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Organocatalytic Michael Addition-Lactonisation of Carboxylic Acids using α,β-Unsaturated Trichloromethyl Ketones as α,β-Unsaturated Ester Equivalents

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Louis C. Morrill,[a] Daniel. G. Stark,[a] James. E. Taylor,[a] Siobhan R. Smith,[a] James A. Squires,[a] Agathe C. A. D'Hollander,[a] Carmen Simal,[a] Peter Shapland,[b] Timothy J. C. O'Riordan[c] and Andrew D. Smith*[a]

Isothiourea HBTM-2.1 catalyses the Michael addition-lactonisation of 2-aryl and 2-alkenylacetic acids and α,β-unsaturated trichloromethyl ketones. Ring-opening of the resulting dihydropyranones and subsequent alcoholysis of the CCl_3 group with an excess of methanol gives a range of diesters in high diastereo- and enantioselectivity (up to 95:5 dr and >99% ee). Sequential addition of two different nucleophiles to a dihydropyranone gives the corresponding differentially substituted diacid derivative.

Introduction

Lewis base organocatalysis is a powerful method for the stereoselective construction of carbon-carbon bonds.[1] In this regard, catalytic asymmetric conjugate additions of ammonium and azolium enolates to electron-deficient alkenes have been widely explored.[2,3] However, the use of α,β-unsaturated esters and amides as Michael acceptors in such processes remains a challenge due to the decreased electrophilicity of such substrates. Strategies to overcome this problem typically make use of more reactive α,β-unsaturated ester equivalents such as *N*-acylpyrroles **1**,[4] 2-acyl imidazoles **2**,[5] activated imides **3**[6] and α-ketophosphonates **4** (Fig. 1i).[7,8]

We have previously reported a number of intra- and intermolecular isothiourea-catalysed Michael addition-cyclisation cascades of electron-deficient Michael acceptors with ammonium enolates generated from carboxylic acids.[9-12] Of particular relevance is our recent report on the use of α-keto-β,γ-unsaturated phosphonates as ester equivalents in an intermolecular Michael addition-lactonisation reaction, giving access to a range of diester products with high levels of stereoselectivity after ring-opening and alcoholysis.[13] However, many α-keto-β,γ-unsaturated phosphonates are not bench-stable and cannot be stored for long periods of time. To alleviate this problem the use of α,β-unsaturated trichloromethyl ketones as alternative, bench-stable α,β-unsaturated ester equivalents seemed an attractive possibility.

Trichloromethyl ketones are versatile synthetic building blocks and have been used as carboxylic acid, ester and amide equivalents by utilising the leaving group ability of the CCl_3 group in haloform-type reactions.[14,15] For example, Friedel-Crafts acylation of heterocycles, in particular pyrrole derivatives, using trichloroacetyl chloride followed by substitution of the CCl_3 group with either alcohol or amine nucleophiles is a widely used reaction sequence in natural product synthesis.[16,17] Shibasaki and co-workers have used trichloromethyl ketones as ester and amide-enolate equivalents in diastereoselective Mannich reactions, with the electron-withdrawing nature of the CCl_3 group allowing catalytic α-deprotonation to form an enolate.[18]

α,β-Unsaturated trichloromethyl ketones have previously been used as ester and amide equivalents of Michael acceptors in a small number of processes.[19] For example, Zhao and co-workers reported the two-step enantioselective diaryl prolinol catalysed epoxidation of α,β-unsaturated trichloromethyl ketones using *tert*-butylhydroperoxide (TBHP) followed by either alcoholysis with methanol or aminolysis with various amines.[19a] Zhao and co-workers have also reported Michael additions of α-cyano ketones into α,β-unsaturated trichloromethyl ketones catalysed by a piperazine/thiourea based bifunctional organocatalyst.[19b] More recently, Wang *et al.* have performed enantioselective vinylogous Michael additions of α,β-unsaturated γ-butyrolactams into α,β-unsaturated trichloromethyl ketones using a chiral quinine-derived squaramide organocatalyst, followed by methanolysis of the CCl_3 group.[19c]

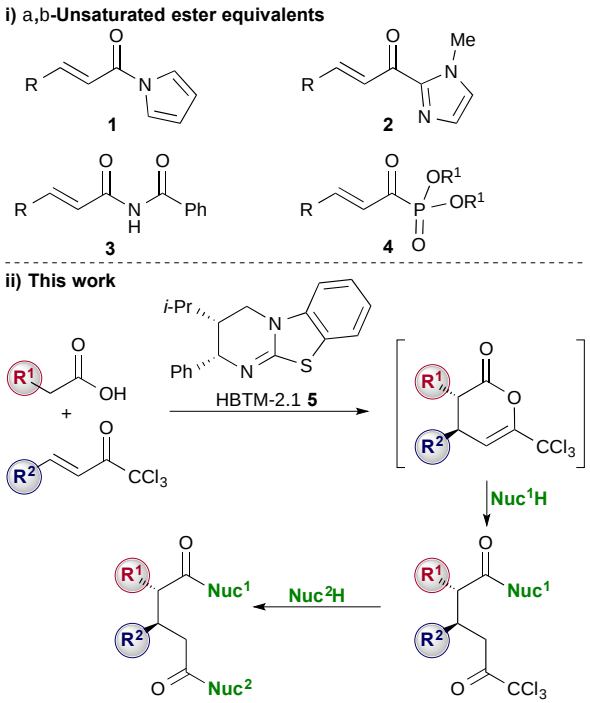


Fig. 1 i) Previously used α,β-unsaturated ester equivalents. ii) Proposed use of α,β-unsaturated trichloromethyl ketones in asymmetric intramolecular Michael addition-lactonisations

Herein an isothiourea-catalysed Michael addition-lactonisation process using 2-aryl and 2-alkenylacetic acids and bench-stable α,β-unsaturated trichloromethyl ketones as ester and amide equivalents is reported (Fig. 1ii). Nucleophilic ring-opening of the initially formed dihydropyranone products followed by either alcoholysis or aminolysis of the CCl_3 group gives access to stereodefined diesters and diamides, respectively. Furthermore in a single example, a relatively slow alcoholysis of the CCl_3 group compared to dihydropyranone ring-opening allowed the sequential addition of two different nucleophiles, leading to the formation of a differentially substituted diacid derivative. This is in contrast to the use of α-keto-β,γ-unsaturated phosphonates where both ring-opening and either alcoholysis or aminolysis of the phosphate group proceeds rapidly and differential functionalisation is not possible.[13]

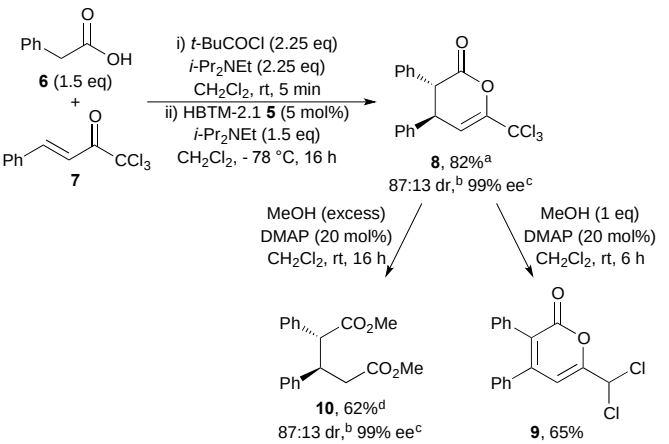
Results and discussion

α,β-Unsaturated trichloromethyl ketone synthesis

First, the reaction of phenylacetic acid **6** with (*E*)-1,1,1-trichloro-4-phenylbut-3-en-2-one **7** was studied. Trichloromethyl ketone **7** was synthesised on gram-scale using a two-step procedure first described by Corey and co-workers.[20] Nucleophilic addition of the CCl_3 anion, generated from trichloroacetic acid and sodium trichloroacetate in *N*,*N*-dimethylformamide (DMF), into (*E*)-cinnamaldehyde followed by Swern oxidation of the resulting trichloromethyl carbinol gave trichloromethyl ketone **7** in 45% yield (4.41 g, 18 mmol) over the two steps. This robust protocol was used for the gram-scale preparation of a range of α,β-unsaturated trichloromethyl ketones, which can be readily stored on the bench-top without undergoing decomposition.[21] An alternative method of synthesising **7** using (*E*)-cinnamaldehyde and $CHCl_3$ in the presence of KOH, followed by oxidation, was unreliable in our hands, with the formation of polymeric mixtures during the first step resulting in low yields.[19a]

Initial studies

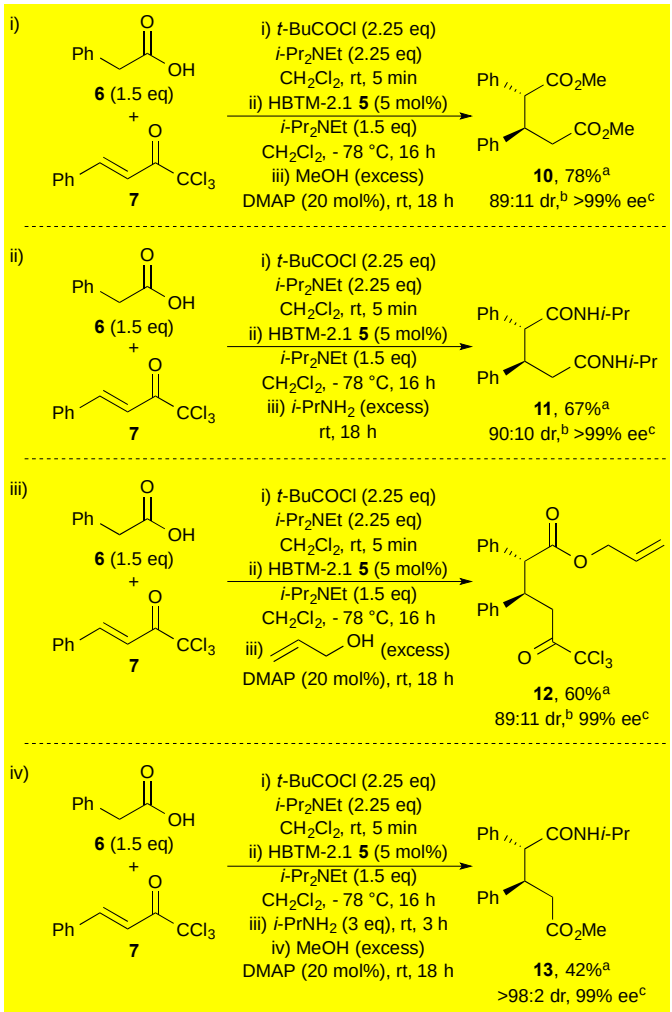
Reaction of trichloromethyl ketone **7** with phenylacetic acid **6** (1.5 eq), using pivaloyl chloride (2.25 eq) to form an *in situ* mixed anhydride, in the presence of isothiourea HBTM-2.1 **5** (5 mol%) and *i*-Pr_2NEt (1.5 eq) at –78 °C gave dihydropyranone **8** in 82% yield as a 87:13 mixture of diastereoisomers, with the major *anti*-diastereoisomer formed in excellent 99% ee (Scheme 1).[22-24] Attempted nucleophilic ring-opening of dihydropyranone **8** with one equivalent of methanol and a catalytic amount of DMAP (20 mol%) led to the unexpected formation of pyranone **9** in 65% yield, presumably through deprotonation to eliminate HCl followed by tautomerisation. Pleasingly, treating dihydropyranone **8** with a large excess of methanol in the presence of DMAP (20 mol%) led to the desired ring-opening and alcoholysis of the CCl_3 group to give a single diastereoisomer of diester **10** in 62% yield and 99% ee after purification by column chromatography. The absolute and relative stereochemistry of diester **10** was confirmed by comparison of data with that previously reported, with all subsequent compounds assigned by analogy.[13]



Scheme. 1 [a] Isolated yield of a mixture of diastereoisomers. [b] Determined by ^1H NMR spectroscopic analysis of the crude reaction mixture. [c] Determined by chiral HPLC analysis of diester **10**. [d] Isolated yield of major diastereoisomer (>98:2 dr).

Next, a one-pot Michael addition-lactonisation followed by *in-situ* ring-opening with methanol was trialled (Scheme 2i). In this case major *anti*-diester **10** was obtained in 78% yield in >99% ee.[25,] The use of alternative ring-opening nucleophiles was then investigated. Reacting phenylacetic acid **6** with trichloromethyl ketone **7** under the standard reaction conditions, followed by ring-opening and aminolysis with an excess of

isopropylamine gave diamide **11** in 90:10 dr, >99% ee and 67% yield (Scheme 2ii). However, the use of secondary amines such as pyrrolidine led to a complex mixture of products.



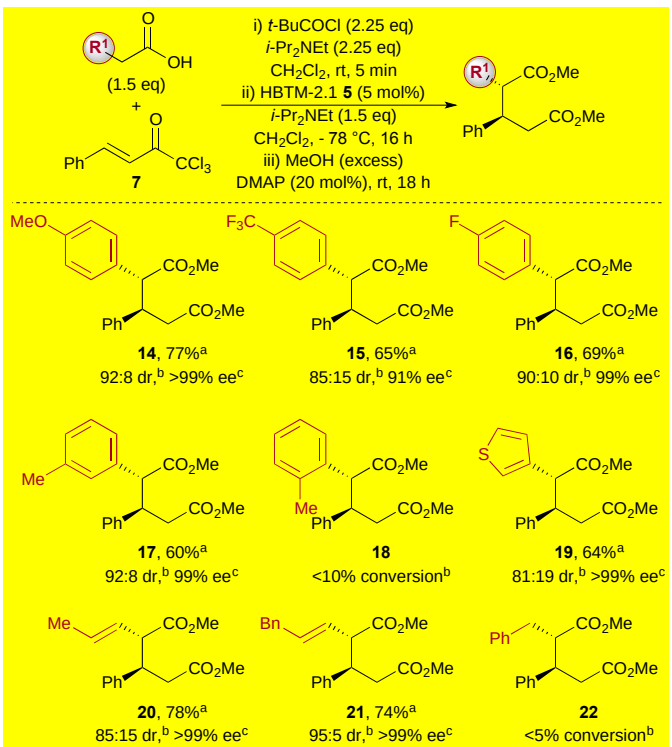
Scheme 2 i) Ring-opening and alcoholysis with MeOH; ii) Ring-opening and aminolysis with isopropylamine; iii) Ring-opening with allyl alcohol; iv) Sequential addition of two nucleophiles. [a] Isolated yield of major diastereoisomer (>98:2 dr). [b] Determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. [c] Determined by chiral HPLC analysis.

Interestingly, use of allyl alcohol as the ring-opening nucleophile afforded monoester product **12** in 60% yield, 89:11 dr and 99% ee, with no substitution of the CCl_3 group observed (Scheme 2iii). This led to the possibility of forming differentially protected diacid derivatives through the sequential addition of two nucleophiles. To test this, the reaction between phenylacetic acid **6** and trichloromethyl ketone **7** was firstly ring-opened with three equivalents of isopropylamine.[26] Upon the disappearance of the initial dihydropyranone product as judged by TLC analysis a large excess of methanol and catalytic DMAP (20 mol%) was added. Pleasingly, γ-ester amide **13** was isolated in 42% yield over the three one-pot reaction steps as a single diastereoisomer in 99% ee (Scheme 2iv).

Scope and generality

With efficient reaction conditions and suitable ring-opening protocols in hand, the scope of this Michael addition-lactonisation process was evaluated through variation of the acetic acid component (Table 1). Phenylacetic acid derivatives bearing electron-donating (4-OMe), electron-withdrawing (4-CF_3) and halogen (4-F) substituents could be employed in this system, affording the corresponding diesters **14-16** with high stereocontrol. *m*-Tolylacetic acid allows formation of diester **17** in 92:8 dr and >99% ee, whereas *o*-tolylacetic acid is not tolerated (presumably due to steric hindrance) and gave <10% conversion into the corresponding diester **18**. Heteroaromatic substitution was possible through use of 3-thiopheneacetic acid, with diester **19** formed in a reduced 81:19 dr but with excellent ee for the major *anti*-diastereoisomer. (*E*)-4-Methyl and (*E*)-4-benzyl alkenoic acids also participate in this process, affording diesters **20** and **21** in good yields and with excellent diastereo- and enantiocontrol. Unfortunately, the use of 3-phenylpropionic acid did not lead to any formation of diester **22** under the standard conditions.

Table 1 Scope of 2-aryl and 2-alkenyl acetic acids

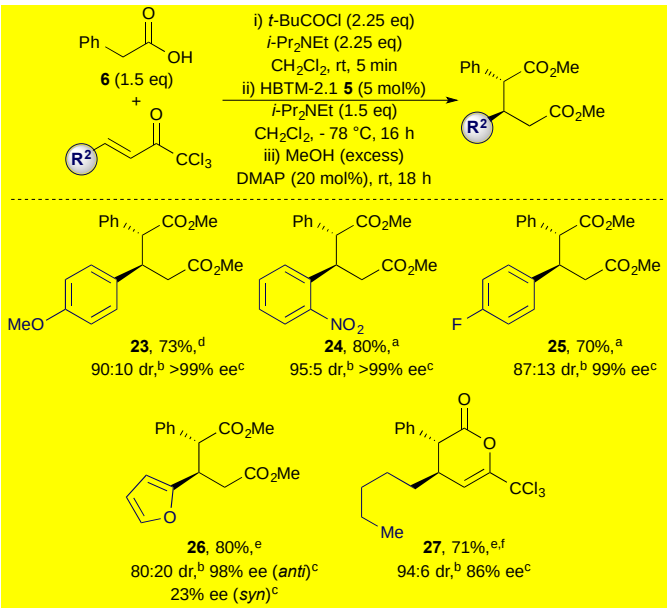


[a] Isolated yield of major diastereoisomer (>98:2 dr) [b] Determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. [c] Determined by chiral HPLC analysis.

To further examine the scope of the reaction a selection of α,β-unsaturated trichloromethyl ketones was examined (Table 2). Within the Michael acceptor, β-aryl groups containing electron-donating (4-OMe), electron-withdrawing (2-NO_2) and halogen (4-F) substituents were tolerated, giving the corresponding diesters **23-25** in high yields with excellent stereocontrol. A

Michael acceptor bearing a heteroaromatic β-2-furyl substituent also participates, giving diester **26** with reduced diastereoselectivity (80:20 dr), although the major diastereoisomer again forms in excellent ee (98%). The incorporation of a β-alkyl substituent proved to be more challenging, with the reaction of a β-pentyl trichloromethyl ketone followed by *in situ* methanolysis giving a complex mixture of products. Further investigation revealed that the Michael addition-lactonisation worked well, with dihydropyranone **27** isolated in 71% yield albeit in a reduced 86% ee. Attempts to ring-open isolated dihydropyranone **27** with either methanol or isopropylamine were also unsuccessful, with a complex mixture of products observed in both cases.

Table 2 Scope of α,β-unsaturated trichloromethyl ketones



[a] Isolated yield of major diastereoisomer (>98:2 dr). [b] Determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. [c] Determined by chiral HPLC analysis. [d] Isolated yield of major diastereoisomer (96:4 dr). [e] Isolated yield of a mixture of diastereoisomers. [f] Steps i) and ii) only.

Proposed mechanism

The proposed mechanism for this process initiates *via* *N*-acylation of HBTM-2.1 **5** with *in situ* formed mixed anhydride **28**, forming acyl ammonium **29** (Fig. 2). Subsequent deprotonation gives the key (*Z*)-ammonium enolate **30**, allowing either an n_o to $\sigma^*_{C\text{-}S}$ interaction or favourable electrostatic stabilisation between the enolate oxygen and the sulfur atom of the isothiourea.[27] Stereoselective Michael addition to α,β-unsaturated trichloromethyl ketone **31** followed by lactonisation gives dihydropyranone **33** and regenerates the catalyst. Ring-opening of dihydropyranone **33** with a nucleophile generates keto-ester **34**, with further alcoholysis of the trichloromethyl ketone into diester **35** proceeding at a slower rate.

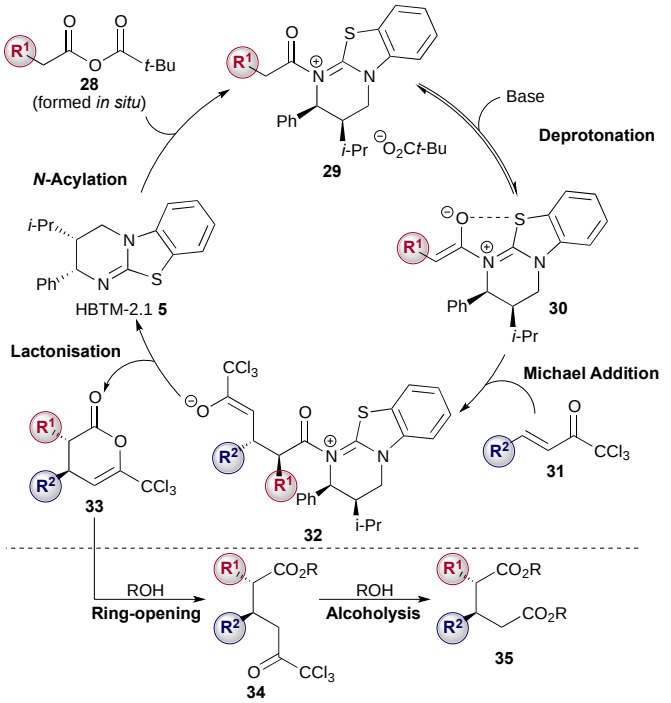


Fig. 2 Proposed mechanism for Lewis base catalysed process.

Conclusions

In conclusion, the Michael addition-lactonisation of a range of 2-aryl and 2-alkenylacetic acids and bench-stable α,β-unsaturated trichloromethyl ketones has been demonstrated. Upon alcoholysis, the initially formed dihydropyranone products are converted into stereodefined diesters, representing a formal conjugate addition into an α,β-unsaturated ester. Slow substitution of the CCl_3 group after ring-opening allowed the formation of a γ-ester amide through sequential addition of two nucleophiles. Further studies within our laboratory are focused towards the continued development of isothioureas in catalysis.

Experimental

General information

Anhydrous CH_2Cl_2 was obtained from an Mbraun SPS-800 system. Petrol is defined as petroleum ether 40-60 °C. All other solvents and commercial reagents were used as supplied without further purification unless stated otherwise.

Room temperature (rt) refers to 20-25 °C. Temperatures of 0 °C and –78 °C were obtained using ice/water and CO_2(s)/acetone baths, respectively. Temperatures between 0 °C and –60 °C for overnight reactions were obtained using an immersion cooler (HAAKE EK 90).

Analytical thin layer chromatography was performed on pre-coated aluminium plates (Kieselgel 60 F_{254} silica). TLC visualisation was carried out with ultraviolet light (254 nm), followed by staining with a 1% aqueous $KMnO_4$ solution and heating. Flash column chromatography was performed on Kieselgel 60 silica in the solvent system stated.

Melting points were recorded on an Electrothermal 9100 apparatus, *dec* refers to decomposition, *sub* refers to sublimation.

Optical rotations were measured on a Perkin Elmer Precisely/Model-341 polarimeter operating at the sodium D line with a 100 mm path cell at 20 °C.

HPLC analyses were obtained on a Shimadzu HPLC consisting of a DGU-20A5 degasser, LC-20AT liquid chromatograph, SIL-20AHT autosampler, CMB-20A communications bus module, SPD-M20A diode array detector and a CTO-20A column oven which allowed the temperature to be set from 25-40 °C. Separation was achieved using Chiralcel OD-H and OJ-H columns or Chiralpak AD-H, AS-H, IA, and IB columns.

Infrared spectra (ν_{max}) were recorded on a Shimadzu IRAffinity-1 Fourier transform IR spectrophotometer as thin films using Pike MIRacle ATR accessory. Analysis was carried out using Shimadzu IRsolution v1.50 and only characteristic peaks are reported.

^{1}H, ^{13}C{^{1}H}, and ^{19}F {^{1}H}NMR spectra were acquired on either a Bruker Avance 300 {δ_H (300 MHz), δ_C (75 MHz), δ_F (282 MHz)}, a Bruker Avance II 400 {δ_H (400 MHz), δ_C (100 MHz), δ_F (376 MHz)} or a Bruker Ultrashield 500 {δ_H (500 MHz), δ_C (125 MHz), δ_F (471 MHz)} spectrometer at ambient temperature in the deuterated solvent stated. Chemical shifts, δ, are quoted in parts per million (ppm) and are referenced to the residual solvent peak. Coupling constants, *J*, are quoted in Hertz (Hz) to the nearest 0.1 Hz. The following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; and br, broad.

Mass spectrometry (*m/z*) data were acquired by electrospray ionisation (ESI), electron impact (EI), chemical ionisation (CI), atmospheric solids analysis probe (ASAP), atmospheric pressure chemical ionisation (APCI) or nanospray ionisation (NSI) at the EPSRC National Mass Spectrometry Service Centre, Swansea.

General procedure A: synthesis of trichloromethyl carbinols

Following a literature procedure,[19c] trichloroacetic acid (1.5 eq) and sodium trichloroacetate (1.5 eq) were added to a solution of the appropriate aldehyde (1 eq) in DMF at 0 °C. The reaction mixture was stirred in the ice/water bath and allowed to warm slowly to rt over 16 h before being diluted with water and extracted with EtOAc (× 3). The combined organic fraction was washed with water (× 3), sat. aq. $NaHCO_3$, dried ($MgSO_4$), filtered and concentrated under reduced pressure to give the crude product, which was purified by flash silica column chromatography.

General procedure B: synthesis of α,β-unsaturated trichloromethyl ketones

Following a literature procedure,[20] a solution of DMSO (8 eq) in CH_2Cl_2 was added dropwise to a solution of oxalyl chloride (4 eq) in CH_2Cl_2 at −60 °C followed by stirring for 2 min at −60 °C. A solution of the appropriate alcohol (1 eq) in CH_2Cl_2 was added dropwise followed by stirring for 15 min at −60 °C. Et_3N (20 eq) was added dropwise and the reaction mixture was stirred and allowed to warm to rt. The reaction mixture was quenched with 2 M HCl and extracted with CH_2Cl_2 (× 3). The combined organic fraction was dried ($MgSO_4$), filtered and concentrated under reduced pressure to give the crude product, which was purified by flash silica column chromatography.

General procedure C: intermolecular Michael addition-lactonisation followed by *in situ* ring-opening

i-Pr_2NEt (2.25 eq) and pivaloyl chloride (2.25 eq) were added to a solution of the appropriate carboxylic acid (1.5 eq) in CH_2Cl_2 (to give 0.1 M trichloromethyl ketone) at rt and the reaction mixture was stirred for 5 min before cooling to −78 °C. HBTM-2.1 (2*S*,3*R*)-**5** (5 mol%), the appropriate α,β-unsaturated trichloromethyl ketone (1 eq) and *i*-Pr_2NEt (1.5 eq) were added in succession and the reaction mixture was stirred at −78 °C for 16 h. The appropriate nucleophile (excess) and DMAP (20 mol%) were added and the reaction mixture was stirred at rt for 24 h. The reaction mixture was diluted with CH_2Cl_2 and washed with 1 M HCl and brine. The organic layer was dried ($MgSO_4$), filtered and concentrated under reduced pressure to give the crude product, which was purified by flash silica column chromatography.

Authentic racemic samples were prepared in an analogous fashion using racemic isothiourea catalyst (*rac*)-HBTM-2.1 **5**.

Preparation of trichloromethyl carbinols

(*E*)-1,1,1-Trichloro-4-phenylbut-3-en-2-ol 36. Following general procedure A, cinnamaldehyde (5.03 mL, 40.0 mmol), DMF (30 mL), trichloroacetic acid (9.80 g, 60.0 mmol) and sodium trichloroacetate (11.1 g, 60.0 mmol) gave, after column chromatography (90:10 Petrol:Et_2O, R_f = 0.20), the title compound **36** (4.78 g, 48%) as an orange oil with spectroscopic data in accordance with the literature.[28] ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 2.92 (1H, d, *J* 5.6, O*H*), 4.75−4.80 (1H, m, C(2)*H*), 6.37 (1H, dd, *J* 15.9, 6.1, C(3)*H*), 6.91 (1H, d, *J* 15.9, C(4)*H*), 7.28−7.39 (3H, m, ArC(3,5)*H* and ArC(4)*H*), 7.43−7.47 (2H, m, ArC(2,6)*H*).

(*E*)-1,1,1-Trichloro-4-(4-methoxyphenyl)but-3-en-2-ol 37. Following general procedure A, 4-methoxycinnamaldehyde (6.49 mL, 40.0 mmol), DMF (30 mL), trichloroacetic acid (9.80 g, 60.0 mmol) and sodium trichloroacetate (11.1 g, 60.0 mmol) gave, after column chromatography (80:20 Petrol:Et_2O, R_f = 0.20), the title compound **37** (9.04 g, 80%) as a white solid; mp 66−68 °C; ν_{max} (ATR) 3356 (O-H), 2967 (C-H), 1653, 1605, 1514; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 2.98 (1H, d, *J* 5.8, O*H*), 3.82 (3H, s, OCH_3), 4.74 (1H, app t, *J* 6.1, C(2)*H*), 6.22 (1H, dd, *J* 15.9, 6.3, C(3)*H*), 6.83 (1H, d, *J* 15.9, C(4)*H*), 6.87−6.91 (2H, m, ArC(3,5)*H*), 7.37−7.39 (2H, m, ArC(2,6)*H*); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ_C: 55.5 (OCH_3), 83.7 (*C*(2)), 103.1 (*C*(1)), 114.2 (Ar*C*(3,5)), 120.4 (*C*(3)), 128.4 (Ar*C*(2,6)), 128.5 (Ar*C*(1)), 136.5 (*C*(4)), 160.1 (Ar*C*(4)); HRMS (APCI$^+$) $C_{11}H_{12}{}^{35}Cl_3O_2$ $[M+H]^+$, found 280.9894, requires 280.9897 (−1.2 ppm).

(*E*)-1,1,1-Trichloro-4-(2-nitrophenyl)but-3-en-2-ol 38. Following general procedure A, 2-nitrocinnamaldehyde (7.09 mL,

40.0 mmol), DMF (100 mL), trichloroacetic acid (9.80 g, 60.0 mmol) and sodium trichloroacetate (11.1 g, 60.0 mmol) gave, after column chromatography (70:30 Petrol:Et_2O, R_f = 0.30), the title compound **38** (3.12 g, 26%) as a white solid; mp 114−116 °C; ν_{max} (ATR) 3291 (O-H), 2973 (C-H), 1607, 1518; ^{1}H NMR (300 MHz, DMSO-d_6) δ_H: 4.83 (1H, app t, *J* 5.8, C(2)*H*), 6.44 (1H, dd, *J* 15.6, 5.9, C(3)*H*), 7.15−7.23 (2H, m, C(4)*H* and ArC*H*), 7.56−7.60 (1H, m, ArC*H*), 7.71−7.76 (2H, m, ArC*H*), 7.99 (1H, d, *J* 8.2, ArC(3)*H*); ^{13}C{^{1}H} NMR (75 MHz, DMSO-d_6) δ_C: 81.5 (*C*(2)), 103.5 (*C*(1)), 124.3 (Ar*C*(3)), 128.6 (Ar*C*), 129.3 (Ar*C*), 129.8 (*C*(4)), 130.0 (*C*(3)), 130.6 (Ar*C*(1)), 133.6 (Ar*C*), 147.8 (Ar*C*(2)); HRMS (APCI$^+$) $C_{10}H_{12}{}^{35}Cl_3NO_3$ $[M+NH_4]^+$, found 312.9907, requires 312.9908 (−0.3 ppm).

(*E*)-1,1,1-Trichloro-4-(4-fluorophenyl)but-3-en-2-ol 39. Following general procedure A, 4-fluorocinnamaldehyde (5.00 g, 33.3 mmol), DMF (30 mL), trichloroacetic acid (8.17 g, 50.0 mmol) and sodium trichloroacetate (9.27 g, 50.0 mmol) gave, after column chromatography (85:15 Petrol:Et_2O, R_f = 0.25), the title compound **39** (4.71 g, 52%) as an orange solid with spectroscopic data in accordance with the literature.[19a] mp 66−64 °C; {Lit.[19a] mp 60−62 °C}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 2.92 (1H, d, *J* 5.7, O*H*), 4.76 (1H, td, *J* 5.9, 1.3, C(2)*H*), 6.29 (1H, ddd, *J* 15.9, 6.1, 0.6, C(3)*H*), 6.87 (1H, d, *J* 15.9, C(4)*H*), 7.01−7.08 (2H, m, ArC(3,5)*H*), 7.38−7.46 (2H, m, ArC(2,6)*H*); ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ_F: −113.18 (ArC(4)*F*).

(*E*)-1,1,1-Trichloro-4-(furan-2-yl)but-3-en-2-ol 40. Following general procedure A, 3-(furan-2-yl)acrylaldehyde (5.00 g, 40.9 mmol), DMF (30 mL), trichloroacetic acid (10.1 g, 61.4 mmol) and sodium trichloroacetate (11.4 g, 61.4 mmol) gave, after column chromatography (85:15 Petrol:Et_2O, R_f = 0.25), the title compound **40** (4.00 g, 40%) as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 2.89 (1H, d, *J* 5.9, O*H*), 4.75 (1H, td, *J* 5.9, 1.3, C(2)*H*), 6.33 (1H, dd, *J* 15.8, 5.8, C(3)*H*), 6.37 (1H, d, *J* 3.3, ArC(3)*H*), 6.41 (1H, dd, *J* 3.3, 1.8, ArC(4)*H*), 6.72 (1H, dd, *J* 15.8, 1.3, C(4)*H*), 7.40 (1H, d, *J* 1.6, ArC(5)*H*). The title compound was carried forward immediately without further characterisation due to instability.

(*E*)-1,1,1-Trichlorononon-3-en-2-ol 41. Following general procedure A, (*E*)-oct-2-enal (5.00 mL, 39.6 mmol), DMF (30 mL), trichloroacetic acid (9.76 g, 59.4 mmol) and sodium trichloroacetate (11.1 g, 59.4 mmol) gave, after column chromatography (95:5 Petrol:Et_2O, R_f = 0.20), the title compound **41** (4.71 g, 48%) as a yellow oil with spectroscopic data in accordance with the literature.[29] ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 0.81−0.95 (3H, m, CH_3), 1.24−1.48 (6H, m, 3 × CH_2), 2.08−2.17 (2H, m, C(5)H_2), 2.72 (1H, d, *J* 5.9, O*H*), 4.51−4.56 (1H, m, C(2)*H*), 5.65 (1H, ddt, *J* 15.5, 6.5, 1.5, C(3)*H*), 6.02 (1H, dtd, *J* 15.5, 6.9, 1.0, C(4)*H*).

Preparation of α,β-unsaturated trichloromethyl ketones

(*E*)-1,1,1-Trichloro-4-phenylbut-3-en-2-one 7. Following general procedure B, oxalyl chloride (6.43 mL, 76.0 mmol) in CH_2Cl_2 (300 mL), DMSO (10.8 mL, 152 mmol) in CH_2Cl_2 (35 mL), (*E*)-1,1,1-trichloro-4-phenylbut-3-en-2-ol **36** (4.78 g, 19.0 mmol) in CH_2Cl_2 (20 mL) and Et_3N (53.0 mL, 380 mmol) gave, after column chromatography (95:5 Petrol:Et_2O, R_f = 0.30), the title compound **7** (4.41 g, 93%) as a yellow solid; mp 56−58 °C; ν_{max} (ATR) 3059, 3030 (C-H), 1707 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 7.35 (1H, d, *J* 15.7, C(3)*H*), 7.43−7.49 (3H, m, ArC(3,5)*H* and ArC(4)*H*), 7.65−7.66 (2H, m, ArC(2,6)*H*), 8.01 (1H, d, *J* 15.7, C(4)*H*); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ_C: 96.6 (*C*(1)), 115.9 (*C*(3)), 129.1 (Ar*C*), 129.3 (Ar*C*), 131.9 (Ar*C*(4)), 133.9 (Ar*C*(1)), 149.8 (*C*(4)), 180.2 (*C*(2)); HRMS (APCI$^+$) $C_{10}H_8{}^{35}Cl_3O$ $[M+H]^+$, found 248.9634, requires 248.9635 (−0.5 ppm).

(*E*)-1,1,1-Trichloro-4-(4-methoxyphenyl)but-3-en-2-one 42. Following general procedure B, oxalyl chloride (6.43 mL, 76.0 mmol) in CH_2Cl_2 (300 mL), DMSO (10.8 mL, 152 mmol) in CH_2Cl_2 (35 mL), (*E*)-1,1,1-trichloro-4-(4-methoxyphenyl)but-3-en-2-ol **37** (5.35 g, 19.0 mmol) in CH_2Cl_2 (20 mL) and Et_3N (53.0 mL, 380 mmol) gave, after column chromatography (90:10 Petrol:Et_2O, R_f = 0.20), the title compound **42** (4.63 g, 87%) as a yellow solid; mp 98−100 °C; ν_{max} (ATR) 3013, 2835 (C-H), 1699 (C=O), 1587 1562, 1508; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 3.87 (3H, s, OCH_3), 6.95 (2H, d, *J* 8.7, ArC(3,5)*H*), 7.21 (1H, d, *J* 15.5, C(3)*H*), 7.60−7.63 (2H, m, ArC(2,6)*H*), 7.97 (1H, d, *J* 15.5, C(4)*H*); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ_C: 55.6 (O*C*H_3), 96.8 (*C*(1)), 113.2 (*C*(3)), 114.7 (Ar*C*(3,5)), 126.7 (Ar*C*(1)), 131.1 (Ar*C*(2,6)), 149.7 (*C*(4)), 162.8 (Ar*C*(4)), 180.3 (*C*(2)); HRMS (APCI$^+$) $C_{11}H_{10}{}^{35}Cl_3O_2$ $[M+H]^+$, found 278.9747, requires 278.9741 (+2.2 ppm).

(*E*)-1,1,1-Trichloro-4-(2-nitrophenyl)but-3-en-2-one 43. Following general procedure B, oxalyl chloride (2.85 mL, 33.6 mmol) in CH_2Cl_2 (150 mL), DMSO (4.78 mL, 67.2 mmol) in CH_2Cl_2 (20 mL), (*E*)-1,1,1-trichloro-4-(2-nitrophenyl)but-3-en-2-ol **38** (2.49 g, 8.40 mmol) in CH_2Cl_2 (100 mL) and Et_3N (23.4 mL, 168 mmol) gave, after column chromatography (75:25 Petrol:Et_2O, R_f = 0.30), the title compound **43** (2.13 g, 86%) as a white solid; mp 56-58 °C; ν_{max} (ATR) 3103, 2857 (C-H), 1715 (C=O), 1605, 1570, 1520; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.24 (1H, d, *J* 15.5, C(3)*H*), 7.60−7.66 (1H, m, ArC*H*), 7.70−7.75 (2H, m, ArC*H*), 8.10−8.12 (1H, m, ArC(3)*H*), 8.43 (1H, d, *J* 15.5, C(4)*H*); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ_C: 96.1 (*C*(1)), 120.7 (*C*(3)), 125.3 (Ar*C*(3)), 129.5 (Ar*C*), 130.1 (Ar*C*(1)), 131.5 (Ar*C*), 133.9 (Ar*C*), 144.9 (*C*(4)), 148.6 (Ar*C*(2)), 179.1 (*C*(2)); HRMS (APCI$^+$) $C_{10}H_7{}^{35}Cl_3NO_3$ $[M+H]^+$, found 293.9491, requires 293.9486 (+1.7 ppm).

(*E*)-1,1,1-Trichloro-4-(4-fluorophenyl)but-3-en-2-one 44. Following general procedure B, oxalyl chloride (3.17 mL, 37.4 mmol) in CH_2Cl_2 (150 mL), DMSO (5.32 mL, 74.7 mmol) in CH_2Cl_2 (20 mL), (*E*)-1,1,1-trichloro-4-(4-fluorophenyl)but-3-en-2-ol **39** (2.52 g, 9.34 mmol) in CH_2Cl_2 (10 mL) and Et_3N (26.1 mL, 187 mmol) gave, after column chromatography (95:5 Petrol:Et_2O, R_f = 0.25), the title compound **44** (2.38 g, 95%) as a white solid with spectroscopic data in accordance with the literature.[19a] mp 59−61 °C; {Lit.[19a] mp 58−60 °C}; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 7.10−7.18 (2H, m, ArC(3,5)*H*), 7.26 (1H, d, *J* 15.6, C(3)*H*), 7.62−7.70 (2H, m, ArC(2,6)*H*), 7.97 (1H, d, *J* 15.6, C(4)*H*); ^{19}F{^{1}H} NMR (471 MHz, $CDCl_3$) δ_F: −106.65 (ArC(4)*F*).

(*E*)-1,1,1-Trichloro-4-(furan-2-yl)but-3-en-2-one 45. Following general procedure B, oxalyl chloride (5.62 mL, 66.3 mmol) in CH_2Cl_2 (300 mL), DMSO (9.43 mL, 133 mmol) in CH_2Cl_2 (30 mL), (*E*)-1,1,1-trichloro-4-(furan-2-yl)but-3-en-2-ol **40** (4.00 g, 16.6 mmol) in CH_2Cl_2 (20 mL) and Et_3N (46.3 mL, 331 mmol) gave, after column chromatography (90:10 Petrol:Et_2O, R_f = 0.35), the title compound **45** (1.00 g, 25%) as a light yellow solid with spectroscopic data in accordance with the literature.[19b] mp 40−42 °C;

{Lit.[19b] mp 42−44 °C}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 6.56 (1H, dd, *J* 3.5, 1.8, ArC(4)*H*), 6.84 (1H, d, *J* 3.6, ArC(3)*H*), 7.21 (1H, d, *J* 15.3, C(3)*H*), 7.57−7.60 (1H, m, ArC(5)*H*), 7.73 (1H, d, *J* 15.3, C(4)*H*).

(*E*)-1,1,1-Trichloronon-3-en-2-one 46. Following general procedure B, oxalyl chloride (6.51 mL, 76.7 mmol) in CH_2Cl_2 (300 mL), DMSO (10.9 mL, 154 mmol) in CH_2Cl_2 (30 mL), (*E*)-1,1,1-trichloronon-3-en-2-ol **41** (4.71 g, 19.2 mmol) in CH_2Cl_2 (200 mL) and Et_3N (53.7 mL, 384 mmol) gave, after column chromatography (97:3 Petrol:Et_2O, R_f = 0.35), the title compound **46** (4.11 g, 88%) as a yellow oil; ν_{max} (ATR) 2928 (C-H), 1722 (C=O), 1625 (C=C); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 0.87−0.93 (3H, m, CH_3), 1.28−1.38 (4H, m, 2 CH_2), 1.48−1.56 (2H, m, C(6)H_2), 2.34 (2H, app qd, *J* 7.2, 1.6, C(5)H_2), 6.73 (1H, dt, *J* 15.3, 1.6, C(3)*H*), 7.34 (1H, dt, *J* 15.4, 7.0, C(4)*H*); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ_C: 14.1 (*C*H_3), 22.5 (*C*H_2), 27.6 (C(6)H_2), 31.5 (CH_2), 33.2 (C(5)H_2), 96.5 (*C*(1)), 119.7 (*C*(3)), 156.0 (*C*(4)), 179.8 (*C*(2)); HRMS (APCI$^+$) $C_9H_{14}{}^{35}Cl_3O$ $[M+H]^+$, found 243.0104, requires 243.0105 (−0.3 ppm).

Preparation of products

(3*R*,4*R*)-3,4-Diphenyl-6-(trichloromethyl)-3,4-dihydro-2*H*-pyran-2-one 8. Phenyl acetic acid (164 mg, 1.2 mmol), *i*-Pr_2NEt (312 µL, 1.8 mmol), pivaloyl chloride (222 µL, 1.8 mmol), in CH_2Cl_2 (8 mL), followed by HBTM-2.1 (2*S*,3*R*)-**5** (12 mg, 0.04 mmol), (*E*)-1,1,1-trichloro-4-phenylbut-3-en-2-one **7** (200 mg, 0.8 mmol), *i*-Pr_2NEt (208 µL, 1.2 mmol) gave crude product (87:13 dr *anti*:*syn*). Column chromatography (92.5:7.5 Petrol:EtOAc, R_f = 0.25) gave title compound **8** (244 mg, 82%) as a white solid (87:13 dr *anti*:*syn*) mp 86−88 °C; ν_{max} (ATR) 1003, 1119, 1454, 1773, 2031, 3063; $[\alpha]_D^{20}$ −0.986 (*c* 0.5 $CHCl_3$); *Data for major anti diastereoisomer:* ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 3.97−4.01 (1H, m, C(4)*H*), 4.05−4.07 (1H, m, C(3)*H*), 6.37 (1H, d, *J* 4.1, C(5)*H*), 7.09 (2H, d, *J* 6.7, Ar*H*), 7.16 (2H, d, *J* 6.4, Ar*H*), 7.27−7.35 (6H, m, Ar*H*); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ_C 45.2 (*C*(3)H), 52.6 (*C*(4)H), 90.1 (*C*Cl_3), 107.8 (*C*(5)H), 127.5 (Ar*C*H), 128.1 (Ar*C*H), 128.2 (Ar*C*H), 128.3 (Ar*C*H), 129.0 (Ar*C*H), 129.3 (Ar*C*H), 135.4 (Ar*C*), 139.4 (Ar*C*), 149.0 (Ar*C*), 166.4 (*C*(2)); *Data for minor syn diastereoisomer;* ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 3.73 (1H, br s, C(4)*H*), 4.28 (1H, d, *J* 7.0, C(3)*H*), 6.54 (1H, d, *J* 6.0, C(5)*H*), 6.76 (2H, d, *J* 6.8, Ar*H*), 6.81 (2H, d, *J* 6.9, Ar*H*), 7.27−7.35 (6H, m, Ar*H*); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ_C 44.6 (*C*(3)H), 50.9 (*C*(4)H), 91.2 (*C*Cl_3), 108.6 (*C*(5)H), 127.2 (Ar*C*H), 128.0 (Ar*C*H), 128.4 (Ar*C*H), 128.7 (Ar*C*H), 128.9 (Ar*C*H), 128.9 (Ar*C*), 129.6 (Ar*C*), 129.8 (Ar*C*H), 149.7 (Ar*C*), 166.1 (*C*(2)); HRMS (NSI$^+$) $C_{18}H_{13}{}^{35}Cl_3O_2Na$ $[M+Na]^+$, found 388.9880, requires 388.9873 (+1.7 ppm).

HPLC or GC analysis not achieved in our hands, ee determined through derivatisation into diester **10**.

6-(Dichloromethyl)-3,4-diphenyl-2*H*-pyran-2-one 9. MeOH (9 µL) in CH_2Cl_2 (2.4 mL) was added to a solution of lactone **8** (81 mg, 0.22 mmol) and DMAP (5 mg, 0.04 mmol) in CH_2Cl_2 (2 mL) at rt and the reaction stirred for 6 h. Column chromatography (85:15 Petrol: EtOAc, R_f = 0.25) gave the title compound **9** (47 mg, 65%) as a white solid; mp 196−197 °C; ν_{max} (ATR) 1348, 1647, 1709, 3001, 3030, 3090; ^{1}H NMR (500 MHz) δ_H: 6.40 (1H, s, C*H*Cl_2), 6.73 (1H, s, C(5)*H*), 7.10−7.12 (2H, m, Ar*H*), 7.16 (2H, m, Ar*H*), 7.23−7.30 (6H, m, Ar*H*); ^{13}C{^{1}H} NMR (125 MHz) δ_C: 65.2 (*C*HCl_2), 107.2 (*C*(5)H), 126.2 (*C*(3)), 128.3 (Ar*C*H), 128.4 (Ar*C*H), 128.7 (Ar*C*H), 128.8 (Ar*C*H), 129.3 (Ar*C*H), 130.8 (Ar*C*H), 133.1 (Ar*C*(4)), 136.8 (C(3)Ar*C*(1)), 151.2 (C(4)Ar*C*(1)), 155.2 (*C*(2)), 161.2 (*C*(6)); HRMS (NSI$^+$) $C_{18}H_{13}{}^{35}Cl_2O_2$ $[M+H]^+$, found 331.0296, requires 331.0287 (+2.7 ppm).

Dimethyl (2*R*,3*R*)-2,3-diphenylpentanedioate 10. *Method A:* MeOH (6 mL) was added to a solution of lactone **8** (140 mg, 0.38 mmol) and DMAP (9 mg, 0.076 mmol) in CH_2Cl_2 (6 mL) and reaction stirred at rt for 16 h. Concentration of reaction under reduced pressure gave crude product (87:13 dr *anti*:*syn*). Column chromatography (80:20 Petrol:Et_2O, R_f = 0.25) gave the title compound **9** (74 mg, 62%) as a white solid (>98:2 dr *anti*:*syn*). All data in accordance to that provided for method B below.

Method B: Following general procedure C, phenylacetic acid (81.6 mg, 0.60 mmol), *i*-Pr_2NEt (156 µL, 0.90 mmol), pivaloyl chloride (111 µL, 0.90 mmol) in CH_2Cl_2 (4 mL), HBTM-2.1 (2*S*,3*R*)-**5** (6.16 mg, 0.02 mmol, 5 mol%), (*E*)-1,1,1-trichloro-4-phenylbut-3-en-2-one **7** (99.8 mg, 0.40 mmol), *i*-Pr_2NEt (104 µL, 0.60 mmol), MeOH (4 mL) and DMAP (9.76 mg, 0.08 mmol) gave the crude product (89:11 dr *anti*:*syn*). Column chromatography (80:20 Petrol:Et_2O, R_f = 0.25) gave the title compound **10** (97.0 mg, 78%) as a white solid (>98:2 dr *anti*:*syn*) with spectroscopic data in accordance with the literature.[13] mp 68−70 °C; {Lit.[13] mp 62−63 °C}; $[\alpha]_D^{20}$ −116.6 (*c* 1.0 $CHCl_3$); {Lit.[13] $[\alpha]_D^{20}$ −125.7 (*c* 0.3 $CHCl_3$) for 97% ee (2*R*,3*R*) stereoisomer}; Chiral HPLC analysis, Chiralpak AD-H (95:5 hexane:IPA, flow rate 1 mLmin^{-1}, 211 nm, 30 °C) t_R(2*S*,3*S*): 10.2 min, t_R(2*R*,3*R*): 11.7 min, >99% ee; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 2.78−2.86 (2H, m, C(4)H*H* and C(4)*H*H), 3.51 (3H, s, C(5)O_2C*H*$_3$), 3.69 (3H, s, C(1)O_2C*H*$_3$), 3.84−3.90 (2H, m, C(2)*H* and C(3)*H*), 7.00−7.02 (2H, m, ArC*H*), 7.03−7.06 (1H, m, ArC*H*), 7.08−7.14 (7H, m, ArC*H*).

(2*R*,3*R*)-*N*^{1},*N*^{5}-Diisopropyl-2,3-diphenylpentanediamide 11. Following general procedure C, phenylacetic acid (81.6 mg, 0.60 mmol), *i*-Pr_2NEt (156 µL, 0.90 mmol), pivaloyl chloride (111 µL, 0.90 mmol) in CH_2Cl_2 (4 mL), HBTM-2.1 (2*S*,3*R*)-**5** (6.16 mg, 0.02 mmol, 5 mol%), (*E*)-1,1,1-trichloro-4-phenylbut-3-en-2-one **7** (99.8 mg, 0.40 mmol), *i*-Pr_2NEt (104 µL, 0.60 mmol), isopropylamine (4 mL) and DMAP (9.76 mg, 0.08 mmol) gave the crude product (90:10 dr *anti*:*syn*). Column chromatography (EtOAc, R_f = 0.35) gave the title compound **11** (100 mg, 67%) as a white solid (>98:2 dr *anti*:*syn*) with spectroscopic data in accordance with the literature.[13] mp 250−252 °C; {Lit.[13] mp 264−266 °C}; $[\alpha]_D^{20}$ −26.0 (*c* 0.1 $CHCl_3$); {Lit.[13] $[\alpha]_D^{20}$ −20.0 (*c* 0.1 $CHCl_3$) for 99% ee (2*R*,3*R*) stereoisomer}; Chiral HPLC analysis, Chiralpak AD-H (95:5 hexane:IPA, flow rate 1 mLmin^{-1}, 211 nm, 30 °C) t_R(2*S*,3*S*): 7.1 min, t_R(2*R*,3*R*): 23.5 min, >99% ee; ^{1}H NMR (400 MHz, CD_3OD) δ_H: 0.72 (3H, d, *J* 6.6, CH_3), 0.94 (3H, d, *J* 6.6, CH_3), 1.03 (3H, d, *J* 6.6, CH_3), 1.18 (3H, d, *J* 6.6, CH_3), 2.50 (1H, dd, *J* 13.3, 11.3, C(4)H*H*), 2.64 (1H, dd, *J* 13.3, 4.1, C(4)*H*H), 3.64−3.73 (2H, m, C(2)*H* and C*H*$(CH_3)_2$), 3.83 (1H, td, *J* 11.3, 4.1, C(3)*H*), 3.95 (1H, heptet, *J* 6.5, C*H*$(CH_3)_2$), 6.97−7.10 (8H, m, ArC*H*), 7.21−7.24 (2H, m, ArC*H*).

Allyl (2*R*,3*R*)-6,6,6-trichloro-5-oxo-2,3-diphenylhexanoate 12. Following general procedure C, phenylacetic acid (81.6 mg, 0.60 mmol), *i*-Pr_2NEt (156 µL, 0.90 mmol), pivaloyl chloride (111 µL, 0.90 mmol) in CH_2Cl_2 (4 mL), HBTM-2.1 (2*S*,3*R*)-**5** (6.16 mg, 0.02

mmol, 5 mol%), (*E*)-1,1,1-trichloro-4-phenylbut-3-en-2-one **7** (99.8 mg, 0.40 mmol), *i*-Pr_2NEt (104 µL, 0.60 mmol), allyl alcohol (4 mL) and DMAP (9.76 mg, 0.08 mmol) gave the crude product (89:11 dr *anti*:*syn*). Column chromatography (95:5 Petrol:Et_2O, R_f = 0.25) gave the title compound **12** (102 mg, 60%) as a white solid (>98:2 dr *anti*:*syn*). mp 90−92 °C; $[\alpha]_D^{20}$ −50.8 (*c* 0.25 CH_2Cl_2); Chiral HPLC analysis, Chiralpak AD-H (95:5 hexane:IPA, flow rate 1 $mLmin^{-1}$, 211 nm, 30 °C) t_R(2*S*,3*S*): 8.1 min, t_R(2*R*,3*R*): 9.5 min, 99% ee; ν_{max} (ATR) 3030, 2945 (C-H), 1746 (C=O), 1726 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 3.35 (1H, dd, *J* 17.7, 3.1, C(4)H*H*), 3.67 (1H, dd, *J* 17.7, 10.2, C(4)*H*H), 3.96 (1H, d, *J* 10.9, C(2)*H*), 4.02 (1H, td, *J* 10.5, 3.1, C(3)*H*), 4.56−4.67 (2H, m, CO_2CHH and CO_2CHH), 5.18−5.23 (2H, m, =C*H*H and =CH*H*), 5.85 (1H, app ddt, *J* 17.1, 10.5, 5.7, =C*H*), 7.03-7.16 (10H, m, Ar*H*); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ_C: 38.8 (*C*(4)), 45.0 (*C*(3)), 57.1 (*C*(2)), 65.8 (CO_2CH_2), 118.8 (CH=CH_2), 127.1 (Ar*C*), 127.6 (Ar*C*), 128.3 (Ar*C*), 128.5 (Ar*C*), 128.5 (Ar*C*), 128.6 (Ar*C*), 131.8 (*C*H=CH_2), 136.4 (Ar*C*), 139.3 (Ar*C*), 172.6 (*C*(1)), 188.1 (*C*(5)); HRMS (NSI^+) $C_{21}H_{20}{}^{35}Cl_3O_3$ $[M+H]^+$, found 425.0474, requires 425.0473 (+0.3 ppm).

Methyl (3*R*,4*R*)-5-(isopropylamino)-5-oxo-3,4-diphenylpentanoate 13. Phenylacetic acid (81.7 mg, 0.60 mmol) was dissolved in CH_2Cl_2 (4 mL) before *i*-Pr_2NEt (156 µL, 0.90 mmol) and pivaloyl chloride (111 µL, 0.90 mmol) were added. After stirring at rt for 5 min the solution was cooled to −78 °C and HBTM-2.1 (2*S*,3*R*)-**5** (6.16 mg, 0.02 mmol, 5 mol%), (*E*)-1,1,1-trichloro-4-phenylbut-3-en-2-one **7** (99.8 mg, 0.40 mmol), *i*-Pr_2NEt (104 µL, 0.60 mmol) were added in succession. The reaction mixture was stirred at −78 °C for 16 h before *i*-$PrNH_2$ (111 µL, 1.30 mmol) was added and the mixture warmed to rt. Upon consumption of the intermediate dihydropyranone by TLC analysis, MeOH (4 mL) and DMAP (9.8 mg, 0.08 mmol) were added and the reaction stirred overnight at rt. The solution was diluted with CH_2Cl_2 and washed with 1M HCl (2 × 20 mL) and brine (2 × 20 mL) before being dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (hexane to 60:40 hexane:EtOAc, R_f = 0.21). The resulting solid was further purified by recrystallisation from Et_2O and hexane to give the title compound **13** (57 mg, 42%) as a white solid (>98:2 dr *anti*:*syn*). mp 110−112 °C; $[\alpha]_D^{20}$ −84.3 (*c* 0.4 $CHCl_3$); Chiral HPLC analysis, Chiralpak AD-H (95:5 hexane:IPA, flow rate 1 $mLmin^{-1}$, 211 nm, 30 °C) t_R(2*S*,3*S*): 23.6 min, t_R(3*R*,4*R*): 26.7 min, 99% ee; ν_{max} (ATR) 3378, 3308, 2974, 1740, 1722, 1659, 1636, 1533, 1452, 1369; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 1.02 (3H, d, *J* 6.54, NCH(CH_3)$_2$), 1.12 (3H, d, *J* 6.54, NCH(CH_3)$_2$), 2.80 (1H, dd, *J* 15.4, 9.3, C(2)*H*H), 2.92 (1H, dd, *J* 15.4, 4.5, C(2)H*H*), 3.50 (3H, s, OCH_3), 3.58 (1H, d, *J* 10.3, C(4)*H*), 3.89 (1H, ddd, *J* 10.3, 9.8, 4.5, C(3)*H*), 4.00−4.11 (1H, m, NC*H*(CH_3)$_2$), 5.42 (1H, br d, *J* 7.6, N*H*), 7.00−7.16 (10H, m, ArC*H*); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ_C: 22.6 (NCH(CH_3)$_2$), 22.9 (NCH(CH_3)$_2$), 38.9 (*C*(2)H_2), 41.7 (*C*(3)H), 45.5 (NCH), 51.6 (OCH_3), 58.4 (*C*(4)H), 126.7 (ArC*H*), 127.1 (ArC*H*), 128.2 (ArC*H*), 128.3 (ArC*H*), 128.4 (ArC*H*), 128.5 (ArC*H*), 138.0 (Ar*C*), 140.9 (Ar*C*), 171.3 (*C*(5)), 172.6 (C(1)); HRMS (NSI^+) $C_{21}H_{26}NO_3$ $[M+H]^+$, found 340.1909, requires 340.1907 (+0.5 ppm).

Dimethyl (2*R*,3*R*)-2-(4-methoxyphenyl)-3-phenylpentanedioate 14. Following general procedure C, 4-methoxyphenylacetic acid (99.7 mg, 0.60 mmol), *i*-Pr_2NEt (156 µL, 0.90 mmol), pivaloyl chloride (111 µL, 0.90 mmol) in CH_2Cl_2 (4 mL), HBTM-2.1 (2*S*,3*R*)-**5** (6.16 mg, 0.02 mmol, 5 mol%), (*E*)-1,1,1-trichloro-4-phenylbut-3-en-2-one **7** (99.8 mg, 0.40 mmol), *i*-Pr_2NEt (104 µL, 0.60 mmol), MeOH (4 mL) and DMAP (9.76 mg, 0.08 mmol) gave the crude product (92:8 dr *anti*:*syn*). Column chromatography (75:25 Petrol:Et_2O, R_f = 0.25) gave the title compound **14** (105 mg, 77%) as a white solid (>98:2 dr *anti*:*syn*) with spectroscopic data in accordance with the literature.[13] mp 96−98 °C; {Lit.[13] mp 99−101 °C}; $[\alpha]_D^{20}$ −126.8 (*c* 0.5 $CHCl_3$); {Lit.[13] $[\alpha]_D^{20}$ −135.1 (*c* 0.2 $CHCl_3$) for >99% ee (2*R*,3*R*) stereoisomer}; Chiral HPLC analysis, Chiralpak AD-H (95:5 hexane:IPA, flow rate 1 $mLmin^{-1}$, 211 nm, 30 °C) t_R(2*S*,3*S*): 16.7 min, t_R(2*R*,3*R*): 22.9 min, >99% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 2.73−2.82 (2H, m, C(4)H*H* and C(4)*H*H), 3.51 (3H, s, C(5)O_2CH_3), 3.69 (3H, s, CH_3), 3.70 (3H, s, CH_3), 3.78−3.83 (2H, m, C(2)*H* and C(3)*H*), 6.64−6.68 (2H, m, C(2)ArC(3,5)*H*), 6.99−7.14 (7H, m, ArC*H*).

Dimethyl (2*R*,3*R*)-3-phenyl-2-(4-(trifluoromethyl)phenyl)-pentanedioate 15. Following general procedure C, 2-(4-(trifluoromethyl)phenyl)acetic acid (122.5 mg, 0.60 mmol), *i*-Pr_2NEt (156 µL, 0.90 mmol), pivaloyl chloride (111 µL, 0.90 mmol) in CH_2Cl_2 (4 mL), HBTM-2.1 (2*S*,3*R*)-**5** (6.16 mg, 0.02 mmol, 5 mol%), (*E*)-1,1,1-trichloro-4-phenylbut-3-en-2-one **7** (99.8 mg, 0.40 mmol), *i*-Pr_2NEt (104 µL, 0.60 mmol), MeOH (4 mL) and DMAP (9.76 mg, 0.08 mmol) gave the crude product (85:15 dr *anti*:*syn*). Column chromatography (90:10 Hexane:EtOAc, R_f = 0.15) gave the title compound **15** (99.0 mg, 65%) as a white solid (>98:2 dr *anti*:*syn*). mp 96−98 °C; $[\alpha]_D^{20}$ −84.8 (*c* 0.8 $CHCl_3$); Chiral HPLC analysis, Chiralpak AD-H (95:5 hexane:IPA, flow rate 1 $mLmin^{-1}$, 211 nm, 30 °C) t_R(2*S*,3*S*): 11.4 min, t_R(2*R*,3*R*): 12.9 min, 91% ee; ν_{max} (ATR) 2954, 1732, 1439, 1325, 1246, 1111; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 2.79−2.82 (2H, m, C(4)H*H* and C(4)*H*H), 3.52 (3H, s, C(5)O_2CH_3), 3.71 (3H, s, C(1)O_2CH_3), 3.83−3.95 (2H, m, C(2)*H* and C(3)*H*), 6.97−7.00 (2H, m, C(3)ArC(2,6)*H*), 7.03−7.15 (3H, m, C(3)ArC(3,4,5)*H*), 7.25 (2H, d, *J* 8.2, C(2)ArC(2,6)*H*), 7.39 (2H, d, *J* 8.2, C(2)ArC(3,5)*H*); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ_C: 39.4 (*C*(4)), 45.5 (*C*(3)), 51.8 (C(5)O_2CH_3), 52.5 (C(1)O_2CH_3), 57.0 (*C*(2)), 124.1 (q, $^1J_{CF}$ 271.9, *C*F_3), 125.3 (q, $^3J_{CF}$ 3.7, C(2)Ar*C*(3,5)) 127.1 (ArC), 128.1 (ArC), 128.5 (ArC), 129.1 (ArC), 129.6 (q, $^2J_{CF}$ 32.4, C(2)Ar*C*(4)), 139.7 (C(2)Ar*C*(1)), 140.7 (C(3)Ar*C*(1)), 171.8 (*C*(5)), 172.8 (*C*(1)); $^{19}F\{^1H\}$ NMR (470 MHz, $CDCl_3$) δ_F: −62.6; HRMS (NSI^+) $C_{20}H_{20}O_4F_3$ $[M+H]^+$, found 381.1309, requires 381.1308 (+0.2 ppm).

Dimethyl (2*R*,3*R*)-2-(4-fluorophenyl)-3-phenylpentanedioate 16. Following general procedure C, 2-(4-fluorophenyl)acetic acid (92.5 mg, 0.60 mmol), *i*-Pr_2NEt (156 µL, 0.90 mmol), pivaloyl chloride (111 µL, 0.90 mmol) in CH_2Cl_2 (4 mL), HBTM-2.1 (2*S*,3*R*)-**5** (6.16 mg, 0.02 mmol, 5 mol%), (*E*)-1,1,1-trichloro-4-phenylbut-3-en-2-one **7** (99.8 mg, 0.40 mmol), *i*-Pr_2NEt (104 µL, 0.60 mmol), MeOH (4 mL) and DMAP (9.76 mg, 0.08 mmol) gave the crude product (90:10 dr *anti*:*syn*). Column chromatography (80:20 Hexane:EtOAc, R_f = 0.27) gave the title compound **16** (91.0 mg, 69%) as a white solid (>98:2 dr *anti*:*syn*) with spectroscopic data in accordance with the literature.[13] mp 84−85 °C; {Lit.[13] mp 86−88 °C}; $[\alpha]_D^{20}$ −114.3 (*c* 0.7 $CHCl_3$); {Lit.[13] $[\alpha]_D^{20}$ −119.5 (*c* 0.2 $CHCl_3$) for 98% ee (2*R*,3*R*) stereoisomer}; Chiral HPLC analysis,

Chiralpak AD-H (95:5 hexane:IPA, flow rate 1 mLmin^{-1}, 211 nm, 30 °C) t_R(2*S*,3*S*): 11.7 min, t_R(2*R*,3*R*): 13.5 min, 99% ee; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 2.74−2.83 (2H, m, C(4)H*H* and C(4)*H*H), 3.51 (3H, s, C(5)O_2CH_3), 3.70 (3H, s, C(1)O_2CH_3), 3.80−3.86 (2H, m, C(2)*H* and C(3)*H*), 6.77−6.85 (2H, m, ArC*H*), 6.95−6.99 (2H, m, ArC*H*), 7.03−7.15 (5H, m, ArC*H*); ^{19}F{^{1}H} NMR (282 MHz, $CDCl_3$) δ_F: −115.6.

Dimethyl (2*R*,3*R*)-3-phenyl-2-(3-tolyl)pentanedioate 17. Following general procedure C, *m*-tolylacetic acid (90 mg, 0.6 mmol), *i*-Pr_2NEt (156 µL, 0.90 mmol, pivalolyl chloride (111 µL 0.90 mmol), in CH_2Cl_2 (4 mL), HBTM-2.1 (2*S*,3*R*)-**5** (6.16 mg, 0.02 mmol), (*E*)-1,1,1-trichloro-4-phenylbut-3-en-2-one **7** (99.8 mg, 0.40 mmol), *i*-Pr_2NEt (104 µL, 0.60 mmol) and MeOH (5 mL) gave the crude product (92:8 dr *anti:syn*). Column chromatography (90:10 Petrol: EtOAc, R_f = 0.22) gave the title compound **17** (79 mg, 60%) as a white solid (>98:2 dr *anti:syn*) with spectroscopic data in accordance with the literature.[13] Mp 72−74 °C {Lit.[13] 73−75 °C}; $[\alpha]_D^{20}$ −135.0 (*c* 0.1 $CHCl_3$); {Lit.[13] $[\alpha]_D^{20}$ −127.4 (*c* 0.1 $CHCl_3$) for 99% ee (2*R*, 3*R*) stereoisomer}; Chiral HPLC analysis, Chiralpak AD-H (95:5 hexane:IPA, flow rate 1 mLmin^{-1}, 211 nm, 30 °C) t_R(2*S*, 3*S*): 8.7 min, t_R (2*R*, 3*R*): 10.4 min, 99% ee; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 2.21 (3H, s, ArCH_3), 2.79−2.84 (2H, m, C(4)*H*H and C(4)H*H*), 3.51 (3H, s, C(5)O_2CH_3), 3.68 (3H, s, C(1)O_2CH_3), 3.80−3.88 (2H, m, C(2)*H* and C(3)*H*), 6.90−6.92 (2H, m, Ar*H*), 6.94 (1H, br s, C(2)Ar(2)*H*), 7.00−7.07 (4H, m, Ar*H*), 7.10−7.13 (2H, m, Ar*H*).

Dimethyl (2*R*,3*R*)-3-phenyl-2-(thiophen-3-yl)pentanedioate 19. Following general procedure C, 3-thiophene acetic acid (85 mg, 0.6 mmol), *i*-Pr_2NEt (156 µL, 0.90 mmol, pivalolyl chloride (111 µL 0.90 mmol), in CH_2Cl_2 (4 mL), HBTM-2.1 (2*S*,3*R*)-**5** (6.16 mg, 0.02 mmol), (*E*)-1,1,1-trichloro-4-phenylbut-3-en-2-one **7** (99.8 mg, 0.40 mmol), *i*-Pr_2NEt (104 µL, 0.60 mmol) and MeOH (5 mL) gave the crude product (81:19 dr *anti:syn*). Column chromatography (90:10 Petrol: EtOAc, R_f = 0.25) gave the title compound **19** (81 mg, 64%) as a white solid (>98:2 dr *anti:syn*) with spectroscopic data in accordance with the literature.[13] Mp 61−64 °C {Lit.[13] 60−64 °C}; $[\alpha]_D^{20}$ −72.0 (*c* 0.5 $CHCl_3$); {Lit.[13] $[\alpha]_D^{20}$ −69.0 (*c* 0.5 $CHCl_3$) for 97% ee (2*R*,3*R*) stereoisomer}; Chiral HPLC analysis, Chiralpak AD-H (95:5 hexane:IPA, flow rate 1 mLmin^{-1}, 211 nm, 30 °C) t_R(2*R*,3*R*): 16.9 min, t_R (2*S*,3*S*): 18.3 min, >99% ee; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 2.75−2.83 (2H, m, C(4)*H*H and C(4)H*H*), 3.52 (3H, s, C(5)O_2CH_3), 3.71 (3H, s, C(1)O_2CH_3), 3.77−3.82 (1H, m, C(3)*H*), 4.00 (1H, d, *J* 10.2, C(2)*H*), 6.85 (1H, dd, *J* 1.1, 5.0, C(2)Ar*H*), 6.91 (1H, dd, *J* 1.0, 2.9, C(2)Ar*H*), 7.00−7.02 (2H, m, C(3)Ar*H*), 7.09−7.12 (2H, m, Ar*H*), 7.14−7.17 (2H, m, Ar*H*).

Dimethyl (2*S*,3*R*)-3-phenyl-2-((*E*)-prop-1-en-1-yl)pentanedioate 20. Following general procedure C, 3-pentenoic acid (61 µL, 0.6 mmol), *i*-Pr_2NEt (156 µL, 0.90 mmol, pivalolyl chloride (111 µL 0.90 mmol), in CH_2Cl_2 (4 mL), HBTM-2.1 (2*S*,3*R*)-**5** (6.16 mg, 0.02 mmol), (*E*)-1,1,1-trichloro-4-phenylbut-3-en-2-one **7** (99.8 mg, 0.40 mmol), *i*-Pr_2NEt (104 µL, 0.60 mmol) and MeOH (5 mL) gave the crude product (85:15 dr *anti:syn*). Column chromatography (90:10 Petrol: EtOAc, R_f = 0.25) gave the title compound **20** (86 mg, 78%) as a colourless oil (>98:2 dr *anti:syn*) with spectroscopic data in accordance with the literature.[13] $[\alpha]_D^{20}$ −67.3 (*c* 0.5 $CHCl_3$); {Lit.[13] $[\alpha]_D^{20}$ −69.0 (*c* 0.5 $CHCl_3$) for >99% ee (2*S*,3*R*) stereoisomer}; Chiral HPLC analysis, Chiralpak OD-H (97:3 hexane:IPA, flow rate 1 mLmin^{-1}, 220 nm, 30 °C) t_R(2*R*,3*S*): 9.82 min, t_R (2*S*,3*R*): 15.5 min, >99% ee; ^{1}H NMR (500MHz, $CDCl_3$) δ_H 1.55 (3H, dd, *J* 1.3, 6.3, C(2)C(3')*H*), 2.69 (2H, d, *J* 7.6, C(4)*H*), 3.27 (1H, d, *J* 8.7, C(3)*H*), 3.52−3.62 (4H, m, C(2)*H* and C(5)O_2CH_3), 3.67 (C(1)O_2CH_3), 5.22−5.44 (2H, m, C(2)C(1')*H* and C(2)C(2')*H*), 7.09−7.12 (2H, m, C(3)Ar*H*), 7.18−7.29 (3H, m, C(3)Ar*H*).

Dimethyl (2*S*,3*R*)-3-phenyl-2-((*E*)-3-phenylprop-1-en-1-yl)-pentanedioate 21. Following general procedure C, (*E*)-5-phenylpent-3-enoic acid (106 mg, 0.60 mmol), *i*-Pr_2NEt (156 µL, 0.90 mmol), pivaloyl chloride (111 µL, 0.90 mmol) in CH_2Cl_2 (4 mL), HBTM-2.1 (2*S*,3*R*)-**5** (6.16 mg, 0.02 mmol, 5 mol%), (*E*)-1,1,1-trichloro-4-phenylbut-3-en-2-one **7** (99.8 mg, 0.40 mmol), *i*-Pr_2NEt (104 µL, 0.60 mmol), MeOH (4 mL) and DMAP (9.76 mg, 0.08 mmol) gave the crude product (95:5 dr *anti*:*syn*). Column chromatography (80:20 Petrol:Et_2O, R_f = 0.25) gave the title compound **21** (105 mg, 74%) as a colourless oil (>98:2 dr *anti*:*syn*) with spectroscopic data in accordance with the literature.[13] $[\alpha]_D^{20}$ −6.7 (*c* 1.0 $CHCl_3$); {Lit.[13] $[\alpha]_D^{20}$ −6.9 (*c* 1.0 $CHCl_3$) for >99% ee (2*S*,3*R*) stereoisomer}; Chiral HPLC analysis, Chiralcel OJ-H (99:1 hexane:IPA, flow rate 1 mLmin^{-1}, 211 nm, 40 °C) t_R(2*S*,3*R*): 44.0 min, t_R(2*R*,3*S*): 48.4 min, 99% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 2.69 (2H, app. d, *J* 7.5, C(4)H*H* and C(4)*H*H), 3.20 (2H, app. d, *J* 6.3, C(2)C(3')*H*H and C(2)C(3')H*H*), 3.33 (1H, t, *J* 9.3, C(2)*H*), 3.53 (3H, s, C(5)O_2CH_3), 3.57−3.63 (1H, m, C(3)*H*), 3.71 (3H, s, C(1)O_2CH_3), 5.34 (1H, ddt, *J* 15.3, 9.3, 1.3, C(2)C(1')*H*), 5.42−5.53 (1H, m, C(2)C(2')*H*), 6.75−6.79 (2H, m, ArC*H*), 7.11−7.32 (8H, m, ArC*H*).

Dimethyl (2*R*,3*R*)-3-(4-methoxyphenyl)-2-phenylpentane-dioate 23. Following general procedure C, phenylacetic acid (81.75 mg, 0.60 mmol), *i*-Pr_2NEt (156 µL, 0.90 mmol), pivaloyl chloride (111 µL, 0.90 mmol) in CH_2Cl_2 (4 mL), HBTM-2.1 (2*S*,3*R*)-**5** (6.16 mg, 0.02 mmol, 5 mol%), (E)-1,1,1-trichloro-4-(4-methoxyphenyl)but-3-en-2-one **42** (112 mg, 0.40 mmol), *i*-Pr_2NEt (104 µL, 0.60 mmol), MeOH (4 mL) and DMAP (9.76 mg, 0.08 mmol) gave the crude product (90:10 dr *anti*:*syn*). Column chromatography (80:20 Hexane:EtOAc, R_f = 0.29) gave the title compound **23** (99.0 mg, 73%) as a thick colourless oil (96:4 dr *anti*:*syn*) with spectroscopic data in accordance with the literature.[13] $[\alpha]_D^{20}$ −98.5 (*c* 0.5 $CHCl_3$); {Lit.[13] $[\alpha]_D^{20}$ −105.7 (*c* 0.2 $CHCl_3$) for 99% ee (2*R*,3*R*) stereoisomer}; Chiral HPLC analysis, Chiralpak AD-H (95:5 hexane:IPA, flow rate 1 mLmin^{-1}, 211 nm, 30 °C) t_R(2*S*,3*S*): 18.7 min, t_R(2*R*,3*R*): 20.1 min, >99% ee; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 2.70−2.84 (2H, m, C(4)H*H* and C(4)*H*H), 3.51 (3H, s, C(5)O_2CH_3), 3.68 (6H, s, C(1)O_2CH_3 and C(3)ArOCH_3), 3.77−3.84 (2H, m, C(2)*H* and C(3)*H*), 6.64 (2H, d, *J* 8.7, C(3)ArC(3,5)*H*), 6.91 (2H, d, *J* 8.7, C(3)ArC(2,6)*H*), 7.10−7.15 (5H, m, C(2)ArC*H*).

Dimethyl (2*R*,3*R*)-3-(2-nitrophenyl)-2-phenylpentanedioate 24. Following general procedure C, phenylacetic acid (81.6 mg, 0.60 mmol), *i*-Pr_2NEt (156 µL, 0.90 mmol), pivaloyl chloride (111 µL, 0.90 mmol) in CH_2Cl_2 (4 mL), HBTM-2.1 (2*S*,3*R*)-**5** (6.16 mg, 0.02 mmol, 5 mol%), (*E*)-1,1,1-trichloro-4-(2-nitrophenyl)but-3-en-2-one **43** (118 mg, 0.40 mmol), *i*-Pr_2NEt (104 µL, 0.60 mmol), MeOH (4 mL) and DMAP (9.76 mg, 0.08 mmol) gave the crude product (95:5 dr *anti*:*syn*). Column chromatography (65:35 Petrol:Et_2O, R_f = 0.25)

gave the title compound **24** (114 mg, 80%) as a light yellow solid (>98:2 dr *anti*:*syn*). mp 76−78 °C; $[\alpha]_D^{20}$ −106.6 (*c* 1.0 $CHCl_3$); Chiral HPLC analysis, Chiralpak AD-H (95:5 hexane:IPA, flow rate 1 mLmin^{-1}, 211 nm, 30 °C) t_R(2*S*,3*S*): 29.0 min, t_R(2*R*,3*R*): 31.1 min, >99% ee; ν_{max} (ATR) 2957 (C-H), 1725 (C=O), 1526 (N-O), 1354 (N-O); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 2.88 (1H, dd, *J* 15.9, 4.4, C(4)H*H*), 2.98 (1H, dd, *J* 15.9, 10.0, C(4)*H*H), 3.52 (3H, s, C(5)O_2CH_3), 3.67 (3H, s, C(1)O_2CH_3), 4.14 (1H, d, *J* 9.5, C(2)*H*), 4.56 (1H, td, *J* 9.7, 4.4, C(3)*H*), 7.13−7.26 (6H, m, ArC*H*), 7.37−7.47 (2H, m, ArC*H*), 7.63 (1H, dd, *J* 8.1, 1.3, C(3)ArC(3)*H*); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ_C: 38.1 (*C*(4)), 39.4 (*C*(3)), 51.9 (C(5)O_2*C*H_3), 52.4 (C(1)O_2*C*H_3), 57.8 (*C*(2)), 124.6 (C(3)Ar*C*(3)H), 127.8 (C(2)Ar*C*(4)H), 128.6 (C(2)Ar*C*(3,5)H and C(3)Ar*C*(4)H), 128.7 (C(2)Ar*C*(2,6)H and C(3)Ar*C*(6)H), 132.5 (C(3)Ar*C*(5)H), 135.2 (C(3)Ar*C*(1)), 136.0 (C(2)Ar*C*(1)), 150.7 (C(3)Ar*C*(2)), 171.5 (*C*(5)), 172.8 (*C*(1)); HRMS (NSI$^+$) $C_{19}H_{20}NO_6$ $[M+H]^+$, found 358.1285, requires 358.1285 (0.0 ppm).

Dimethyl (2*R*,3*R*)-3-(4-fluorophenyl)-2-phenylpentanedioate 25. Following general procedure C, phenylacetic acid (81.6 mg, 0.60 mmol), *i*-Pr_2NEt (156 µL, 0.90 mmol), pivaloyl chloride (111 µL, 0.90 mmol) in CH_2Cl_2 (4 mL), HBTM-2.1 (2*S*,3*R*)-**5** (6.16 mg, 0.02 mmol, 5 mol%), (*E*)-1,1,1-trichloro-4-(4-fluorophenyl)but-3-en-2-one **44** (107 mg, 0.40 mmol), *i*-Pr_2NEt (104 µL, 0.60 mmol), methanol (4 mL) and DMAP (9.76 mg, 0.08 mmol) gave the crude product (87:13 dr *anti*:*syn*). Column chromatography (75:25 Petrol:Et_2O, R_f = 0.25) gave the title compound **25** (92.0 mg, 70%) as a colourless oil (>98:2 dr *anti*:*syn*) with spectroscopic data in accordance with the literature.[13] $[\alpha]_D^{20}$ −119.6 (*c* 0.75 $CHCl_3$); {Lit.[13] $[\alpha]_D^{20}$ −114.3 (*c* 0.1 $CHCl_3$) for 98% ee (2*R*,3*R*) stereoisomer}; Chiral HPLC analysis, Chiralcel OD-H (95:5 hexane:IPA, flow rate 1 mLmin^{-1}, 211 nm, 30 °C) t_R(2*R*,3*R*): 10.2 min, t_R(2*S*,3*S*): 11.1 min, 99% ee; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 2.75 (1H, dd, *J* 15.4, 10.0, C(4)H*H*), 2.82 (1H, dd, *J* 15.4, 4.4, C(4)*H*H), 3.52 (3H, s, C(5)O_2CH_3), 3.69 (3H, s, C(1)O_2CH_3), 3.79 (1H, d, *J* 10.9, C(2)*H*), 3.86 (1H, app. td, *J* 10.4, 4.4, C(3)*H*), 6.77−6.82 (2H, m, C(3)ArC(3,5)*H*), 6.94−6.97 (2H, m, C(3)ArC(2,6)*H*), 7.08−7.17 (5H, m, ArC*H*); ^{19}F{^{1}H} NMR (470 MHz, $CDCl_3$) δ_F: −115.92 (C(3)ArC(4)*F*).

Dimethyl (2*R*,3*R*)-3-(furan-2-yl)-2-phenylpentanedioate 26.

Following general procedure C, phenylacetic acid (81.7 mg, 0.60 mmol), *i*-Pr_2NEt (156 µL, 0.90 mmol), pivaloyl chloride (111 µL, 0.90 mmol) in CH_2Cl_2 (4 mL), HBTM-2.1 (2*S*,3*R*)-**5** (6.16 mg, 0.02 mmol, 5 mol%), (E)-1,1,1-trichloro-4-(furan-2-yl)but-3-en-2-one **45** (95.8 mg, 0.40 mmol), *i*-Pr_2NEt (104 µL, 0.60 mmol), MeOH (4 mL) and DMAP (9.76 mg, 0.08 mmol) gave the crude product (80:20 dr *anti*:*syn*). Column chromatography (90:10 Hexane:EtOAc, R_f = 0.14) gave the title compound **26** (97.0 mg, 80%) as a colourless oil (80:20 dr *anti*:*syn*). $[\alpha]_D^{20}$ −75.6 (*c* 0.6 $CHCl_3$); ν_{max} (ATR) 2953, 1730, 1454, 1435, 1350, 1269, 1148; *Data for major anti diastereoisomer:* Chiral HPLC analysis, Chiralpak AD-H (95:5 hexane:IPA, flow rate 1 mLmin^{-1}, 211 nm, 30 °C) t_R(2*S*,3*S*): 10.9 min, t_R(2*R*,3*R*): 12.3 min, 98% ee; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 2.71-2.74 (1H, m, C(4)*H*^{A}H^B), 2.81−2.89 (1H, m, C(4)H^A*H*^{B}), 3.61 (3H, s, C(5)O_2CH_3), 3.69 (3H, s, C(1)O_2CH_3), 3.97−4.02 (2H, m, C(2)*H* and C(3)*H*), 5.81 (1H, dd, *J* 3.3, 0.6, C(3)ArC(3)*H*), 6.06 (1H, dd, *J* 3.3, 1.9, C(3)ArC(4)*H*), 7.15−7.25 (6H, m, C(2)ArC*H* and C(3)ArC(5)*H*); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ_C: 36.9 (*C*(4)), 39.4 (*C*(3)), 51.8 (C(5)O_2CH_3), 52.3 (C(1)O_2CH_3), 55.0 (*C*(2)), 107.5 (C(3)Ar*C*(3)), 110.0 (C(3)Ar*C*(4)), 127.5 (C(2)Ar*C*), 128.3 (C(2)Ar*C*), 128.4 (C(2)Ar*C*), 136.5 (C(2)Ar*C*(1)), 141.4 (C(3)Ar*C*(5)), 153.3 (C(3)Ar*C*(1)), 171.8 (*C*(5)), 173.0 (*C*(1)); *Data for minor syn diastereoisomer:* Chiral HPLC analysis, Chiralpak AD-H (95:5 hexane:IPA, flow rate 1 mLmin^{-1}, 211 nm, 30 °C) t_R(major): 13.8 min, t_R(minor): 16.9 min, 23% ee; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 2.38 (1H, dd, *J* 15.7, 4.4, C(4)*H*^{A}H^B), 2.46 (1H, dd, *J* 15.7, 9.6, C(4)H^A*H*^{B}), 3.50 (3H, s, C(5)O_2CH_3), 3.51 (3H, s, C(1)O_2CH_3), 4.03−4.09 (2H, m, C(2)*H* and C(3)*H*), 6.16 (1H, d, *J* 3.2, C(3)ArC(3)*H*), 6.27 (1H, dd, *J* 3.2, 1.9, C(3)ArC(4)*H*), 7.27−7.42 (6H, m, C(2)ArC*H* and C(3)ArC(5)*H*); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ_C: 36.1 (*C*(4)), 38.7 (*C*(3)), 51.6 (C(5)O_2CH_3), 52.1 (C(1)O_2CH_3), 55.2 (*C*(2)), 106.8 (C(3)Ar*C*(3)), 110.3 (C(3)Ar*C*(4)), 128.1 (C(2)Ar*C*), 128.7 (C(2)Ar*C*), 129.0 (C(2)Ar*C*), 136.0 (C(2)Ar*C*(1)), 141.8 (C(3)Ar*C*(5)), 154.4 (C(3)Ar*C*(1)), 171.9 (*C*(5)), 172.8 (*C*(1)); HRMS (NSI$^+$) $C_{17}H_{19}O_5$ $[M+H]^+$, found 303.1228, requires 303.1227 (+0.3 ppm).

(3*R*,4*R*)-4-Pentyl-3-phenyl-6-(trichloromethyl)-3,4-dihydro-2*H*-pyran-2-one 27. Phenylacetic acid (81.7 mg, 0.60 mmol) was dissolved in CH_2Cl_2 (4 mL) before *i*-Pr_2NEt (156 µL, 0.90 mmol) and pivaloyl chloride (111 µL, 0.90 mmol) were added. After stirring at rt for 5 min the solution was cooled to −78 °C and HBTM-2.1 (2*S*,3*R*)-**5** 6.16 mg, 0.02 mmol, 5 mol%), (*E*)-1,1,1-trichlorononon-3-en-2-one **46** (97 mg, 0.40 mmol), *i*-Pr_2NEt (104 µL, 0.60 mmol) were added in succession. The reaction mixture was stirred at −78 °C for 16 h before being concentrated under reduced pressure and purified by column chromatography (neat hexane to 96:4 hexane:EtOAc, R_f = 0.20) to give the title compound **27** (105 mg, 71%) as a white solid (94:6 dr *anti*:*syn*). mp 42−44 °C; $[\alpha]_D^{20}$ −62.1 (*c* 1.0 $CHCl_3$); Chiral HPLC analysis, Chiralpak AD-H (99:1 hexane:IPA, flow rate 1 mLmin^{-1}, 211 nm, 30 °C) t_R(2*R*,3*R*): 15.9 min, t_R(2*S*,3*S*): 17.7 min, 86% ee; ν_{max} (ATR) 2955, 2928, 2859, 1778, 1497, 1454, 1173, 1155, 1115, 1101; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 0.87 (3H, t, *J* 6.7, CH_3), 1.24−1.50 (8H, m, (CH_2)$_4$), 2.81-2.89 (1H, m, C(4)*H*), 3.68 (1H, d, *J* 8.1, C(3)*H*), 6.20 (1H, d, *J* 4.2, C(5)*H*), 7.19−7.24 (2H, m, ArC(2,6)*H*), 7.29−7.42 (3H, m, ArC(3,4,5)*H*); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ_C: 14.1 (*C*H_3), 22.5 (*C*H_2), 25.8 (*C*H_2), 31.6 (*C*H_2), 32.9 (*C*H_2), 38.1 (*C*(4)H), 49.9 (*C*(3)H), 90.2 (*C*Cl_3), 108.4 (*C*(5)H), 128.2 (Ar*C*(4)H), 128.2 (Ar*C*(2,6)H), 129.1 (Ar*C*(3,5)H), 135.7 (Ar*C*(1)), 148.2 (*C*(6)), 167.4 (*C*(2)); HRMS (NSI$^+$) $C_{17}H_{18}{}^{35}Cl_3O_2$ $[M+H]^+$, found 359.0369, requires 359.0367 (+0.6 ppm).

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Notes and references

[a] EaStCHEM, School of Chemistry, University of St Andrews, North Haugh, St Andrews, KY16 9ST, UK.
[b] GSK, Gunnels Wood Road, Stevenage, Hertfordshire, SG1 2NY, UK.
[c] Syngenta, Jealott's Hill International Research Centre, Bracknell, RG42 6EY, UK.

† Electronic Supplementary Information (ESI) available: ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra of all novel compounds and relevant HPLC traces. See DOI: 10.1039/c000000x/

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23 Optimal conditions were the same as those previously obtained in related processes, see ref 12e.

24 Authentic racemic sample of all products were prepared using (*rac*)-HBTM-2.1 **5** as the catalyst.

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