(3a) or COAr*C*(4)), 128.92 (COAr*C*(4) or *C*(3a)), 128.94 (Ar*C*H), 129.6 (COAr*C*(2,6)), 132.1 (COAr*C*(3,5)), 135.0 (COAr*C*(1)), 158.8 (*C*(7a)), 166.9 (C(2)*C*O), 197.3 (*C*OAr); *m/z* (NSI$^+$) 885 ([2M(^{83}Br) + Na]$^+$, 55%), 883 ([2M(^{81}Br) + Na]$^+$, 100%), 881 ([2M(^{79}Br) + Na]$^+$, 47%), 454 ([M(^{81}Br) + Na]$^+$, 60%), 452 ([2M(^{79}Br) + Na]$^+$, 61%); HRMS (NSI$^+$) $C_{21}H_{20}NO_4{}^{79}BrNa$[M+Na]$^+$ found 452.0468 requires 452.0455 (–2.9 ppm).

1-(4-Chlorophenyl)-2-((2*S*,3*R*)-2-(morpholine-4-carbonyl)-2,3-dihydrobenzofuran-3-yl)ethan-1-one 20

Following the general procedure, enone-acid **14** (63 mg, 0.20 mmol), distilled *i*Pr$_2$NEt (38 µL, 0.22 mmol) in anhydrous CH_2Cl_2 (3 mL) at rt for 20 min followed by distilled 2,4,6-trichlorobenzoyl chloride (34 µL, 0.22 mmol) at rt for 2 h followed by NHC precatalyst **10** (7.4 mg, 0.02 mmol, 10 mol%) *then* distilled *i*Pr$_2$NEt (88 µL, 0.50 mmol) at 0 ºC for 24 h followed by ring-opening with morpholine (26 µL, 0.30 mmol) at 0 ºC for 4 h gave a crude dark green oil (236 mg, 95:5 dr) that was purified using Biotage® Isolera™ 4 [SNAP Ultra 10 g, 36 mL·min^{-1}, pentane : EtOAc (100:0 10 CV, 100:0 to 50:50 20 CV, 50:50 15 CV)] to give the title compound (57 mg, 74%, > 95:5 dr) as a yellow oil. $[\alpha]_D^{20}$ +19.7 (*c* 0.51, $CHCl_3$); Chiral HPLC AS-H (98:2 hexane : IPA, flow rate 1.00 mL·min^{-1},211 nm, 40 ºC) t_R minor: 39.1 min, t_R minor: 59.6 min, 94:6 er; ν_{max} (film) cm^{-1} 1678 (C=O ketone), 1645 (N–C=O amide I), 1587, 1479, 1460, 1443, 1231, 1113, 1092; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 3.08 (1H, dd, *J* 18.4, 4.2, C(3)C*H*^{A}H^B), 3.26 (1H, ddd, *J* 13.3, 6.7, 3.1, (C*H*^{A}H^B)^1), 3.37 (1H, ddd, *J* 11.4, 6.3, 3.1, (C*H*^{A}H^B)^2), 3.47–3.51 (1H, m, (CH^A*H*^{B})^1), 3.53–3.62 (3H, m, (CH^A*H*^{B})^2 and (C*H*$_2$)^3), 3.67–3.78 (3H, m, C(3)CH^A*H*^{B} and (C*H*$_2$)^4), 4.37 (1H, td, *J* 9.1, 4.2, C(3)*H*), 5.65 (1H, d, *J* 8.6, C(2)*H*), 6.87–6.94 (2H, m, Ar*H* × 2), 7.13–7.21 (2H, m, Ar*H* × 2), 7.40–7.47 (2H, m, COArC(3,5)*H*), 7.82–7.91 (2H, m, COArC(2,6)*H*); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ_C: 40.0 (*C*(3)), 40.7 (C(3)*C*H$_2$), 42.0 ((*C*H$_2$)^1), 46.0 ((*C*H$_2$)^3), 66.1 ((*C*H$_2$)^4), 66.5 ((*C*H$_2$)^2), 79.8 (*C*(2)), 110.1 (Ar*C*H), 121.4 (Ar*C*H), 124.0 (Ar*C*H), 128.9 ((Ar*C*H) and *C*(3a)), 129.1 (COAr*C*(3,5)), 129.6 (COAr*C*(2,6)), 134.6 (COAr*C*), 140.1 (COAr*C*), 158.8 (*C*(7a)), 166.9 (C(2)*C*O), 197.1 (*C*OAr); *m/z* (NSI$^+$) 795 ([2M(^{37}Cl) + Na]$^+$, 76%), 793 ([2M(^{35}Cl) + Na]$^+$, 100%), 408 ([M(^{35}Cl) + Na]$^+$, 90%); HRMS (NSI$^+$) $C_{21}H_{20}NO_4{}^{35}ClNa$ [M+Na]$^+$ found 408.0973 requires 408.0964 (–2.2 ppm).Selected data for minor *trans*-diastereoisomer ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 4.57–4.63 (1H, m, C(3)*H*), 5.13 (1H, d, *J* 5.9, C(2)*H*), 6.79–6.83 (2H, m, Ar*H* × 2).

2-((2*S*,3*R*)-2-(Morpholine-4-carbonyl)-2,3-dihydrobenzofuran-3-yl)-1-(4-(trifluoromethyl)phenyl)ethan-1-one 21

Following the general procedure, enone-acid **15** (70 mg, 0.20 mmol), distilled *i*Pr$_2$NEt (38 µL, 0.22 mmol) in anhydrous CH_2Cl_2 (3 mL) at rt for 20 min followed by distilled 2,4,6-trichlorobenzoyl chloride (34 µL, 0.22 mmol) at rt for 2 h followed by NHC precatalyst **10** (7.4 mg, 0.02 mmol, 10 mol%) *then* distilled *i*Pr$_2$NEt (88 µL, 0.50 mmol) at 0 ºC for 24 h followed by ring-opening with morpholine (26 µL, 0.30 mmol) at 0 ºC for 4 h gave a crude dark orange oil (70 mg, > 95:5 dr) that was purified using Biotage® Isolera™ 4 [SNAP Ultra 10 g, 36 mL·min^{-1}, pentane : EtOAc (100:0 10 CV, 100:0 to 50:50 20 CV, 50:50 15 CV)] to give the title compound (46 mg, 55%) as a dark orange oil. $[\alpha]_D^{20}$ +29.0 (*c* 0.50, $CHCl_3$); Chiral HPLC OD-H (92:8 hexane : IPA, flow rate 1.00 mL·min^{-1}, 211 nm, 40 ºC) t_R minor: 35.6 min, t_R major: 46.6 min, 93:7 er; ν_{max} (film) cm^{-1} 1684 (C=O ketone), 1653 (N–C=O amide I), 1479, 1458, 1325, 1234, 1169, 1113, 1067; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 3.12 (1H, dd, *J* 18.5, 4.2, C(3)C*H*^{A}H^B), 3.26 (1H, ddd, *J* 13.4, 6.7, 3.1, (C*H*^{A}H^B)^1), 3.40 (1H, ddd, *J* 11.1, 6.1, 3.1, (C*H*^{A}H^B)^2), 3.49–3.54 (1H, m, (CH^A*H*^{B})^1), 3.55–3.61 (3H, m, (CH^A*H*^{B})^2 and (C*H*$_2$)^3), 3.66–3.80 (2H, m, (C*H*$_2$)^4), 3.81 (1H, dd, *J* 18.5, 9.6, C(3)CH^A*H*^{B}), 4.37 (1H, td, *J* 9.1, 4.2, C(3)*H*), 5.65 (1H, d, *J* 8.5, C(2)*H*), 6.88–6.95 (2H, m, Ar*H* × 2), 7.12–7.23 (2H, m, Ar*H* × 2), 7.72 (2H, d, *J* 8.2, COArC(3,5)*H*), 8.00–8.06 (2H, m, COArC(,5)*H*); ^{19}F{^{1}H} NMR (377 MHz, $CDCl_3$) δ_F: –63.2; ^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ_C: 39.9 (*C*(3)), 41.1 (C(3)*C*H$_2$), 42.0 ((*C*H$_2$)^1), 46.0 ((*C*H$_2$)^3), 66.2 ((*C*H$_2$)^4), 66.5 ((*C*H$_2$)^2), 79.7 (*C*(2)), 110.2 (Ar*C*H), 121.5 (Ar*C*H), 123.48(1C, q, $^1J_{CF}$ 272.8, *C*F$_3$), 124.0 (Ar*C*H), 125.8 (2C, q, $^3J_{CF}$ 3.5, COAr*C*(3,5)), 128.5 (COAr*C*(2,6)), 128.8 (*C*(3a)), 129.0 (Ar*C*H), 134.8 (1C, q, $^2J_{CF}$ 32.7, COAr*C*(4)), 138.9 (COAr*C*(1)), 158.8 (*C*(7a)), 166.9 (C(2)*C*O), 197.4 (*C*OAr); *m/z* (NSI$^+$) 862 ([2M (^{20}F, ^{19}F$_2$) + Na]$^+$, 28%), 861 ([2M (^{19}F$_3$) + Na]$^+$, 58%), 443 ([M (^{20}F, ^{19}F$_2$) + Na]$^+$, 25%), 442 ([2M (^{19}F$_3$) + Na]$^+$, 100%); HRMS (NSI$^+$) $C_{22}H_{20}O_4N^{19}F_3$ [M + Na]$^+$ found 442.1237 requires 442.1231(–1.3 ppm). Selected data for minor *trans*-diastereoisomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 3.07 (1H, app d, *J* 7.6, C(3)C*H*^{A}H^B), 4.54 (1H, app q, *J* 8.4, C(3)*H*), 5.14 (1H, d, *J* 6.0, C(2)*H*), 6.62–6.71 (1H, m, Ar*H*), 6.78–6.85 (1H, m, Ar*H*), 7.01–7.10 (1H, m, Ar*H*), 8.24 (1H, d, *J* 8.3, Ar*H*).

2-((2*S*,3*R*)-2-(Morpholine-4-carbonyl)-2,3-dihydrobenzofuran-3-yl)-1-(*p*-tolyl)ethan-1-one 22

Following the general procedure, enone-acid **16** (59 mg, 0.20 mmol), distilled *i*Pr$_2$NEt (38 µL, 0.22 mmol) in anhydrous CH_2Cl_2 (3 mL) at rt for 20 min followed by distilled 2,4,6-trichlorobenzoyl chloride (34 µL, 0.22 mmol) at rt for 2 h followed by NHC precatalyst **10** (7.4 mg, 0.02 mmol, 10 mol%) *then* distilled *i*Pr$_2$NEt (88 µL, 0.50 mmol) at 0 ºC for 24 h followed by ring-opening with morpholine (26 µL, 0.30 mmol) at 0 ºC for 4 h gave a crude orange oil (221 mg, 90:10 dr) that was purified using Biotage® Isolera™ 4 [SNAP Ultra 10 g, 36 mL·min^{-1}, pentane : EtOAc (100:0 10 CV, 100:0 to 50:50 20 CV, 50:50 15 CV)] to give the title compound (39 mg, 54%, 91:9 dr) as a yellow oil. $[\alpha]_D^{20}$ +31.3 (*c* 0.51, $CHCl_3$); Chiral HPLC OD-H (94:6 hexane : IPA, flow rate 1.00 mL·min^{-1}, 211 nm, 40 ºC) t_R minor: 37.6 min, t_R minor: 62.6 min, 83:17 er; ν_{max} (film) cm^{-1} 1674 (C=O ketone), 1653 (N–C=O amide I), 1607, 1479, 1458, 1234, 1115; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 2.41 (3H, s, C*H*$_3$), 3.12 (1H, dd, *J* 18.3, 4.3, C(3)C*H*^{A}H^B), 3.23–3.35 (2H, m, (C*H*^{A}H^B)^1 and (C*H*^{A}H^B)^2), 3.46 (1H, ddd, *J* 13.2, 6.7, 3.1, (CH^A*H*^{B})^1), 3.51–3.59 (3H, m, (CH^A*H*^{B})^2 and (C*H*$_2$)^3), 3.65–3.74 (3H, m, C(3)CH^A*H*^{B} and (C*H*$_2$)^4), 4.42 (1H, td, *J* 9.2, 4.2, C(3)*H*), 5.68 (1H, d, *J* 8.8, C(2)*H*), 6.87–6.92 (2H, m, Ar*H* × 2), 7.13–7.20 (2H, m, Ar*H* × 2), 7.21–7.28 (2H, m, COArC(3,5)*H*), 7.81–7.87 (2H, m, COArC(2,6)*H*).; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ_C: 21.7 (*C*H$_3$), 40.0 (*C*(3)), 40.6 (C(3)*C*H$_2$), 41.9 ((*C*H$_2$)^1), 46.0 ((*C*H$_2$)^3), 66.1 ((*C*H$_2$)^4), 66.5 ((*C*H$_2$)^2), 79.9 (*C*(2)), 110.00 (Ar*C*H), 121.2 (Ar*C*H), 124.0 (Ar*C*H), 128.3 (COAr*C*(2,6)), 128.8 (Ar*C*H), 129.1 (*C*(3a)), 129.4 (COAr*C*(3,5)), 133.8 (COAr*C*(4)), 144.6 (COAr*C*(1)), 159.0 (*C*(7a)), 167.0 (C(2)*C*O), 197.8 (*C*OAr); *m/z* (NSI$^+$) 388 ([M + Na]$^+$, 64%), 366 [M+H]$^+$, 100%); HRMS (NSI$^+$) $C_{22}H_{24}NO_4$ [M + H]$^+$ found 366.1700 requires 366.1702 (+0.6 ppm). Selected data for minor *trans*-diastereoisomer: Chiral HPLC OD-H (94:6 hexane : IPA, flow rate 1.00 mL·min^{-1}, 211 nm, 40 ºC) t_R minor: 42.8 t_R major: 57.4 min, 59:41 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 4.57 (1H, m, C(3)*H*), 5.15 (1H, d, *J* 5.8, C(2)*H*), 6.81 (1H, m, Ar*H*), 7.86 (2H, m, Ar*H* × 2).

1-(4-Methoxyphenyl)-2-((2*S*,3*R*)-2-(morpholine-4-carbonyl)-2,3-dihydrobenzofuran-3-yl)ethan-1-one 23

Following the general procedure, enone-acid **17** (63 mg, 0.20 mmol), distilled *i*Pr$_2$NEt (38 µL, 0.22 mmol) in anhydrous CH_2Cl_2 (3 mL) at rt for 20 min followed by distilled 2,4,6-trichlorobenzoyl chloride (34 µL, 0.22 mmol) at rt for 2 h followed by NHC precatalyst **10** (7.4 mg, 0.02 mmol, 10 mol%) *then* distilled *i*Pr$_2$NEt (88 µL, 0.50 mmol) at 0 ºC for 24 h followed by ring-opening with morpholine (26 µL, 0.30 mmol) at 0 ºC for 4 h gave a crude yellow oil (472 mg, 84:16 dr) that was purified using Biotage® Isolera™ 4 [SNAP Ultra 10 g, 36 mL·min^{-1}, CH_2Cl_2 : EtOAc (100:0 10 CV, 100:0 to 50:50 20 CV, 50:50 15 CV)] to give the title compound (39 mg, 51%, 92:8 dr) as a yellow oil. $[\alpha]_D^{20}$ +12.0 (*c* 0.49, $CHCl_3$); Chiral HPLC OD-H (94:6 hexane : IPA, flow rate 1.00 mL·min^{-1}, 211 nm, 40 ºC) t_R minor: 78.1 min, t_R major: 110.2 min, 83:17 er; ν_{max} (film) cm^{-1} 1670 (C=O ketone), 1653 (N–C=O amide I), 1599, 1479, 1458, 1263, 1234, 1171, 1115; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 3.08 (1H, dd, *J* 18.1, 4.2, C(3)C*H*^{A}H^B), 3.19–3.34 (2H, m, (C*H*^{A}H^B)^1 and (C*H*^{A}H^B)^2), 3.42–3.48 (1H, m, (CH^A*H*^{B})^1), 3.48–3.60 (3H, m, (CH^A*H*^{B})^2 and (C*H*$_2$)^3), 3.59–3.72 (3H, m, C(3)CH^A*H*^{B} and (C*H*$_2$)^4), 3.87 (3H, s, OC*H*$_3$), 4.42 (1H, td, *J* 9.2, 4.2, C(3)*H*), 5.67 (1H, d, *J* 8.8, C(2)*H*), 6.86–6.97 (4H, m, Ar*H* × 2 and COArC(3,5)*H*), 7.11–7.22 (2H, m, Ar*H* × 2), 7.85–7.98 (2H, m, COArC(2,6)*H*); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ_C: 40.1 (*C*(3)), 40.3 (C(3)*C*H$_2$), 41.9 ((*C*H$_2$)^1), 46.0 ((*C*H$_2$)^3), 55.5 ((OCH$_3$)), 66.1 ((*C*H$_2$)^4), 66.5 ((*C*H$_2$)^1), 79.9 (*C*(2)), 110.0 (Ar*C*H), 113.9 (COAr*C*(3,5)), 121.2 (Ar*C*H), 124.4 (Ar*C*H), 128.8 (Ar*C*H), 129.2 (*C*(3a)), 129.4 (COAr*C*(1)), 130.5 (COAr*C*(2,6)), 159.0 (*C*(7a)), 163.9 (COAr*C*(4)), 167.0 (C(2)*C*O), 196.6 (*C*OAr);

m/z (NSI$^+$) 785 ([2M + Na]$^+$, 100%), 404 ([M + Na]$^+$, 77%); HRMS (NSI$^+$) $C_{22}H_{23}NO_3$ [M+Na]$^+$ found 404.168 requires 404.1466 (–0.6 ppm). Selected data for minor *trans*-diastereoisomer: Chiral HPLC OD-H (94:6 hexane : IPA, flow rate 1.00 mL·min^{-1}, 211 nm, 40 ºC) t_R major: 88.3 min, t_R minor: 124.0 min, 58:42 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 4.57 (1H, m, C(3)*H*), 5.16 (1H, d, *J* 5.8, C(2)), 6.78–6.86 (2H, m, Ar*H*).

1-Phenyl-2-((2*S*,3*R*)-2-(piperidine-1-carbonyl)-2,3-dihydrobenzofuran-3-yl)ethan-1-one 25

Following the general procedure, enone-acid **9** (56 mg, 0.20 mmol), distilled *i*Pr$_2$NEt (38 µL, 0.22 mmol) in anhydrous CH_2Cl_2 (3 mL) at rt for 20 min followed by distilled 2,4,6-trichlorobenzoyl chloride (34 µL, 0.22 mmol) at rt for 2 h followed by NHC precatalyst **10** (7.4 mg, 0.02 mmol, 10 mol%) *then* distilled *i*Pr$_2$NEt (88 µL, 0.50 mmol) at 0 ºC for 24 h followed by ring-opening with piperidine (30 µL, 0.30 mmol) at 0 ºC for 19 h gave a crude brown oil (276 mg, > 95:5 dr) that was purified using Biotage® Isolera™ 4 [SNAP Ultra 10 g, 36 mL min^{-1}, pentane : EtOAc (95:5 5 CV, 95:5 to 80:20 15 CV, 80:20 10 CV)] to give the title compound (46 mg, 65%, > 95:5 dr) as a yellow oil. $[\alpha]_D^{20}$ –18.7 (*c* 1.13, $CHCl_3$); Chiral HPLC OD-H (95:5 hexane : IPA, flow rate 1.00 mL·min^{-1}, 211 nm, 30 ºC) t_R minor: 25.9 min, t_R major: 64.8 min, 96:4 er; ν_{max} (film) cm^{-1} 1682 (C=O ketone), 1647 (N–C=O amide I), 1597, 1477, 1449, 1242, 1227; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 1.30–1.40 (1H, m, (C*H*^{A}H^B)^1), 1.43–1.74 (5H, m, (CH^{A}H^B)^1, (CH_2)^2 and CH_2)^3), 2.93 (1H, ddd, *J* 12.8, 8.8, 3.6, (C*H*^{A}H^B)^4), 3.12 (1H, dd, *J* 18.1, 5.6, C(3)C*H*^{A}H^B)), 3.27 (1H, ddd, *J* 13.3, 8.2, 3.2, (C*H*^{A}H^B)^5), 3.48–3.53 (1H, m, (CH^A*H*^{B})^5), 3.57 (1H, dd, *J* 18.1, 8.2, C(3)CH^A*H*^{B}), 3.67 (1H, ddd, *J* 13.0, 6.4, 3.3, (CH^A*H*^{B})^4), 4.41 (1H, td, *J* 8.3, 5.5, C(3)*H*), 5.66 (1H, d, *J* 8.6, C(2)*H*), 6.83–6.93 (2H, m, Ar*H* × 2), 7.11–7.19 (2H, m, Ar*H* × 2), 7.40–7.47 (2H, m, COArC(3,5)*H*), 7.52–7.59 (1H, m, COArC(4)*H*), 7.88–7.94 (2H, m, COArC(2,6)*H*); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ_C: 24.4 (*C*H$_2$), 25.4 ((*C*H$_2$)^1), 26.2 (*C*H$_2$), 39.9(*C*(3)), 40.6 (C(3)*C*H$_2$), 42.8 ((CH$_2$)^4), 46.6 ((*C*H$_2$)^5), 80.8 (*C*(2)), 110.1 (Ar*C*H), 121.2 (Ar*C*H), 124.3 (Ar*C*H), 128.2 (COAr*C*(2,6)), 128.66 (COAr*C*(3,5)), 128.75 (Ar*C*H), 129.4 (*C*(3a)), 133.4 (COAr*C*(4)), 136.5 (COAr*C*(1)), 158.9 (*C*(7a)), 166.3 (C(2)*C*O), 198.0 (*C*OPh); *m/z* (NSI$^+$) 350 ([M + H]$^+$, 100%); HRMS (NSI$^+$) $C_{22}H_{24}NO_3$ [M+H]$^+$ found 250.1752 requires 350.1751 (+0.4 ppm). Selected data for minor *trans*-diastereoisomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 3.35–3.39 (1H, m, C(3)CH_2 × 1), 4.57–4.63 (1H, m, C(3)*H*), 5.17 (1H, d, *J* 6.0, C(2)*H*), 6.80–6.83 (1H, m, Ar*H*), 7.70–7.77 (2H, m, COAr*H* × 2), 7.95–7.99 (2H, m, COAr*H* × 2).

(2*S*,3*R*)-*N*-Benzyl-3-(2-oxo-2-phenylethyl)-2,3-dihydrobenzofuran-2-carboxamide 11

Following the general procedure, enone-acid **9** (56 mg, 0.20 mmol), distilled *i*Pr$_2$NEt (38 µL, 0.22 mmol) in anhydrous CH_2Cl_2 (3 mL) at rt for 20 min followed by distilled 2,4,6-trichlorobenzoyl chloride (34 µL, 0.22 mmol) at rt for 2 h followed by NHC precatalyst **10** (7.4 mg, 0.02 mmol, 10 mol%) *then* distilled *i*Pr$_2$NEt (88 µL, 0.50 mmol) at 0 ºC for 24 h followed by ring-opening with BnNH$_2$ (33 µL, 0.30 mmol) at 0 ºC for 19 h gave a crude brown oil (234 mg, > 95:5 dr) that was purified using Biotage® Isolera™ 4 [SNAP Ultra 10 g, 36 mL·min^{-1}, pentane : EtOAc (95:5 5 CV, 95:5 to 80:20 15 CV, 80:20 20 CV)] to give the title compound (47 mg, 64%, > 95:5 dr) as a beige solid. mp 163–165 ºC; $[\alpha]_D^{20}$ –93.9 (*c* 0.99, $CHCl_3$); Chiral HPLC AS-H (90:10 hexane : IPA, flow rate 1.00 mL·min^{-1}, 211 nm, 30 ºC) t_R major: 16.2 min, t_R major: 28.0 min, 97:3 er; ν_{max} (film) cm^{-1} 3360 (N–H), 1682 (C=O ketone), 1647 (N–C=O amide I), 1595, 1522 (N–H amide II), 1472, 1456, 1362, 1215; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 3.10 (1H, dd, *J* 17.5, 9.3, C(3)C*H*^{A}H^B), 3.48 (1H, dd, *J* 17.5, 4.6, C(3)CH^A*H*^{B}), 4.40 (1H, dd, *J* 14.7, 5.8, NHC*H*^{A}H^B), 4.48 (1H, td, *J* 9.4, 4.6, C(3)*H*), 4.62 (1H, dd, *J* 14.7, 6.5, NHCH^A*H*^{B}), 5.31 (1H, d, *J* 9.4, C(2)*H*), 6.82–6.91 (2H, m, Ar*H* × 2), 7.10 (1H, br t, *J* 6.4, N*H*), 7.12–7.18 (1H, m, Ar*H*), 7.23 (1H, ddt, *J* 7.5, 1.4, 0.6, Ar*H*), 7.27–7.37 (5H, m, NHCH$_2$Ar*H* × 5), 7.39–7.45 (2H, m, COArC(3,5)*H*), 7.52–7.57 (1H, m, COArC(4)*H*), 7.79–7.83 (2H, m, COArC(2,6)*H*); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ_C: 39.5 (*C*(3)), 39.9 (C(3)*C*H$_2$), 43.0 (NH*C*H$_2$), 83.8 (*C*(2)), 109.8 (Ar*C*H), 122.0 (Ar*C*H), 125.8 (Ar*C*H), 127.7 (NHCH$_2$Ar*C*H × 2), 128.0 (COAr*C*(2,6)), 128.1 (Ar*C*H × 2), 128.6 (COAr*C*(3,5)), 128.80 (NHCH$_2$Ar*C*H), 128.83 (NHCH$_2$Ar*C*H and Ar*C*H), 129.7 (*C*(3a)), 133.2 (COAr*C*(4)), 136.8 (COAr*C*(1)), 138.0 (NHCH$_2$Ar*C*(1)), 157.7 (*C*(7a)), 168.9 (C(2)*C*O), 197.5 (*C*OPh); *m/z* (NSI$^+$) 372 ([M + H]$^+$, 100%); HRMS (NSI$^+$) $C_{24}H_{22}NO_3$ [M+H]$^+$ found 372.1596 requires 372.1594 (+0.5 ppm). Selected data for minor *trans*-diastereoisomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 3.67 (1H, dd, *J* 17.6, 4.8, C(3)CH_2 × 1), 4.54–4.57 (1H, m, C(3)*H*), 4.92 (1H, d, *J* 6.9, C(2)*H*), 7.46–7.51 (2H, m, COAr*H* × 2), 7.98–8.02 (2H, m, COAr*H* × 2).

(2*S*,3*R*)-*N*,*N*-Diethyl-3-(2-oxo-2-phenylethyl)-2,3-dihydrobenzofuran-2-carboxamide 26

Following the general procedure, enone-acid **9** (56 mg, 0.20 mmol), distilled *i*Pr$_2$NEt (38 µL, 0.22 mmol) in anhydrous CH_2Cl_2 (3 mL) at rt for 20 min followed by distilled 2,4,6-trichlorobenzoyl chloride (34 µL, 0.22 mmol) at rt for 2 h followed by NHC precatalyst **10** (7.4 mg, 0.02 mmol, 10 mol%) *then* distilled *i*Pr$_2$NEt (88 µL, 0.50 mmol) at 0 ºC for 24 h followed by ring-opening with Et$_2$NH (104 µL, 1.0 mmol) at 0 ºC for 19 h gave a crude dark orange oil (254 mg, 90:10 dr) that was purified using Biotage® Isolera™ 4 [SNAP Ultra 10 g, 36 mL·min^{-1}, pentane : EtOAc (95:5 5 CV, 95:5 to 80:20 15 CV, 80:20 10 CV)] to give the title compound (46 mg, 69%, 95:5 dr) as an orange oil. $[\alpha]_D^{20}$ –1.6 (*c* 0.74, $CHCl_3$); Chiral HPLC OD-H (95:5 hexane : IPA, flow rate 1.00 mL·min^{-1}, 211 nm, 30 ºC) t_R minor: 17.1 min, t_R major: 34.9 min, 93:7 er; ν_{max} (film) cm^{-1} 1682 (C=O ketone), 1645 (N–C=O amide I), 1597, 1477, 1449, 1238, 1225; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 0.87 (3H, t, *J* 7.1, N(CH$_2$C*H*$_3$)^1), 1.25 (3H, t, *J* 7.2, N(CH$_2$C*H*$_3$)^2), 2.99 (1H, dq, *J* 13.3, 7.1, N(C*H*^{A}H^{B}CH$_3$)^1), 3.10–3.24 (1H, m, N(C*H*^{A}H^{B}CH$_3$)^2), 3.20 (1H, dd, *J* 18.6, 4.9, C(3)*H*^{A}H^B), 3.43–3.52 (1H, m, N(CH^A*H*^{B}CH$_3$)^1), 3.53–3.64 (1H, m, N(CH^A*H*^{B}CH$_3$)^2), 3.71 (1H, dd, *J* 18.6, 8.8, C(3)H^A*H*^{B}), 4.42 (1H, td, *J* 8.8, 4.9, C(3)*H*), 5.60 (1H, d, *J* 8.7, C(2)*H*), 6.83–6.92 (2H, m, Ar*H* × 2), 7.12–7.18 (2H, m, Ar*H* × 2), 7.40–7.45 (2H, m, COArC(3,5)*H*), 7.51–7.57 (1H, m, COArC(4)*H*), 7.88–7.93 (2H, m, COArC(2,6)*H*); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ_C: 12.7 (N(CH$_2$*C*H$_3$)^1), 14.5 (N(CH$_2$*C*H$_3$)^2), 39.7 (*C*(3)), 40.6 (N(*C*H$_2$CH$_3$)^1), 41.1 (C(3)*C*H$_2$), 41.9 (N(CH$_2$*C*H$_3$)^2), 80.6 (*C*(2)), 110.0 (Ar*C*H), 121.1 (Ar*C*H), 124.2 (Ar*C*H), 128.1 (COAr*C*(2,6)), 128.6 (COAr*C*(3,5)), 128.7 (Ar*C*H), 129.4 (*C*(3a)), 133.4 (COAr*C*(4)), 136.4 (COAr*C*(1)), 159.1 (*C*(7a)), 167.2 (C(2)*C*O), 198.1 (*C*OPh); *m/z* (NSI$^+$) 338 ([M + H]$^+$, 100%); HRMS (NSI$^+$) $C_{21}H_{24}NO_3$ [M+H]$^+$ found 338.1472 requires 338.1751 (+0.4 ppm). Selected data for minor *trans*-diastereoisomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 1.19 (3H, t, *J* 7.1, N(CH$_2$C*H*$_3$)^1), 1.25 (3H, t, *J* 7.1, N(CH$_2$C*H*$_3$)^2), 3.26–3.39 (4H, m, C*H*$_2$ × 2), 4.51–4.59 (1H, m, C(3)*H*), 5.13 (1H, d, *J* 6.0, C(2)*H*), 6.81 (1H, m, Ar*H*), 7.71–7.77 (1H, m, COArC(4)*H*), 7.95–7.98 (2H, m, COArC(2,6)*H*).

(2*S*,3*R*)-Methyl 3-(2-oxo-2-phenylethyl)-2,3-dihydrobenzofuran-2-carboxylate 27

Following the general procedure, enone-acid **9** (56 mg, 0.20 mmol), distilled *i*Pr$_2$NEt (38 µL, 0.22 mmol) in anhydrous CH_2Cl_2 (3 mL) at rt for 20 min followed by distilled 2,4,6-trichlorobenzoyl chloride (34 µL, 0.22 mmol) at rt for 2 h followed by NHC precatalyst **10** (7.4 mg, 0.02 mmol, 10 mol%) *then* distilled *i*Pr$_2$NEt (88 µL, 0.50 mmol) at 0 ºC for 24 h followed by ring-opening with MeOH (82 µL, 2.0 mmol) and DMAP (4.9 mg, 0.04 mmol, 20 mol%) at 0 ºC for 19 h gave a crude brown oil (199 mg, 95:5 dr) that was purified using Biotage® Isolera™ 4 [SNAP Ultra 10 g, 36 mL·min^{-1}, pentane : EtOAc (100:0 5 CV, 100:0 to 80:20 15 CV, 80:20 5 CV)] to give the title compound (36 mg, 60%, > 95:5 dr) as a limpid oil. $[\alpha]_D^{20}$ –16.7 (*c* 0.76, $CHCl_3$); Chiral HPLC AD-H (90:10 hexane : IPA, flow rate 1.00 mL·min^{-1}, 211 nm, 30 ºC) t_R minor: 13.3 min, t_R major: 14.5 min 96:4 er; ν_{max} (film) cm^{-1} 1749 (C=O ester), 1717, 1684 (C=O ketone), 1653, 1597, 1558, 1506, 1479, 1209; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 3.30 (1H, dd, *J* 17.9, 6.5, C(3)C*H*^{A}H^B), 3.37 (1H, dd, *J* 17.9, 7.7, C(3)CH^A*H*^{B}), 3.62 (3H, s, OC*H*$_3$), 4.48–4.55 (1H, m, C(3)*H*), 5.39 (1H, d, *J* 9.2, C(2)*H*), 6.86–6.94 (2H, m, Ar*H* × 2), 7.14–7.21 (2H, m, Ar*H* × 2), 7.43–7.50 (2H, m, COArC(3,5)*H*), 7.55–7.60 (1H, m, COArC(4)*H*), 7.90–7.95 (2H, m, COACr(2,6)*H*); ^{13}C{^{1}H} (101 MHz, $CDCl_3$) δc: 40.1 (*C*(3)CH$_2$ or *C*(3)), 40.2 (*C*(3) *C*(3)CH$_2$) 52.2 (OCH$_3$), 82.6 (*C*(2)), 110.1 (Ar*C*H), 121.5 (Ar*C*H), 124.4 (Ar*C*H), 128.0 (COAr*C*(2,6)), 128.5 (*C*(3a)), 128.7 (COAr*C*(3,5)), 129.0 (Ar*C*H), 133.5 (COAr*C*(4)), 136.5 (COAr*C*(1)), 158.7 (*C*(7 a)), 169.9 (*C*O$_2$CH$_3$), 197.4 (*C*OPh); *m/z* (NSI$^+$) 297 ([M + H]$^+$, 100%); HRMS (NSI$^+$) $C_{18}H_{17}O_4$ [M + H]$^+$ found 297.1124 requires 297.1121 (+0.9 ppm). Selected data for Minor *trans*-diastereoisomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 3.83 (3H, s, OC*H*$_3$), 4.31 (1H, dd, *J* 13.2, 6.6, C(3)*H*), 4.91 (1H, d, *J* 5.8, C(2)*H*), 7.96–8.00 (2H, m, Ar*H* × 2).

(4a*S*,10b*R*)-3-Phenyl-4a,10b-dihydropyrano[4,3-c]chromen-1(5*H*)-one 29

Enone-acid **28** (59 mg, 0.20 mmol, 1.0 equiv) and distilled *i*Pr$_2$NEt (38 µL, 0.22 mmol, 1.1 equiv) were stirred at rt for 20 min in anhydrous CH_2Cl_2 (3.0 mL) with 4 Å molecular sieves. Distilled 2,4,6-trichlorobenzoyl chloride (34 µL, 0.22 mmol, 1.1 equiv) was added and the reaction mixture was stirred at rt for 2 h. NHC precatalyst **10** (14.7, 0.04 mmol, 20 mol%) and distilled *i*Pr$_2$NEt (88 µL, 0.50 mmol, 2.5 equiv) were added and the reaction mixture was stirred at rt for 2.5 h. The reaction mixture was concentrated under reduced pressure to give a crude green oil (201 mg, > 95:5 dr) that was purified using Biotage® Isolera™ 4 [SNAP

Ultra 10 g, 36 mL·min^{-1}, Hexane : EtOAc (100:0 5 CV, 100:0 to 80:20 15 CV, 80:20 10 CV)] to give the title compound (40 mg, 72%, > 95:5 dr) as a yellow solid, with data in accordance with the literature.[12c] $[\alpha]_D^{20}$ –147.2 (*c* 1.04, $CHCl_3$);Chiral HPLC AD-H (95:5 hexane : IPA, flow rate 1 mL·min^{-1}, 211 nm, 40 ºC) t_R major: 14.3 min, t_R minor: 19.9 min, 99:1 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 3.26 (1H, dddd, *J* 8.2, 6.7, 5.0, 3.1, C(4a)*H*), 3.98–4.08 (2H, m, C(5)*H*^{A}H^B and C(10b)*H*), 4.25 (1H, ddd, *J* 11.3, 3.1, 1.2, C(5)H^A*H*^{B}), 5.81 (1H, d, *J* 5.0, C(4)*H*), 6.86 (1H, dd, *J* 8.2, 1.2, C(7)*H*), 6.98 (1H, td, *J* 7.5, 1.3, C(8)*H*), 7.18–7.24 (1H, m, C(9)*H*), 7.30–7.34 (1H, m, C(10)*H*), 7.35–7.40 (3H, m, C(3)ArC(3,4,5)*H*), 7.59–7.65 (2H, m, C(3)ArC(2,6)*H*); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ_C: 31.0 (*C*(4a)), 40.1 (*C*(10b)), 66.0 (*C*(5)), 98.7 (*C*(4)), 115.4 (*C*(10a)), 117.3 (*C*(9)), 121.3 (*C*(8)), 124.9 (C(3)Ar*C*(2,6)), 128.7 (C(3)Ar*C*(3,5)), 129.5 (C(3)Ar*C*(4) or *C*(9)), 129.6 (*C*(9) or C(3)Ar*C*(4)), 131.2 (*C*(10)), 131.8 (C(3)Ar*C*(1)), 151.8 (*C*(3)), 153.9 (*C*(6a)), 167.7 (*C*(1)).

(*E*)-3-((5-Oxo-5-phenylpent-3-en-1-yl)oxy)propanoic acid 30

A solution of $BnNMe_3OH$ (Triton B 40%, 3.18 mL, 7.0 mmol, 10 mol%) in MeOH was concentrated under reduced pressure before adding 3-buten-1-ol (66 mL, 77 mmol, 1.1 equiv). The reaction mixture was stirred for 30 min at rt before adding *tert*-butyl acrylate (10.3 mL, 70 mmol, 1.0 equiv). The reaction mixture was stirred at 50 ºC for 18 h, cooled to rt and filtered through a pad of Celite and silica using CH_2Cl_2 (150 mL). The organic layer was concentrated under reduced pressure to give *tert*-butyl 3-(but-3-en-1-yloxy)propanoate as a crude pale yellow oil (11.9 g, 77%), which was used in the next step without further purification. The crude sample of *tert*-butyl 3-(but-3-en-1-yloxy)propanoate (2.0 g, ~10 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (290 mL) and cooled to –78°C. A stream of O_3 in air was bubbled through. Upon the change of colour of the reaction mixture to blue, the O_3 stream was stopped and air only was bubbled through for 5 min at –78°C. DMS (1.5 mL. 20 mmol, 2.0 equiv) was added, and after 10 min, the reaction mixture was left to slowly warm to rt. 1-Phenyl-2-(triphenyl-l5-phosphanylidene)ethan-1-one (4.2 g, 11 mmol, 1.1 equiv) was added and the reaction was stirred at rt for 16 h. 10% Citric acid was added and the mixture extracted with CH_2Cl_2 (× 3). The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure to give a brown oil. This crude product was dissolved in CH_2Cl_2 (20 mL) before slowly adding TFA (3.8 mL, 50 mmol, 5.0 equiv) and stirring at rt for 17 h. The reaction mixture was concentrated under reduced pressure, diluted in EtOAc and basified to pH 10 using saturated $NaHCO_3$. The aqueous was washed with EtOAc (× 3) then acidified to pH 5 using 10% citric acid and extracted with EtOAc (× 3). The organic was dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the title compound (317 mg, 13%) as a yellow oil that was used in the next step without further purification. ν_{max} (film) cm^{-1} 2876, 1418, 1668, 1620, 1597, 1287, 1111; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 2.56–2.64 (4H, m, C*H*$_2$CH$_2$CO$_2$H and C(2)*H*$_2$), 3.63–3.66 (2H, m, OC(1)*H*$_2$), 3.74 (2H, t, *J* 6.3, C*H*$_2$CO$_2$H), 6.94 (1H, m, C(4)*H*), 7.02 (1H, m, C(3)*H*), 7.43–7.48 (2H, m, COArC(3,5)*H*), 7.52–7.58 (1H, m, COArC(4)*H*), 7.90–7.93 (2H, m, COArC(2,6)*H*); ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 33.0 (*C*(2)), 34.8 (*C*H$_2$CH$_2$CO$_2$H), 66.0 (*C*(1)), 69.3 (*C*H$_2$CO$_2$H), 127.5 (*C*(4)), 128.55 (Ar*C*H × 2), 128.63 (Ar*C*H × 2), 132.8 (Ar*C*(4)H), 137.7 (Ar*C*(1)), 146.0 (*C*(3)), 176.8 (*C*O$_2$H), 190.9 (*C*OPh); *m/z* (APCI$^+$) 249 ([M + H] $^+$, 100%); HRMS (APCI$^+$) $C_{14}H_{16}O_4$ [M + H]$^+$ found 249.1120 requires 249.1121 (–0.5 ppm).

(4a*R*,8a*S*)-3-Phenyl-4a,5,8,8a-tetrahydro-1*H*,6*H*-pyrano[3,4-*c*]pyran-1-one 31

Enone-acid **30** (50 mg, 0.20 mmol, 1.0 equiv) and distilled *i*Pr$_2$NEt (38 µL, 0.22 mmol, 1.1 equiv) were stirred at rt for 20 min in anhydrous CH_2Cl_2 (3.0 mL) with 4 Å molecular sieves. Distilled 2,4,6-trichlorobenzoyl chloride (34 µL, 0.22 mmol, 1.1 equiv) was added and the reaction mixture was stirred at rt for 2 h. NHC precatalyst **10** (14.7, 0.04 mmol, 20 mol%) and distilled *i*Pr$_2$NEt (88 µL, 0.50 mmol, 2.5 equiv) were added and the reaction mixture was stirred at rt for 20 h. The reaction mixture was diluted with EtOAc and washed with brine (× 3). The organic was dried over $MgSO_4$, filtered and concentrated under reduced pressure to give a crude brown-green oil (44 mg, > 95:5 dr) that was purified using Biotage® Isolera™ 4 [SNAP Ultra 10 g, 36 mL·min^{-1}, Hexane : EtOAc (95:5 5 CV, 95:5 to 70:30 15 CV, 70:30 10 CV)] to give the title compound (23 mg, 50%) as a yellow oil. $[\alpha]_D^{20}$ +20.0 (*c* 1.0 $CHCl_3$); Chiral HPLC AS-H (95:5 hexane : IPA, flow rate 1 mL·min^{-1}, 211 nm, 40 ºC) t_R minor: 14.6 min, t_R major: 21.1 min, > 99:1er; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.62 (1H, dtd, *J* 14.5, 10.5, 4.1, C(5)*H*^{A}H^B), 1.76–1.84 (1H, m, C(5)H^A*H*^{B}), 2.76–2.86 (2H, m, C(4a)*H* and C(8a)*H*), 3.50 (1H, td, *J* 11.2, 2.5, C(6)*H*^{A}H^B), 3.61 (1H, dd, *J* 11.8, 3.0, C(8)*H*^{A}H^B), 3.97 (1H, dt, *J* 11.5, 3.7, C(6)H^A*H*^{B}), 4.50–4.59 (1H, m, C(8)H^A*H*^{B}), 5.86 (1H, d, *J* 5.8, C(4)*H*), 7.32–7.41 (3H, m, C(3)Ar*H* including C(3)Ar(4)*H*), 7.59–7.66 (2H, m, C(3)Ar*H*). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 29.8 (*C*(5)), 30.9 (*C*(4a)), 39.7 (*C*(8a)), 65.3 (*C*(8)), 67.2 (*C*(6)), 104.0 (*C*(4)), 124.7 (C(3)Ar*C*H), 128.7 (C(3)Ar*C*H), 129.3 (C(3)Ar*C*(4)), 132.2 (C(3)Ar*C*(1)), 150.3 (*C*(3)), 168.6 (*C*(1)); *m/z* (ESI$^+$) 253 ([M + Na]$^+$, 48%), 271 ([M + Na + H_2O]$^+$, 100%); HRMS (ESI$^+$) $C_{14}H_{14}O_3Na$ [M + Na]$^+$ found 253.0833 requires 253.0841 (–0.852 ppm).

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References and notes

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Supplementary Material

For NMR spectra and HPLC traces see the Supporting Information.

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