Enantioselective NHC-Catalyzed Redox [4+2]-hetero-Diels-Alder Reactions using α,β -Unsaturated Trichloromethyl ketones as Amide Equivalents

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α,β -Unsaturated trichloromethyl ketones are suitable α,β -unsaturated amide and ester equivalents in N-heterocyclic carbene (NHC)-catalyzed redox hetero-Diels-Alder reactions with azolium enolates generated from α -aryloxyaldehydes. The initially formed *syn*-dihydropyranone products can be isolated, or can undergo ring-opening with benzylamine followed by aminolysis of the resulting CCl₃ ketone to form a range of diamides with high diastereo- and enantioselectivity (up to >95:5 dr and >99% ee).

Introduction

N-Heterocyclic carbenes (NHCs) are valuable Lewis base organocatalysts that can react through a number of distinct catalytic activation modes.¹ For example, azolium enolates are versatile intermediates that react with a range of electrophiles to form a wide variety of synthetically useful products. Azolium enolates have been accessed through reaction of NHCs with ketenes,² α -reducible aldehydes,³⁻⁷ unfunctionalized aldehydes in the presence of an oxidant,⁸ and activated carboxylic acids or esters in the presence of a base.⁹ NHC-redox catalysis proceeding through addition of an NHC to an aldehyde bearing an α -reducible functional group is a particularly efficient method of forming azolium enolates.¹⁰ α -Reducible aldehydes that have been used for this purpose include α -chloroaldehydes,³ enals,⁴ α -aryloxyaldehydes,⁵ and formyl cyclopropanes⁶ (Scheme 1a).

We have demonstrated that α -aryloxyaldehydes are bench-stable azolium enolate precursors that can be utilized in a number of asymmetric NHC-catalyzed redox [4+2]-cycloaddition reactions.⁷ For example, azolium enolates generated from α -aryloxyaldehydes react with substituted trifluoromethyl ketones to form dihydropyranones with high levels of stereoselectivity (Scheme 1b).^{7d} The NHC-catalyzed redox reaction of α -aryloxyaldehydes and *N*-aryl-*N'*-aryldiazenes to synthesize enantiomerically enriched α -amino acid derivatives has also been explored.^{7c} While NHC-catalyzed asymmetric cycloadditions of azolium enolates with electron-deficient enones are widely reported, the use of α,β -unsaturated amides and esters remains a significant challenge due to the decreased electrophilicity of these substrates. This problem has been overcome in other Lewis based-catalyzed conjugate additions through the use of more reactive α,β -unsaturated amide/ester equivalents such as *N*-acylpyrroles,¹¹ 2-acyl imidazoles,¹² activated imides,¹³ α -ketophosphonates,^{14,15} and trichloromethyl

Scheme 1. Azolium enolate precursors for [4+2] hetero-Diels-Alder reactions

ketones.^{16,17} However, the use of α,β -unsaturated amide and ester equivalents in NHC-catalyzed cycloaddition reactions remains unexplored.

Of particular relevance is the use of trichloromethyl ketones as carboxylic acid, ester and amide equivalents in processes that use the leaving group ability of the CCl₃ ketone in haloform-type reactions.¹⁸⁻²⁰ α,β -Unsaturated trichloromethyl ketones have previously been utilized as Michael acceptors in a small number of organocatalytic reactions.^{16,17} Zhao and co-workers reported the enantioselective epoxidation of α,β -unsaturated trichloromethyl ketones with *tert*-butylhydroperoxide (TBHP) catalyzed by diaryl prolinol **2**.^{16a} Trichloromethyl ketone **3** undergoes either aminolysis or alcoholysis to provide the corresponding amide or ester products without loss in enantioselectivity (Scheme 2a). Various bifunctional H-bonding/Lewis bases have also been used to catalyze the conjugate addition of nucleophiles including α -cyano ketones,^{16b} α,β -unsaturated γ -butyrolactones,^{16c} and azlactones^{16d} into α,β -unsaturated trichloromethyl ketones. We have reported the

Scheme 2. Use of α,β -unsaturated trichloromethyl ketones as amide and ester equivalents

addition-lactonization of substituted acetic acids and α,β -unsaturated trichloromethyl ketones.¹⁷ The initially formed *anti*-dihydropyranones **8** undergo ring-opening followed by alcoholysis of the CCl_3 ketone with methanol to give a range of diesters **9** with high levels of diastereo- and enantioselectivity (Scheme 2b). This methodology is limited to the use of either 2-aryl or 2-alkenylacetic acids and gives preferential access to the *anti*-diastereoisomer of the dihydropyranone intermediates.

Herein the use of α -aroyloxyaldehydes as azolium enolate precursors in [4+2] hetero-Diels-Alder reactions with α,β -unsaturated trichloromethyl ketones is investigated, with the *syn*-dihydropyranone products formed in good yields with high levels of diastereo- and enantioselectivity. Subsequent ring-opening followed by aminolysis of the CCl_3 ketone gives access to a wide range of diamide products without loss of enantioselectivity (Scheme 2c). In one case, the sequential addition of two different nucleophiles led to the formation of a differentially substituted diacid derivative. The methodology described is complementary to the related isothiurea-catalyzed process as it allows access to 3-alkyl-substituted dihydropyranones and preferentially gives the *syn*-diastereoisomer of the products.

Results and Discussion

[4+2] Cycloaddition: Optimization and Generality.

First, the NHC-catalyzed redox [4+2] hetero-Diels-Alder reaction between an azolium enolate generated from α -aroyloxyaldehyde **10** and α,β -unsaturated trichloromethyl ketone **1** was studied. α -Aroyloxyaldehydes were prepared in one-step on a gram-scale from the parent aldehyde and 4-nitrobenzoic acid under oxidative conditions using a modified procedure of that described by Ishihara and co-workers.²¹ Trichloromethyl ketones were prepared on a gram-scale using a two-step procedure first reported by Corey and co-workers starting from the corresponding α,β -unsaturated aldehyde and can be stored for a number of months without decomposition.²² Initial studies found that α -aroyloxyaldehyde **10** reacts with trichloromethyl ketone **1** using 10 mol% triazolium NHC precatalyst **11** and triethylamine in THF at room temperature, giving dihydropyranone **12** in 57% yield and >95:5 dr, with the major *syn*-diastereoisomer formed in excellent >99% ee (Table 1, entry 1).²³ The reaction proceeds in a number of different solvents, with CH_2Cl_2 giving dihydropyranone **12** in an improved 67% yield without compromising the stereoselectivity (Table 1, entries 2-4). Lowering the catalyst loading to 5 mol% gave comparable results (Table 1, entry 5), however

further decreases in the amount of catalyst led to a significant reduction in isolated yield. Finally,

performing

Table 1. Reaction optimization^a

Entry	Solvent	11 (mol%)	t / h	dr ^b	Yield (%)	ee (%) ^c
1	THF	10	5	>95:5	57	>99
2	Et ₂ O	10	1.5	>95:5	55	>99
3	PhMe	10	1.5	>95:5	55	>99
4	CH ₂ Cl ₂	10	1	>95:5	67	>99
5	CH ₂ Cl ₂	5	3.5	>95:5	66	>99
6 ^d	CH ₂ Cl ₂	5	3.5	>95:5	84	>99

^aReactions performed on 0.2 mmol scale. ^bDetermined by analysis of crude ¹H NMR spectra. ^cDetermined by chiral HPLC analysis. ^dReaction performed on a 1.2 mmol scale.

the reaction on a larger scale (1.2 mmol) gave *syn*-dihydropyranone **12** in 84% yield as a single diastereoisomer in >99% ee (Table 1, entry 6).

The scope and generality of this procedure was studied through variation of the substituents on both the α -aryloxyaldehyde and trichloromethyl ketone components (Table 2). A range of α -aryloxyaldehyde substituents was tolerated under the previously optimized reaction conditions, forming functionalized *syn*-dihydropyranones **12-19** with excellent levels of diastereo- and enantioselectivity. A higher catalyst loading (10 mol% **11**) was required to

form dihydropyranones **14** and **15**, as lower levels of diastereoselectivity were obtained over extended reaction times with a lower catalyst loading. For example, dihydropyranone **14** was formed in 65:35 dr after 48 hours under the standard reaction conditions using 5 mol% **11**, with both diastereoisomers formed with high enantioselectivity (98% *ee*_{syn}, >99% *ee*_{anti}). Increasing

Table 2. Use of trichloromethyl ketones in NHC-redox catalyzed [4+2] hetero-Diels-Alder reactions

Ar = 4-NO₂C₆H₄

12-19

Product	dr ^b	Product	dr ^b
Yield ^a (time)	<i>ee</i> ^c	Yield ^a (time)	<i>ee</i> ^c
<p>12 84% (4 h)</p>	>95:5 (>99%)	<p>13 81% (4 h)</p>	>95:5 (>99%)
<p>14 60% (8 h)^d</p>	90:10 (99%)	<p>15 65% (4 h)^d</p>	>95:5 (>99%)
<p>16 45% (24 h)^e</p>	85:15 (N/D) ^f	<p>17 93% (3 h)</p>	>95:5 (>99%)
<p>18 81% (2 h)</p>	>95:5 (>99%)	<p>19 26% (24 h)^d</p>	>95:5 (>99%)

^aIsolated yield of major *syn*-diastereoisomer. ^bDetermined by analysis of crude ¹H NMR spectra. ^cDetermined by chiral HPLC analysis. ^dReaction performed using 10 mol% **11**. ^eIsolated as a mixture of diastereoisomers. ^f*ee* could not be determined by either chiral HPLC or chiral GC analysis.

the catalyst loading to 10 mol% allowed dihydropyranone **14** to be formed in 90:10 dr, with the major *syn*-diastereoisomer isolated in 60% yield and 99% ee. Similarly, dihydropyranone **15** was formed in 90:10 dr after 26 hours using 5 mol% **11**, whereas increasing the catalyst loading to 10 mol% allowed a single diastereoisomer to be isolated in 65% yield after 4 hours in >99% ee. Within the trichloromethyl ketone, β -aryl groups containing electron-donating (4-MeOC₆H₄) and electron-withdrawing halogen (4-BrC₆H₄) substituents were well tolerated, forming *syn*-dihydropyranones **17** and **18** as single diastereoisomers in excellent yields and >99% ee. However, β -alkyl substitution was less well tolerated, forming *syn*-dihydropyranone **19** in a low 26% yield despite using 10 mol% **11** for an extended reaction time, although the diastereo- and enantioselectivity remained high.

To investigate the drop in diastereoselectivity observed for the reactions with some of the α -aryloxyaldehyde substituents an epimerization experiment was performed. Treating isolated *syn*-dihydropyranone **14** (90:10 dr, 99% ee) with triethylamine in CD₂Cl₂ at room temperature resulted in a mixture of *syn*-**14** and *anti*-**20** (67:33 dr), with both diastereoisomers obtained in >99% ee (Scheme 3). This is consistent with a base-promoted epimerization of the C(3) stereocenter, which accounts for the loss in diastereoselectivity in reactions that required extended reaction times upon changing the α -aryloxyaldehyde component.

Scheme 3. Base-promoted epimerization of **14**

Trichloromethyl ketones as Ester and Amide Equivalents.

Next, the synthetic utility of the trichloromethyl substituent as an ester/amide equivalent was examined. It was hoped that treating the crude *syn*-dihydropyranone products with an excess of a suitable nucleophile (alcohol or amine) would lead to ring-opening followed by alcoholysis/aminolysis of the CCl₃ ketone. Pleasingly, adding an excess of benzylamine to crude *syn*-dihydropyranone **12** led to formation of the expected diamide **21** in excellent 85% yield as a single diastereoisomer in >99% ee (Scheme 4a). In contrast, treating crude *syn*-dihydropyranone **12** with DMAP (20 mol%) and an excess of methanol gave a mixture of trichloroketoester **22** and diester **23**, with both formed with high levels of

Scheme 4. Use of trichloromethyl ketones as ester and amide equivalents

stereoselectivity (Scheme 4b).²⁴ The observation that only partial alcoholysis of the CCl₃ ketone had occurred led to the possibility of a sequential ring-opening and CCl₃ ketone displacement using two different nucleophiles. Firstly, benzyl alcohol and DMAP (20 mol%) were used to ring-open the initial *syn*-dihydropyranone product with subsequent addition of benzylamine (1.2 eq) leading to aminolysis of the CCl₃ ketone to give γ -ester amide **24** in 32% yield and >99% ee over the three reaction steps (Scheme 4c). This reactivity is in contrast to the use of α -keto- β,γ -unsaturated phosphonates as ester/amide equivalents in related reactions where both ring-opening and either alcoholysis or aminolysis of the phosphate group occurs rapidly and therefore differential substitution is not possible.^{14d} Moreover, dihydropyranones formed from related reactions using α,β -unsaturated trifluoromethyl ketones undergo ring-opening with no alcoholysis / aminolysis of the trifluoromethyl ketone observed.^{7d} The utility of trichloromethyl ketones as amide equivalents in this NHC-catalyzed redox [4+2] cycloaddition process was

Table 3. NHC-redox catalyzed [4+2] cycloaddition followed by ring-opening and aminolysis

Reaction scheme: α -keto ester (1.5 eq, Ar = 4-NO₂C₆H₄) + trichloromethyl ketone (1.5 eq) $\xrightarrow[\text{CH}_2\text{Cl}_2, \text{rt}]{\text{i) 11 (5 mol\%), Et}_3\text{N (1.5 eq)}}$ intermediate $\xrightarrow[\text{rt, 16 h}]{\text{ii) BnNH}_2 \text{ (excess)}}$ Product **21, 25-33**

Product	dr ^b	Product	dr ^b
Yield ^a (time)	ee ^c	Yield ^a (time)	ee ^c

^aIsolated yield of major *syn*-diastereoisomer. ^bDetermined by analysis of crude ¹H NMR spectra. ^cDetermined by chiral HPLC analysis. ^dReaction performed using 10 mol% **11**. ^eee could not be determined by either chiral HPLC or chiral GC analysis.

further assessed using a range of substituted α -aroyloxyaldehydes and α,β -unsaturated trichloromethyl ketones (Table 3). The cycloaddition reactions were performed under the previously optimized conditions and the initially formed *syn*-dihydropyranones underwent ring-opening and aminolysis with benzylamine. The resulting diamide products **21**, **25-33** were conveniently purified by trituration and did not require column chromatography.²⁵

A number of substituted α -aroyloxyaldehydes was successfully applied in this process, forming diamides **21**, **25-27** in high yields as single diastereoisomers and in excellent ee. Benzyl substituted diamide **27** was formed with lower diastereoselectivity (80:20 dr), which is consistent with base-promoted epimerization of dihydropyranone **16** under the reaction conditions (*cf.* Table 2). A wide range of substituted trichloromethyl ketone derivatives was also tolerated, including those containing electron-donating aryl (4-MeOC₆H₄), electron-withdrawing aryl (2-NO₂C₆H₄) and heteroaromatic substituents, forming functionalized diamides **28-32** in good yields with excellent levels of stereocontrol. As observed previously, the incorporation of a β -alkyl substituent led to a significantly lower yield of diamide **33**. The relative and absolute configuration of diamide **28** was confirmed by X-ray crystallographic analysis,²³ with the stereochemistry of all other products assigned by analogy.

Proposed Mechanism.

The proposed catalytic cycle starts with nucleophilic addition of the free NHC into the α -aroyloxyaldehyde, with the resulting adduct **34** likely to be the resting state of the catalyst (Scheme 5).^{7b,26} Deprotonation forms the Breslow intermediate, which can eliminate 4-nitrobenzoate to form an enol that undergoes further deprotonation into the key azolium enolate intermediate. Consistent with the work of Bode and co-workers,²⁷ the azolium enolate is thought to undergo an asynchronous *endo*-hetero-Diels-Alder reaction with the α,β -unsaturated trichloromethyl ketone. Elimination of the catalyst generates the *syn*-dihydropyranone product, which can undergo ring-opening using benzylamine or an alcohol, with aminolysis of the resulting trichloromethyl ketone proceeding at a relatively slower rate.

Scheme 5. Proposed mechanism

Conclusion

α,β -Unsaturated trichloromethyl ketones act as amide equivalents in NHC-catalyzed redox [4+2] hetero-Diels-Alder reactions with azolium enolates generated from bench-stable α -aryloxyaldehydes. The initially formed *syn*-dihydropyranones can be isolated in good yields with excellent levels of diastereo- and enantioselectivity. The dihydropyranone products undergo facile ring-opening with benzylamine and further aminolysis of the resulting CCl_3 ketone leads to the formation of diamides. A wide range of both α -aryloxyaldehydes and α,β -unsaturated trichloromethyl ketones can be utilized in this process, generating functionalized diamide products in high yields with excellent levels of stereoselectivity.

Experimental Section

General: All reactions were performed in flame dried glassware using anhydrous solvents. All reagents were obtained from commercial sources and were used without further purification. Room temperature (rt) refers to 20–25 °C, with temperatures of 0 °C and –10 °C

obtained using ice/water and ice/water/salt baths, respectively. Optical rotations were recorded with a path length of 1 dm and concentrations, *c*, are quoted in g/100 mL. All chiral HPLC traces were compared with an authentic racemic trace prepared using (*rac*)-**11**. Infra-red spectra were recorded as thin films using an ATR accessory. ¹H NMR spectra were acquired at either 300, 400, 500 or 700 MHz, ¹³C{¹H} NMR spectra were acquired at either 75, 101 or 126 MHz, and ¹⁹F{¹H} NMR spectra were acquired at either 282, 376, or 471 MHz. Chemical shifts are quoted in parts per million (ppm) relative to the residual solvent peak, coupling constants, *J*, are quoted in Hertz (Hz). NMR peak assignments were confirmed using 2D ¹H COSY, 2D ¹H NOESY, 2D ¹H-¹³C HMBC and 2D ¹H-¹³C HSQC where necessary. Mass spectrometry (*m/z*, HRMS) data were acquired using either atmospheric pressure chemical ionisation (APCI) or nanospray ionisation (NSI) using a TOF mass analyser.

NHC-precatalyst **11** was synthesized on a gram-scale according to a literature procedure.²⁸ Commercially available reagents were used as supplied without further purification unless stated otherwise.

Preparation of α -Aroyloxyaldehydes

1-Oxopropan-2-yl 4-nitrobenzoate (10). Prepared according to a previously reported procedure as a beige solid with data in accordance with literature.^{7b} mp 74–76 °C {lit.^{7b} mp 78–80 °C}; ¹H NMR (300 MHz, CDCl₃) δ_{H} : 1.59 (3H, d, *J* 7.2, CH₃), 5.39 (1H, q, *J* 7.2, CHCH₃), 8.24–8.37 (4H, m, 4-NO₂ArH), 9.67 (1H, s, CHO).

1-Oxo-3-phenylpropan-2-yl 4-nitrobenzoate. Prepared according to a previously reported procedure as a beige solid with data in accordance with literature.^{7b} mp 91–93 °C {lit.^{7b} mp 85–86 °C}; ¹H NMR (300 MHz, CDCl₃) δ_{H} : 3.22 (1H, dd, *J* 14.5, 8.4, CH^AH^B), 3.35 (1H, dd,

J 14.5, 5.0, $\text{CH}^{\text{A}}\text{H}^{\text{B}}$), 5.52 (1H, dd, J 8.3, 5.0, CHCH_2), 7.27–7.38 (4H, m, ArH), 8.15–8.23 (2H, m, 4- NO_2ArH), 8.26–8.35 (2H, m, 4- NO_2ArH), 9.68 (1H, s, CHO).

4-(1,3-Dioxoisindolin-2-yl)-1-oxobutan-2-yl 4-nitrobenzoate. Phthalic anhydride (4.5 g, 34 mmol, 1.0 eq) and 4-aminobutan-1-ol (3.1 mL, 34 mmol, 1.0 eq) were heated in toluene (100 mL) at reflux under Dean-Stark conditions for 3 h. The reaction mixture was allowed to cool to rt before being concentrated to give 2-(4-hydroxybutyl)-2,3-dihydro-1*H*-isoindole-1,3-dione as a pale yellow solid (7.0 g, 32 mmol, 95%), with spectroscopic data in accordance with the literature;²⁹ mp 47–49 °C {lit.²⁹ mp 48–49 °C}; ¹H NMR (500 MHz, CDCl_3) δ_{H} : 1.64 (2H, p, J 6.6, NCH_2CH_2), 1.80 (2H, p, J 7.3, $\text{N}(\text{CH}_2)_2\text{CH}_2$), 3.71 (2H, t, J 6.4, NCH_2), 3.76 (2H, t, J 7.2, $\text{N}(\text{CH}_2)_3\text{CH}_2$), 7.73 (2H, dd, J 5.5, 3.0, ArH), 7.86 (2H, dd, J 5.4, 3.1, ArH).

A solution of oxalyl chloride (2.3 mL, 27 mmol, 2.0 eq) in CH_2Cl_2 (50 mL) was cooled to –78 °C before a solution of DMSO (2.14 mL, 30 mmol, 2.2 eq) in CH_2Cl_2 (10 mL) was added dropwise. After stirring for 15 min a solution of 2-(4-hydroxybutyl)-2,3-dihydro-1*H*-isoindole-1,3-dione (3.0 g, 14 mmol, 1.0 eq) in CH_2Cl_2 (10 mL) was added dropwise. The reaction mixture was stirred for 15 min before Et_3N (5.7 mL, 41 mmol, 3.0 eq) was added dropwise. The reaction was stirred for 5 min before warming to rt and stirring for an additional 15 min. The reaction was diluted with CH_2Cl_2 , washed with 1 M HCl and brine. The organic layer was dried over Na_2SO_4 , filtered and concentrated to give the crude product that was purified by flash silica column chromatography (70:30 petrol : EtOAc) to give 4-(1,3-dioxo-2,3-dihydro-1*H*-isoindol-2-yl)butanal as a white solid (1.7 g, 7.9 mmol, 57%), with spectroscopic data in accordance with the literature;³⁰ mp 66–68 °C; {lit.³⁰ mp 72–74 °C}; ¹H NMR (500 MHz, CDCl_3) δ_{H} : 2.04 (2H, p, J 7.0, NCH_2CH_2), 2.51–2.62 (2H, m,

N(CH₂)₂CH₂), 3.73–3.80 (2H, m, NCH₂), 7.74 (2H, dd, *J* 5.4, 3.1, NCOAr*H*), 7.87 (2H, dd, *J* 5.5, 3.0, Ar*H*), 9.79 (1H, t, *J* 1.1, CHO).

From an adapted procedure of Ishihara *et al.*,²¹ 4-(1,3-dioxo-2,3-dihydro-1*H*-isoindol-2-yl)butanal (1.7 g, 7.9 mmol), 4-nitrobenzoic acid (2.0 g, 12 mmol), *n*-Bu₄NI (0.58 g, 1.6 mmol) and piperidine (78 μL, 0.79 mmol) were dissolved in EtOAc (40 mL) and *t*-BuOOH (5–6 M solution in decane, 1.57 mL) was added. The reaction mixture was heated at 50 °C for 5 h before being cooled to rt and quenched with Na₂SO₄. The phases were separated and the aqueous extracted with EtOAc (× 2). The combined organics were washed with sat. aq. NaHCO₃ (× 2) and brine (× 2) before being dried over MgSO₄, filtered and concentrated. The crude product was purified by flash silica column chromatography (70:30 petrol : EtOAc) to give 4-(1,3-dioxoisindolin-2-yl)-1-oxobutan-2-yl 4-nitrobenzoate as a pale orange solid (1.9 g, 4.8 mmol, 62%); mp 38–41 °C; *v*_{max} (film) 1705 (br, C=O); ¹H NMR (300 MHz, CDCl₃) δ_H: 2.26–2.38 (1H, m, NCH₂CH^AH^B), 2.40–2.51 (1H, m, NCH₂CH^AH^B), 3.95 (2H, t, *J* 6.5, NCH₂), 5.35 (1H, dd, *J* 9.3, 3.7, CHCHO), 7.65–7.84 (4H, m, Ar*H*), 8.19–8.26 (4H, m, 4-NO₂Ar*H*), 9.62 (1H, s, CHO); ¹³C{¹H} NMR (75 MHz, CDCl₃) δ_C: 27.4 (NCH₂CH₂), 34.2 (NCH₂), 77.4 (CHCHO), 123.5 (NCOArC(2)), 123.7 (ArC(2)), 131.1 (ArC(3)), 131.9 (NCOArC(1)), 134.1 (ArC(1)), 134.4 (NCOArC(1)), 150.9 (CO₂), 164.2 (ArC(4)), 168.2 (NCOAr), 196.3 (CHO); HRMS (APCI⁺) C₁₉H₁₅N₂O₇ [M+H]⁺ found 383.0874, requires 383.0874 (+0.1 ppm).

1-(4-Methoxyphenyl)-3-oxopropan-2-yl 4-nitrobenzoate. Prepared according to a previously reported procedure as a viscous yellow oil with data in accordance with the literature.^{7c} ¹H NMR (300 MHz, CDCl₃) δ_H: 3.17 (1H, dd, *J* 14.6, 8.1, C(1)*H*^AH^B), 3.29 (1H, dd, *J* 14.6, 5.1, C(1)*H*^AH^B), 3.78 (3H, s, ArOCH₃), 5.47 (1H, dd, *J* 8.0, 5.0, C(2)*H*), 6.85 (2H,

d, J 8.6, MeOArC(3,5) H), 7.19 (2H, d, J 8.6, MeOArC(2,6) H), 8.20 (2H, d, J 8.6, 4-NO₂ArC(2,6) H), 8.31 (2H, d, J 8.6, 4-NO₂ArC(3,5) H), 9.66 (1H, s, CHO).

1-(Benzo[d][1,3]dioxol-5-yl)-3-oxopropan-2-yl 4-nitrobenzoate. Prepared according to a previously reported procedure as a viscous orange oil with data in accordance with the literature.^{7c} ¹H NMR (300 MHz, CDCl₃) δ_H : 3.14 (1H, dd, J 14.6, 8.2, C(1) $H^A H^B$), 3.26 (1H, dd, J 14.6, 5.0, C(1) $H^A H^B$), 5.46 (1H, dd, J 8.1, 5.0, C(2) H), 5.94 (2H, s, OCH₂O), 6.69–6.77 (3H, m, ArCH), 8.21 (2H, d, J 8.9, 4-NO₂ArC(2,6) H), 8.32 (2H, d, J 8.9, 4-NO₂ArC(3,5) H), 9.66 (1H, s, CHO).

1-Oxohexan-2-yl 4-nitrobenzoate. Prepared according to a previously reported procedure as a yellow oil with data in accordance with literature.^{7b} ¹H NMR (400 MHz, CDCl₃) δ_H : 0.95 (3H, t, J 7.2, CH₃), 1.37–1.45 (2H, m, CH₂), 1.45–1.54 (2H, m, CH₂), 1.93 (2H, ddd, J 15.5, 14.6, 8.5, CH₂), 5.31 (1H, dd, J 8.3, 4.7, CH), 8.25–8.35 (4H, m, 4-NO₂ArH), 9.64 (1H, d, J 0.5, CHO).

Preparation of α,β -Unsaturated Trichloromethyl ketones

(E)-1,1,1-Trichloro-4-phenylbut-3-en-2-one (I). Prepared according to a previously reported procedure as a white solid with data in accordance with literature.¹⁷ mp 57–59 °C {lit.¹⁷ mp 59 °C}; ¹H NMR (300 MHz, CDCl₃) δ_H : 7.34 (1H, d, J 15.6, C(3) H), 7.41–7.52 (3H, m, ArH), 7.61–7.70 (2H, m, ArH), 8.01 (1H, d, J 15.6, C(4) H).

(E)-1,1,1-Trichloro-4-(4-methoxyphenyl)but-3-en-2-one. Prepared according to a previously reported procedure as a white solid with data in accordance with literature.¹⁷ mp 98–100 °C {lit.¹⁷ mp 98–100 °C}; ¹H NMR (400 MHz, CDCl₃) δ_H : 3.87 (3H, s, OCH₃), 6.92–6.99 (2H, m, ArH), 7.21 (1H, d, J 15.6, C(3) H), 7.58–7.65 (2H, m, ArH), 7.97 (1H, d, J 15.5, C(4) H).

(*E*)-4-(4-Bromophenyl)-1,1,1-trichlorobut-3-en-2-one. From an adapted procedure of Patil and Singh,³¹ reactivated MnO₂ (2.0 g, 23.mmol)³² was added portion-wise to a solution of (*E*)-3-(4-bromophenyl)prop-2-en-1-ol (491 mg, 2.3 mmol) and in CH₂Cl₂ (9.8 mL) and stirred at rt for 3.5 h. The mixture was filtered through Celite[®] and concentrated to give (*E*)-3-(4-bromophenyl)acrylaldehyde (413 mg, 88%) as a brown solid that was used without further purification with data in accordance with literature.³³ ¹H NMR (300 MHz, CDCl₃) δ_H: 6.70 (1H, dd, *J* 16.0, 7.6, C(2)*H*), 7.43–7.38 (2H, m, Ar*H*), 7.48–7.43 (1H, m, C(3)*H*), 7.62–7.54 (2H, m, Ar*H*), 9.71 (1H, d, *J* 7.6, CHO).

Following the procedure by Zhao *et al.*,^{16a} (*E*)-3-(4-bromophenyl)acrylaldehyde (387 mg, 1.83 mmol, 1.0 eq) was added to a solution of CHCl₃ (293 μL, 3.66 mmol, 2.0 eq) in DMF (1.3 mL) at rt. The reaction mixture was stirred at rt for 20 min then cooled to 0 °C before a solution of KOH (205 mg, 3.66 mmol, 2.0 eq) in EtOH (660 μL) was added dropwise. The reaction was stirred at 0 °C for 2 h. The reaction mixture was acidified with 1 M HCl and extracted with EtOAc (× 2). The combined organics were washed with water (× 2) and brine (× 3) before being dried over MgSO₄, filtered and concentrated to give ((*E*)-4-(4-bromophenyl)-1,1,1-trichlorobut-3-en-2-ol (562 mg, 93%) as a brown oil that was used without further purification. ¹H NMR (300 MHz, CDCl₃) δ_H: 4.76 (1H, dd, *J* 5.9, 1.3, C(1)*H*), 6.37 (1H, dd, *J* 15.9, 5.9, C(2)*H*), 6.85 (1H, br d, C(3)*H*), 7.27–7.35 (2H, m, Ar*H*), 7.43–7.52 (2H, m, Ar*H*).

Following the procedure described by Evans *et al.*,³⁴ ((*E*)-4-(4-bromophenyl)-1,1,1-trichlorobut-3-en-2-ol (562 mg, 1.70 mmol, 1.0 eq) and distilled Et₃N (711 μL, 5.10 mmol, 3.0 eq) were dissolved in anhydrous CH₂Cl₂ (13.5 mL). A solution of sulfur trioxide pyridine complex (812 mg, 5.10 mmol, 3.0 eq) in distilled DMSO (2.7 mL) was added dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 24 h before adding again sulfur trioxide pyridine complex (812 mg, 5.10 mmol, 3.0 eq). The reaction mixture was stirred at rt for 48 h

before being diluted in water (10 mL), extracted with Et₂O (2 × 20 mL) and washed successively with sat. aq. CuSO₄ (20 mL), sat. aq. NaHCO₃ (2 × 20 mL) and brine (2 × 20 mL). The organic layer was dried over MgSO₄, filtered and concentrated to give (*E*)-4-(4-bromophenyl)-1,1,1-trichlorobut-3-en-2-one (583 mg, quant.) as a brown solid that was used without further purification with data in accordance with literature.^{16a} ¹H NMR (300 MHz, CDCl₃) δ_H: 7.32 (1H, d, *J* 15.7, C(2)*H*), 7.48–7.65 (4H, m, Ar*H*), 7.93 (1H, d, *J* 15.6, C(3)*H*).

(*E*)-1,1,1-Trichloronon-3-en-2-one. Prepared according to a previously reported procedure as a yellow oil with data in accordance with literature.¹⁷ ¹H NMR (400 MHz, CDCl₃) δ_H: 0.87–0.93 (3H, m, CH₃), 1.28–1.38 (4H, m, CH₂ × 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*).

(*E*)-1,1,1-Trichloro-4-(4-fluorophenyl)but-3-en-2-one. Prepared according to a previously reported procedure as a white solid with data in accordance with literature.¹⁷ mp 66–64 °C {lit.^{16a} mp 60–62 °C}; ¹H NMR (500 MHz, CDCl₃) 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*); ¹⁹F{¹H} NMR (471 MHz, CDCl₃) δ_F: –106.65(ArC(4)*F*).

(*E*)-1,1,1-Trichloro-4-(2-nitrophenyl)but-3-en-2-one. Prepared according to a previously reported procedure as a white solid with data in accordance with literature.¹⁷ mp 56–58 °C {lit.¹⁷ mp 56–58 °C}; ¹H NMR (400 MHz, CDCl₃) δ_H: 7.24 (1H, d, *J* 15.5, C(3)*H*), 7.60–7.66 (1H, m, Ar*CH*), 7.70–7.75 (2H, m, Ar*CH*), 8.10–8.12 (1H, m, ArC(3)*H*), 8.43 (1H, d, *J* 15.5, C(4)*H*).

(*E*)-1,1,1-Trichloro-4-(furan-2-yl)but-3-en-2-one. Prepared according to a previously reported procedure as a white solid with data in accordance with literature.¹⁷ mp 40–42 °C {lit.^{16a} mp 42–44 °C}; ¹H NMR(400 MHz, CDCl₃) 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).

General Procedure for the NHC-catalyzed Redox Synthesis of *syn*-Dihydropyranones:

The appropriate α -aroyloxyaldehyde (0.30 mmol, 1.5 eq), the appropriate trichloromethylketone (0.20 mmol, 1.0 eq) and NHC precatalyst **11** (0.010 mmol, 5 mol% or 0.020 mmol, 10 mol%) were dissolved in anhydrous CH₂Cl₂ (2.7 mL). Et₃N (0.30 mmol, 1.5 eq) was added and the reaction mixture was stirred at rt until complete by TLC analysis. The mixture was diluted in EtOAc (10 mL) and washed with sodium bisulfite aq. 40% (10 mL) and brine (10 mL). The organic layer was dried over MgSO₄, filtered and concentrated to give the crude product that was purified by flash silica column chromatography.

(3S,4S)-3-Methyl-4-phenyl-6-(trichloromethyl)-3,4-dihydro-2H-pyran-2-one (12).

Following the general procedure, 1-oxopropan-2-yl 4-nitrobenzoate **10** (402 mg, 1.80 mmol), (*E*)-1,1,1-trichloro-4-phenylbut-3-en-2-one **1** (300 mg, 1.20 mmol), NHC precatalyst **11** (22.1 mg, 0.060 mmol) and Et₃N (251 μ L, 1.80 mmol) in anhydrous CH₂Cl₂ (16.2 mL) at rt for 3.5 h gave a crude brown solid (>95:5 dr) that was purified by flash silica column chromatography (90:10 hexane : EtOAc) to give the title compound (307 mg, 84%) as a white solid. mp 142–145 °C; $[\alpha]_D^{20}$ +237.5 (*c* 0.41, CH₂Cl₂); Chiral HPLC AD-H (95:5 hexane : IPA, flow rate 1.0 mL·min⁻¹, 220 nm, 30 °C) *t*_R major: 5.9- min, *t*_R minor: 7.1 min, >99% ee; $\nu_{\max}$ (film, cm⁻¹) 1776 (C=O), 1674 (C=C), 1601 (Ar C=C), 1493 (Ar C=C), 1454 (Ar C=C); ¹H NMR (400 MHz, CDCl₃) δ _H: 1.06 (3H, d, *J* 6.9, CH₃), 3.08 (1H, p, *J* 6.9, C(3)*H*), 3.75 (1H, t, *J* 6.8, C(4)*H*), 6.42 (1H, d, *J* 6.5, C(5)*H*), 7.04–7.14 (2H, m, C(4)ArCH), 7.28–7.39 (3H, m, C(4)ArCH); ¹³C{¹H} NMR (126 MHz, CDCl₃) δ _C: 12.1 (CH₃), 38.2 (C(3)), 42.4 (C(4)), 90.1 (CCl₃), 108.0 (C(5)), 128.1 (C(4)ArCH), 128.3 (C(4)ArCH), 129.2 (C(4)ArCH), 135.8 (C(4)ArC(1)), 149.5 (C(6)), 168.6 (C(2)); *m/z* (APCI⁺) 307 [(M(³⁵Cl₂, ³⁷Cl)+H]⁺, 100%), 305 [(M(³⁵Cl₃)+H]⁺, 98%); HRMS (APCI⁺) C₁₃H₁₂³⁵Cl₃O₂ [M+H]⁺ found 304.9903, requires 304.9897 (+1.5 ppm).

(3*S*,4*S*)-3-Benzyl-4-phenyl-6-(trichloromethyl)-3,4-dihydro-2*H*-pyran-2-one (13).

Following the general procedure, 1-oxo-3-phenylpropan-2-yl 4-nitrobenzoate (90 mg, 0.30 mmol), (*E*)-1,1,1-trichloro-4-phenylbut-3-en-2-one **1** (50 mg, 0.20 mmol), NHC precatalyst **11** (3.7 mg, 0.010 mmol) and Et₃N (42 μ L, 0.30 mmol) in anhydrous CH₂Cl₂ (2.7 mL) at rt for 4 h gave a brown oil (>95:5 dr) that was purified by column chromatography (90:10 petrol : EtOAc) to give the title compound (62 mg, 95% pure, 81%) as a light red oil. $[\alpha]_{\text{D}}^{20} +167.7$ (*c* 0.43, CH₂Cl₂); Chiral HPLC AS-H (99:1 hexane : IPA, flow rate 0.5 mL·min⁻¹, 211 nm, 30 °C) *t*_R minor: 16.6 min, *t*_R major: 19.2 min, >99% ee; ν_{max} (film, cm⁻¹) 1780 (C=O), 1670 (C=C), 1603 (Ar C=C), 1495 (Ar C=C), 1454 (Ar C=C); ¹H NMR (400 MHz, CDCl₃) δ_{H} : 2.35–2.46 (1H, m, C(3)CH^AH^B), 3.21–3.34 (2H, m, C(3)CH^AH^B and C(3)H), 3.65–3.72 (1H, m, C(4)H), 6.37 (1H, d, *J* 6.8, C(5)H), 7.01–7.08 (2H, m, ArH), 7.11 (2H, m, ArH), 7.29–7.41 (6H, m, ArH); ¹³C{¹H} (101 MHz, CDCl₃) δ_{C} : 32.0 (CH₂), 39.9 (C(4)), 44.8 (C(3)), 90.1 (CCl₃), 108.6 (C(5)), 126.8 (ArCH), 128.3 (ArCH $\times$ 2), 128.4 (ArCH), 128.7 (ArCH $\times$ 2), 128.9 (ArCH $\times$ 2), 129.3 (ArCH $\times$ 2), 135.9 (C(3)ArC(1)), 137.8 (C(2)CH₂ArC(1)), 149.1 (C(6)), 167.8 (C(2)); *m/z* (APCI⁺) 381 ([M(³⁵Cl₃)+H]⁺, 100%); HRMS (APCI⁺) C₁₉H₁₆O₂³⁵Cl₃ [M+H]⁺ found 381.0204, requires 381.0210 (–1.7 ppm).

2-(2-((3*S*,4*S*)-2-Oxo-4-phenyl-6-(trichloromethyl)-3,4-dihydro-2*H*-pyran-3-yl)ethyl)iso-indoline-1,3-dione (**14**). Following the general procedure 4-(1,3-dioxoisindolin-2-yl)-1-oxobutan-2-yl 4-nitrobenzoate (115 mg, 0.30 mmol), (*E*)-1,1,1-trichloro-4-phenylbut-3-en-2-one **1** (50 mg, 0.20 mmol), NHC precatalyst **11** (7.4 mg, 0.020 mmol, 10 mol%) and Et₃N (42 μ L, 0.30 mmol) in anhydrous CH₂Cl₂ (2.7 mL) at rt for 7 h gave a brown solid (90:10 dr) that was purified by column chromatography (90:10 petrol : EtOAc) to give the title compound (55 mg, 60%) as a white solid. mp 132 °C (*dec*); $[\alpha]_{\text{D}}^{20} +271.2$ (*c* 0.16, CHCl₃); Chiral HPLC OD-H (97:3 hexane : IPA, flow rate 1.0 mL·min⁻¹, 211 nm, 30 °C) *syn*: *t*_R minor: 34.3 min, *t*_R major: 42.2 min, >99% ee, *anti*: *t*_R major: 51.3 min, *t*_R minor: 59.2 min, >99% ee; ν_{max} (film,

cm⁻¹) 1772 and 1701 (C=O isoxindole), 1701 (C=O); ¹H NMR (500 MHz, CDCl₃) δ_H: 1.50–1.60 (1H, m, C(3)CH^AH^B), 2.06–2.16 (1H, m, C(3)CH^AH^B), 2.95 (1H, q, *J* 7.0, C(3)*H*), 3.76–3.85 (1H, m, C(3)CH₂CH^AH^B), 3.85–3.92 (1H, m, C(3)CH₂CH^AH^B), 4.00 (1H, t, *J* 7.0, C(4)*H*), 6.42 (1H, d, *J* 6.9, C(5)*H*), 7.12–7.16 (2H, m, Ar*H*), 7.29–7.38 (3H, m, Ar*H*), 7.70–7.75 (2H, m, C(3)(CH₂)₂Ar(2,5)*H*), 7.83–7.88 (2H, m, C(3)(CH₂)₂Ar(3,4)*H*); ¹³C{¹H} (101 MHz, CDCl₃) δ_C: 26.3 (CH₂), 35.6(CH₂), 40.7 (C(3)), 40.9 (C(4)), 90.0 (CCl₃), 108.1 (C(5)), 123.4 (ArCH × 2), 128.0 (ArCH × 2), 128.5 (ArCH), 129.4 (ArCH × 2), 132.0 (NPhthArC), 134.1 (ArCH), 135.7 (NPhthArC), 149.3 (C(3)ArC(1)), 167.5 (C(2)), 168.4 (C=O × 2); *m/z* (NSI⁺) 951 ([2M(³⁵Cl₂, ³⁷Cl)+Na]⁺, 100%), 949 ([2M(³⁵Cl₃)+Na]⁺, 85%), 486 ([M(³⁵Cl₃)+Na]⁺, 85%); HRMS (NSI⁺) C₂₂H₁₆O₄N₁³⁵Cl₃Na [M+Na]⁺ found 486.0041, requires 486.0037 (+0.8 ppm).

(3S,4S)-3-(4-Methoxybenzyl)-4-phenyl-6-(trichloromethyl)-3,4-dihydro-2H-pyran-2-one (**15**). Following the general procedure, 1-(4-methoxyphenyl)-3-oxopropan-2-yl 4-nitrobenzoate (99 mg, 0.30 mmol), (*E*)-1,1,1-trichloro-4-phenylbut-3-en-2-one **1** (50 mg, 0.20 mmol), NHC precatalyst **11** (7.4 mg, 0.020 mmol) and Et₃N (42 μL, 0.30 mmol) in anhydrous CH₂Cl₂ (2.7 mL) at rt for 26 h gave a brown oil (>95:5 dr) that was purified by column chromatography (95:5 petrol : EtOAc) to give the title compound (53 mg, 65%) as a yellow oil. [α]_D²⁰ +300.0 (*c* 0.81, CHCl₃); Chiral HPLC AD-H (99:1 hexane : IPA, flow rate 1.0 mL·min⁻¹, 220 nm, 30 °C) t_R minor: 18.5 min, t_R major: 20.7 min, >99% ee; ν_{max} (film, cm⁻¹) 1780 (C=O), 1612 (C=C), 1514 (Ar C=C), 1456, 1250 (Ph–O–CH₃); ¹H NMR (500 MHz, CDCl₃) δ_H: 2.35 (1H, dd, *J* 14.4, 9.1, C(3)CH^AH^B), 3.15–3.27 (2H, m, C(3)CH^AH^B and C(3)*H*), 3.68 (1H, t, *J* 6.8, C(4)*H*), 3.81 (3H, s, CH₃O), 6.36 (1H, d, *J* 6.7, C(5)*H*), 6.85 (2H, dd, *J* 9.1, 2.5, C(3)CH₂ArC(3,5)*H*), 6.99–7.08 (4H, m, C(3)CH₂ArC(2,6)*H* and C(4)ArC(3,5)*H*), 7.31–7.39 (3H, m, C(4)ArC(2,4,6)*H*); ¹³C{¹H} (126 MHz, CDCl₃) δ_C: 31.1 (C(3)CH₂), 39.9 (C(4)), 45.0 (C(3)), 55.3 (OCH₃), 90.1 (CCl₃), 108.6 (C(5)), 114.0

(C(3)CH₂ArC(3,5)), 128.3 (ArCH), 128.4 (ArCH), 129.2 (ArCH), 129.7(ArCH), 129.7 (ArCH), 129.9 (ArCH), 136.0 (C(4)ArC(1)), 149.1 (C(6)), 158.4 (C(3)CH₂ArC(4)), 167.9 (C(2)); *m/z* (NSI⁺) 462 ([M(³⁵Cl₂, ³⁷Cl)+MeOH+NH₄]⁺, 51%), 460 ([M(³⁵Cl₃)+MeOH+NH₄]⁺, 52%), 445 ([M(³⁵Cl₂, ³⁷Cl)+MeOH+H]⁺, 65%), 443 ([M(³⁵Cl₃)+MeOH+H]⁺, 67%), 432 ([M(³⁵Cl, ³⁷Cl₂)+NH₄]⁺, 30%), 430 ([M(³⁵Cl₂, ³⁷Cl)+NH₄]⁺, 97%), 428 ([M(³⁵Cl₃)+NH₄]⁺, 100%), 411 ([M(³⁵Cl₂, ³⁷Cl)+H]⁺, 43%); HRMS (NSI⁺) C₂₀H₁₈O₃Cl₃ [M+H]⁺ found 411.0321, requires 411.0316 (+1.2 ppm).

(3*S*,4*S*)-(-3-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-4-phenyl-6-(trichloromethyl)-3,4-dihydro-2*H*-pyran-2-one (**16**). Following the general procedure, 1-(benzo[*d*][1,3]dioxol-5-yl)-3-oxopropan-2-yl 4-nitrobenzoate (103 mg, 0.30 mmol), (*E*)-1,1,1-trichloro-4-phenylbut-3-en-2-one **1** (50 mg, 0.20 mmol), NHC precatalyst **11** (3.7 mg, 0.010 mmol) and Et₃N (42 μL, 0.30 mmol) in anhydrous CH₂Cl₂ (2.7 mL) at rt for 26 h gave a brown oil (85:15 dr) that was purified by column chromatography (95:5 petrol : EtOAc) to give the title compound (38 mg, 45%) as a white solid. mp 145–147 °C; [α]_D²⁰ +230.4 (*c* 0.51, CH₂Cl₂); ee could not be determined by either chiral HPLC or GC; ν_{max} (film, cm⁻¹) 1780 (C=O), 1504, 1489 and 1445 (Ar C=C), 1246 (C-O); ¹H NMR (500 MHz, CDCl₃) δ_H: 2.33 (1H, dd, *J* 14.5, 9.1, C(3)CH^AH^B), 3.15 (1H, dd, *J* 14.5, 5.3, C(3)CH^AH^B), 3.18–3.22 (1H, m, C(3)*H*), 3.71 (1H, t, *J* 6.7, C(4)*H*), 5.96 (2H, dd, *J* 4.6, 1.4, OCH₂O), 6.37 (1H, d, *J* 6.8, C(5)*H*), 6.53 (1H, dd, *J* 7.9, 1.5, C(3)CH₂ArC(6)*H*), 6.61 (1H, *app* d, *J* 1.6, C(3)CH₂ArC(4)*H*), 6.75 (1H, d, *J* 7.9, C(3)CH₂ArC(7)*H*), 7.05–7.07 (2H, m, C(4)ArC(3,5)*H*), 7.32–7.39 (3H, m, C(4)ArC(2,4,6)*H*); ¹³C{¹H} (126 MHz, CDCl₃) δ_C: 31.8 (C(4)CH₂), 39.9 (C(4)), 45.1 (C(3)), 90.1 (CCl₃), 101.0 (OCH₂O), 108.4 (C(3)CH₂ArC(7)), 108.6 (C(5)), 109.1 (C(3)CH₂ArC(4)), 122.0 (C(3)CH₂ArC(6)), 128.3 (C(4)ArCH), 128.4 (C(4)ArCH), 129.3 (C(4)ArCH), 131.4 (C(3)CH₂ArC(5)), 135.9 (C(4)ArC(1)), 146.4 (C(3)CH₂ArC(3a)), 147.8 (C(3)CH₂ArC(7a)), 149.0 (C(6)), 167.8 (C(2)); *m/z* (NSI⁺) 481 ([M(³⁵Cl₂, ³⁷Cl)+MeOH+Na]⁺, 65%), 479

($[\text{M}(^{35}\text{Cl}_3)+\text{MeOH}+\text{Na}]^+$, 67%), 449 ($[\text{M}(^{35}\text{Cl}_2, ^{37}\text{Cl})+\text{Na}]^+$, 50%), 447 ($[\text{M}(^{35}\text{Cl}_3) +\text{Na}]^+$, 52%), 444 ($[\text{M}(^{35}\text{Cl}_2, ^{37}\text{Cl})+\text{NH}_4]^+$, 31%), 442 ($[\text{M}(^{35}\text{Cl}_3)+\text{NH}_4]^+$, 34%), 429 ($[\text{M}(^{35}\text{Cl}, ^{37}\text{Cl}_2)+\text{H}]^+$, 30%), 427 ($[\text{M}(^{35}\text{Cl}_2, ^{37}\text{Cl})+\text{H}]^+$, 94%), 425 ($[\text{M}(^{35}\text{Cl}_3)+\text{H}]^+$, 100%); HRMS (NSI^+) $\text{C}_{20}\text{H}_{16}\text{O}_4 ^{35}\text{Cl}_3 [\text{M}+\text{H}]^+$ found 425.0107, requires 425.0109 (−0.4 ppm).

(3S,4S)-3-Benzyl-4-(4-methoxyphenyl)-6-(trichloromethyl)-3,4-dihydro-2H-pyran-2-one

(17). Following the general procedure, 1-oxo-3-phenylpropan-2-yl 4-nitrobenzoate (270 mg, 0.90 mmol), (*E*)-1,1,1-trichloro-4-(4-methoxyphenyl)but-3-en-2-one (168 mg, 0.60 mmol), NHC precatalyst **11** (11.1 mg, 0.030 mmol) and Et_3N (126 μL , 0.90 mmol) in anhydrous CH_2Cl_2 (8.2 mL) at rt for 3 h gave a brown oil (>95:5 dr) that was purified by column chromatography (90:10 petrol : EtOAc) to give the title compound (229 mg, 93%) as a white solide. mp 109–111 °C; $[\alpha]_{\text{D}}^{20} +369.6$ (*c* 0.575, CH_2Cl_2); Chiral HPLC AD-H (98:2 hexane : IPA, flow rate 1.0 mL·min^{−1}, 220 nm, 30 °C) t_{R} minor: 11.2 min, t_{R} major: 12.6 min, 99% ee; ν_{max} (film, cm^{−1}) 1778 (C=O), 1609 (C=C), 1512 (Ar C=C), 1252 (Ph-O-CH₃); ¹H NMR (500 MHz, CDCl_3) δ_{H} : 2.41 (1H, dd, *J* 15.8, 10.6, C(3)CH^AH^B), 3.23–3.30 (2H, m, C(3)CH^AH^B and C(3)H), 3.62 (1H, t, *J* 6.7, C(4)H), 3.82 (3H, s, CH₃), 6.35 (1H, d, *J* 6.8, C(5)H), 6.87–6.97 (4H, m, C(4)ArH), 7.10–7.14 (2H, m, ArH), 7.24–7.28 (1H, m, ArH), 7.30–7.35 (2H, m, ArH); ¹³C{¹H} (126 MHz, CDCl_3) δ_{C} : 32.0 (CH₂), 39.1 (C(4)), 45.0 (C(3)), 55.3 (CH₃O), 90.1 (CCl₃), 108.9 (C(5)), 114.6 (C(4)ArCH), 126.8 (C(3)CH₂ArCH), 127.6 (C(4)ArC(1)), 128.7 (C(3)CH₂ArCH), 129.0 (C(3)CH₂ArCH), 129.4 (C(4)ArCH), 137.9 (C(3)CH₂ArC), 148.8 (C(6)), 159.6 (C(4)ArC(4)), 168.0 (C(2)); *m/z* (APCI⁺) 411 ($[\text{M}(^{35}\text{Cl}_3)+\text{H}]^+$, 100%), 303 ($[\text{M}(^{35}\text{Cl}_3)-4-\text{OMeC}_6\text{H}_4]^+$, 70%); HRMS (APCI⁺) $\text{C}_{20}\text{H}_{17} ^{35}\text{Cl}_3\text{O}_3 [\text{M}+\text{H}]^+$ found 411.0313, requires 411.0316 (−0.7 ppm).

(3S,4S)-3-Benzyl-4-(4-bromophenyl)-6-(trichloromethyl)-3,4-dihydro-2H-pyran-2-one (18).

Following the general procedure, 1-oxo-3-phenylpropan-2-yl 4-nitrobenzoate (90 mg, 0.30 mmol), (*E*)-4-(4-bromophenyl)-1,1,1-trichlorobut-3-en-2-one (70 mg, 0.20 mmol), NHC

precatalyst **11** (3.7 mg, 0.010 mmol) and Et₃N (42 μ L, 0.30 mmol) in anhydrous CH₂Cl₂ (2.7 mL) at rt for 1.5 h gave a brown oil (>95:5 dr) that was purified by column chromatography (90:10 petrol : EtOAc) to give the title compound (60 mg, 95% pure, 55%) as a yellow oil. $[\alpha]_D^{20} +71.4$ (*c* 0.29, CH₂Cl₂); Chiral HPLC OD-H (97:3 hexane : IPA, flow rate 1.0 mL·min⁻¹, 220 nm, 30 °C) *t*_R major: 10.3 min, *t*_R minor: 11.7 min, >99% ee; $\nu_{\max}$ (film, cm⁻¹) 1780 (C=O), 1661 (C=C); ¹H NMR (400 MHz, CDCl₃) δ_H : 2.33–2.42 (1H, m, C(3)CH^AH^B), 3.24–3.35 (2H, m, C(3)CH^AH^B and C(3)H), 3.64 (1H, t, *J* 6.7, C(4)H), 6.33 (1H, d, *J* 6.8, C(5)H), 6.86–6.93 (2H, m, C(4)ArC(2,6)H), 7.07–7.12 (2H, m, C(3)ArH), 7.27–7.36 (3H, m, C(3)ArH), 7.46–7.52 (2H, m, C(4)ArC(3,5)H); ¹³C{¹H}(101 MHz, CDCl₃) δ_C : 32.0 (CH₂), 39.2 (C(4)), 44.4 (C(3)), 90.2 (CCl₃), 108.0 (C(5)), 123.0 (C(4)ArC(1)), 127.0 (C(3)CH₂ArCH), 128.8 (C(3)CH₂ArCH), 128.9 (C(3)CH₂ArCH), 129.9 (C(4)ArC(2,6)), 132.4 (C(4)ArC(3,5)), 135.1 (C(4)ArC(4)), 137.8 (C(3)CH₂ArC), 146.6 (C(6)), 167.7 (C(2)); *m/z* (APCI⁺) 463 ([M(³⁵Cl,³⁷Cl₂,⁷⁹Br)+H]⁺, 60%), 461 ([M(³⁵Cl₂,³⁷Cl,⁷⁹Br)+H]⁺, 100%), 458 ([M(³⁵Cl₃,⁷⁹Br)+H]⁺, 50%); HRMS (APCI⁺) C₁₉H₁₅O₂⁷⁹Br³⁵Cl₃ [M+H]⁺ found 458.9312, requires 458.9316 (–0.8 ppm).

(3S,4S)-3-Methyl-4-pentyl-6-(trichloromethyl)-3,4-dihydro-2H-pyran-2-one (**19**).

Following the general procedure, 1-oxopropan-2-yl 4-nitrobenzoate **10** (67 mg, 0.30 mmol), (*E*)-1,1,1-trichloronon-3-en-2-one (49 mg, 0.20 mmol), NHC precatalyst **11** (7.4 mg, 0.020 mmol) and Et₃N (42 μ L, 0.30 mmol) in anhydrous CH₂Cl₂ (2.7 mL) at rt for 22 h gave a crude brown solid (>95:5 dr) that was purified by flash silica column chromatography (95:5 hexane: EtOAc) to give the title compound (15 mg, >95% pure, 26%) as a yellow oil. $[\alpha]_D^{20} +8.9$ (*c* 0.44, CHCl₃); Chiral GC analysis Restek Rt-bDEXcst (length: 30 m, thickness: 0.250 mm, film thickness 0.25 μ m) carrier gas: He, linear velocity: 20.0 cm·s⁻¹, temperature: 160 °C *t*_R minor: 105.3 min, *t*_R major: 106.9 min, >99% ee; $\nu_{\max}$ (film, cm⁻¹) 1782 (C=O), 1668 (C=C), 1458 (Ar C=C); ¹H NMR (400 MHz, CDCl₃) δ_H : 0.88 (3H, t, *J* 6.9, CH₃), 1.26 (3H, d,

J 7.0, C(3)CH₃), 1.27–1.40 (7H, m, C(4)CH^AH^B and CH₃(CH₂)₃), 1.50–1.55 (1H, m, C(4)CH^AH^B), 2.53–2.64 (1H, m, C(4)H), 2.81 (1H, p, *J* 7.0, C(3)H), 6.18 (1H, d, *J* 5.8, C(5)H); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ_C: 11.3 (C(3)CH₃), 14.0 (CH₃), 22.4 (CH₃CH₂), 26.0 (CH₃(CH₂)₂CH₂), 28.8 (C(4)CH₂), 31.8 (CH₃CH₂CH₂), 35.3 (C(4)), 36.9 (C(3)), 90.1 (CCl₃), 109.2 (C(5)), 148.4 (C(6)), 169.9 (C(2)); *m/z* (APCI⁺) 319 ([M(³⁵Cl₂, ³⁷Cl)+H₃O]⁺, 62%), 317 ([M(³⁵Cl₃)+H₃O]⁺, 65%), 303 ([M(³⁵Cl, ³⁷Cl₂)+H]⁺, 30%), 301 ([M(³⁵Cl₂, ³⁷Cl)+H]⁺, 95%), 299 ([M(³⁵Cl₃)+H]⁺, 100%); HRMS (APCI⁺) C₁₂H₁₇³⁵Cl₃O₂⁺ [M+H]⁺ found 299.0366, requires 299.0367 (–0.3 ppm).

Epimerization of 14: In an NMR tube, 2-(2-((3*S*,4*S*)-2-oxo-4-phenyl-6-(trichloromethyl)-3,4-dihydro-2*H*-pyran-3-yl)ethyl)isoindoline-1,3-dione **14** (13.2 mg, 0.028 mmol, 1.0 eq) was dissolved in CD₂Cl₂ before Et₃N (5.9 μL, 0.42 mmol, 1.5 eq) was added. The ratio between the two diastereoisomers were monitored by ¹H NMR comparing the ratio between *syn*-C(5)H (δ_H 6.21 (1H, d, *J* 3.7)) and *anti*-C(5)H (δ_H 6.45 (1H, d, *J* 6.9)). Chiral HPLC OD-H (97:3 hexane : IPA, flow rate 1.0 mL·min^{–1}, 211 nm, 30 °C) *syn*: t_R minor: 34.3 min, t_R major: 42.2 min, >99% ee, *anti*: t_R major: 51.3 min, t_R minor: 59.2 min, >99% ee.

General Procedure for the NHC-catalyzed redox [4+2]-hetero-Diels-Alder reaction followed by ring-opening and aminolysis: The appropriate α-aryoxyaldehyde (0.30 mmol, 1.5 eq), the appropriate trichloromethyl ketone (0.20 mmol, 1.0 eq) and NHC precatalyst **11** (0.010 mmol, 5 mol% or 0.020 mmol, 10 mol%) were dissolved in anhydrous CH₂Cl₂ (2.7 mL). Et₃N (0.30 mmol, 1.5 eq) was added and the reaction mixture was stirred at rt until complete by TLC analysis. The mixture was diluted in EtOAc (10 mL) and washed with water (10 mL × 2), sodium bisulfite aq. 40% (10 mL × 2), and brine (10 mL × 2). The organic layer was dried over MgSO₄, filtered and concentrated. The crude *syn*-dihydropyranone was dissolved in anhydrous CH₂Cl₂ (6.6 mL) and benzylamine (60 mmol, 300 eq, 6.6 mL) was added. The reaction mixture was stirred at rt for 16 h before being

diluted in EtOAc (20 mL) and washed with 1 M HCl (20 mL $\times$ 3), sat. aq. NaHCO₃ (20 mL $\times$ 3) and brine (20 mL $\times$ 3). The organic layer was dried over MgSO₄, filtered and concentrated to give the crude product that was triturated in Et₂O then dispersed in CHCl₃ and concentrated to give the desired diamide.

(2*S*,3*S*)-*N*¹,*N*⁵-Dibenzyl-2-methyl-3-phenylpentanediamide (**21**). Following the general procedure, 1-oxopropan-2-yl 4-nitrobenzoate **10** (67 mg, 0.30 mmol), (*E*)-1,1,1-trichloro-4-phenylbut-3-en-2-one **1** (50 mg, 0.20 mmol), NHC precatalyst **11** (3.7 mg, 0.010 mmol) and Et₃N (42 μ L, 0.30 mmol) in anhydrous CH₂Cl₂ (2.7 mL) at rt for 3.5 h gave a crude orange solid (>95:5 dr). The crude was stirred in anhydrous CH₂Cl₂ (6.6 mL) with benzylamine (6.6 mL, 60 mmol) at rt for 16 h to give a crude beige solid (dr>95:5) that was triturated in Et₂O to give the title compound (70 mg, 85%) as a white solid. mp 172–174 °C; [α]_D²⁰ –8.7 (*c* 0.53, CHCl₃); Chiral HPLC AD-H (90:10 hexane : IPA, flow rate 1.0 mL·min^{–1}, 211 nm, 30 °C) *t*_R minor: 15.3 min, *t*_R major: 19.1 min, >99% ee; *v*_{max} (film, cm^{–1}) 3283 (N–H), 3258 (N–H), 1636 (C=O), 1558 (N–C=O), 1541 (N–C=O), 1495, 1454, 1435; ¹H NMR (400 MHz, CDCl₃) δ _H: 1.20 (3H, d, *J* 6.9, C(2)CH₃), 2.48 (1H, dd, *J* 13.8, 8.6, C(4)*H*^A*H*^B), 2.67 (1H, p, *J* 7.0, C(2)*H*), 2.91 (1H, dd, *J* 13.8, 6.9, C(4)*H*^A*H*^B), 3.36 (1H, q, *J* 7.7, C(3)*H*), 4.14 (1H, dd, *J* 14.7, 5.2, N¹CH^A*H*^B), 4.24 (1H, dd, *J* 14.9, 5.4, N⁵CH^A*H*^B), 4.31 (1H, dd, *J* 14.7, 6.1, N¹CH^A*H*^B), 4.38 (1H, dd, *J* 14.8, 6.1, N⁵CH^A*H*^B), 5.58 (1H, br t, *J* 5.0, N¹*H*), 6.10 (1H, br t, *J* 5.0, N⁵*H*), 6.87–6.96 (3H, dd, *J* 6.6, 2.8, Ar*H*), 6.97–7.02 (3H, m, Ar*H*), 7.11–7.18 (3H, m, Ar*H*), 7.19–7.26 (8H, m); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ _C: 16.0 (C(2)CH₃), 40.5 (C(4)), 43.3 (NCH₂), 43.4 (NCH₂), 45.7 (C(2)), 46.4 (C(3)), 127.1 (ArCH), 127.27 (ArCH), 127.33 (ArCH), 127.5 (ArCH), 127.7 (ArCH), 128.3 (ArCH), 128.6 (ArCH), 137.9 (NCH₂ArC(1)), 138.1 (NCH₂ArC(1)), 141.3 (C(3)ArC), 171.4 (C(5)), 174.0 (C(1)); *m/z* (NSI⁺) 823 ([2M+Na]⁺, 44%), 423 ([M+Na]⁺, 42%), 401 ([M+H]⁺, 100%); HRMS (NSI⁺) C₂₆H₂₉O₂N₂ [M+H]⁺ found 401.2221, requires 401.2224 (–0.6 ppm).

(2*S*,3*S*)-Methyl 6,6,6-trichloro-2-methyl-5-oxo-3-phenylhexanoate (**22**) and (2*S*,3*S*)-Dimethyl 2-methyl-3-phenylpentanedioate (**23**). 1-Oxopropan-2-yl 4-nitrobenzoate **10** (0.30 mmol, 67 mg, 1.5 eq), (*E*)-1,1,1-trichloro-4-phenylbut-3-en-2-one **1** (0.20 mmol, 50 mg, 1.0 eq) and NHC precatalyst **11** (0.010 mmol, 3.7 mg, 5 mol%) were dissolved in anhydrous CH₂Cl₂ (2.7 mL). Et₃N (0.30 mmol, 42 μ L, 1.5 eq) was added and the reaction mixture was stirred at rt for 3.5 h. The mixture was diluted in EtOAc (10 mL) and washed with water (10 mL $\times$ 2), sodium bisulfite aq. 40% (10 mL $\times$ 2) and brine (10 mL $\times$ 2). The organic layer was dried with MgSO₄, filtered and concentrated to give a crude orange solid (>95:5 dr). The crude was dissolved in anhydrous CH₂Cl₂ (2.4 mL) with MeOH (60 mmol, 2.4 mL, 300 eq) and DMAP (0.04 mmol, 5.0 mg, 20 mol%). The reaction mixture was stirred at rt for 16 h before being concentrated to give a crude orange oil (>95:5 dr) that was purified by flash silica column chromatography (98:2 to 90:10 hexane: EtOAc) to give:

22 (35 mg, 50%) as a colourless oil. $[\alpha]_D^{20}$ -17.3 (*c* 1.60, CHCl₃); Chiral HPLC AD-H (99:1 hexane : IPA, flow rate 1.0 mL $\cdot$ min⁻¹, 211 nm, 30 $^{\circ}$ C) *t*_R minor: 8.0 min, *t*_R major: 9.7 min, >99% ee; $\nu_{\max}$ (film, cm⁻¹) 1734 (C=O), 1456, 1198, 1167; ¹H NMR (400 MHz, CDCl₃) δ_H : 1.23 (3H, d, *J* 7.0, C(2)CH₃), 2.86 (1H, p, *J* 7.0, C(2)H), 3.49 (2H, dd, *J* 6.9, 2.7, C(4)H₂), 3.52 (3H, s, C(1)OCH₃), 3.54–3.62 (1H, m, C(3)H), 7.17–7.24 (3H, m, ArH), 7.24–7.31 (2H, m, ArH); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ_C : 14.8 (C(2)CH₃), 36.8 (C(4)), 44.0 (C(3)), 44.7 (C(2)), 51.6 (C(1)OCH₃), 96.2 (C(6)), 127.3 (ArCH), 128.1 (ArCH $\times$ 2), 128.4 (ArCH $\times$ 2), 140.3 (C(3)ArC(1)), 174.9 (C(1)), 188.7 (C(5)); *m/z* (APCI⁺) 356 ([M(³⁵Cl₂,³⁷Cl)+NH₄]⁺, 34%), 354 ([M(³⁵Cl₃)+NH₄]⁺, 34%), 341 ([M(³⁵Cl,³⁷Cl₂)+H]⁺, 34%), 339 ([M(³⁵Cl₂,³⁷Cl)+H]⁺, 99%), 337 ([M(³⁵Cl₃)+H]⁺, 100%); HRMS (APCI⁺) C₁₄H₁₅O₃³⁵Cl₃ [M+H]⁺ found 337.0160, requires 337.0164 (+1.3 ppm).

23 (10 mg, 20%, 85% pure) as a yellow oil.^{35,36} $[\alpha]_{\text{D}}^{20} +0.46$ (*c* 0.44, CHCl₃); Chiral HPLC AD-H (99:1 hexane : IPA, flow rate 1.0 mL·min⁻¹, 211 nm, 30 °C) major diastereoisomer: *t*_R minor: 13.8 min, *t*_R major: 15.1 min, 98% ee, minor diastereoisomer: *t*_R minor: 12.3 min, *t*_R major: 13.0 min, >99% ee; *v*_{max} (film, cm⁻¹) 1734 (C=O), 1456, 1453, 1258, 1198, 1161; ¹H NMR (400 MHz, CDCl₃) δ_{H} : 1.18 (3H, d, *J* 7.0, C(2)CH₃), 2.69 (1H, dd, *J* 15.7, 9.7, C(4)H^AH^B), 2.74–2.87 (2H, m, C(4)H^AH^B and C(2)H), 3.41–3.48 (1H, m, C(3)H), 3.50 (3H, s, C(1)OCH₃), 3.54 (3H, s, C(5)OCH₃), 7.14–7.23 (3H, m, ArH), 7.24–7.30 (2H, m, ArH); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ_{C} : 14.4 (C(2)CH₃), 37.0 (C(4)), 44.5 (C(3)), 45.1 (C(2)), 51.5 (C(1)OCH₃), 51.6 (C(5)OCH₃), 126.9 (C(3)ArCH), 127.8 (C(3)ArCH × 2), 128.3 (C(3)ArCH × 2), 141.3 (C(3)ArC(1)), 172.4 C(5), 175.2 C(2); *m/z* (NSI⁺) 251 ([M+H]⁺, 100%); HRMS (NSI⁺) C₁₄H₁₉O₄ [M+H]⁺ found 251.1279, requires 251.1278 (+0.5 ppm).

(2*S*,3*S*)-Benzyl 5-(benzylamino)-2-methyl-5-oxo-3-phenylpentanoate (**24**). 1-Oxopropan-2-yl 4-nitrobenzoate **10** (0.30 mmol, 67 mg, 1.5 eq), (*E*)-1,1,1-trichloro-4-phenylbut-3-en-2-one **1** (0.20 mmol, 50 mg, 1.0 eq) and NHC precatalyst **11** (0.010 mmol, 3.7 mg, 5 mol%) were dissolved in anhydrous CH₂Cl₂ (2.7 mL). Et₃N (0.30 mmol, 42 μ L, 1.5 eq) was added and the reaction mixture was stirred at rt for 3.5 h. The mixture was diluted in EtOAc (10 mL) and washed with water (10 mL × 2), sodium bisulfite aq. 40% (10 mL × 2), and brine (10 mL × 2). The organic layer was dried over MgSO₄, filtered and concentrated to give a crude orange solid (77 mg, >95:5 dr). The crude was dissolved in anhydrous CH₂Cl₂ (6.6 mL) with BnOH (60 mmol, 6.6 mL, 300 eq) and DMAP (0.04 mmol, 5 mg, 20 mol%). The reaction mixture was stirred at rt for 16 h before being concentrated. Excess BnOH was removed by Kugelrohr distillation to give a crude orange oil (105 mg, >95:5 dr). The oil was stirred in anhydrous CH₂Cl₂ (2.6 mL) with benzylamine (2.6 mL, 0.24 mmol, 1.2 eq) at rt for 16 h. The reaction mixture was diluted in EtOAc (20 mL) and wash with 1 M HCl (20 mL × 3), sat. aq. NaHCO₃ (20 mL × 3) and brine (20 mL × 3). The organic layer was dried over MgSO₄, filtered and

concentrated to give a crude orange oil (105 mg, >95:5 dr) that was purified by Biotage® Isolera™ 4 [SNAP Ultra 10 g, 36 mL min⁻¹, hexane : EtOAc (80:20 1 CV, 80:20 to 50:50 15 CV, 50:50 5 CV)] to give the title compound (26 mg, 32%) as a yellow solid. mp 98–100 °C; $[\alpha]_D^{20} +6.92$ (*c* 0.52, CHCl₃); Chiral HPLC AD-H (90:10 hexane : IPA, flow rate 1.0 mL·min⁻¹, 211 nm, 30 °C) *t*_R minor: 19.7 min, *t*_R major: 26.2 min, >99% ee; *v*_{max} (film, cm⁻¹) 3319, 3269, 1720 (C(1)=O), 1643 (C(5)=O), 1549 (N–C=O), 1495, 1454, 1256; ¹H NMR (400 MHz, CDCl₃) δ_H : 1.24 (3H, d, *J* 7.0, C(2)CH₃), 2.44 (1H, dd, *J* 14.0, 9.8, C(4)H^AH^B), 2.79 (1H, dd, *J* 14.0, 5.6, C(4)H^AH^B), 2.82–2.92 (1H, m, C(2)H), 3.40–3.50 (1H, m, C(3)H), 4.18 (1H, dd, *J* 14.8, 5.3, NCH^AH^B), 4.34 (1H, dd, *J* 14.8, 6.2, NCH^AH^B), 4.88 (1H, d, *J* 12.3, OCH^AH^B), 4.93 (1H, d, *J* 12.3, OCH^AH^B), 5.51 (1H, t, *J* 5.1, NH), 6.87–6.94 (2H, m, ArH), 7.09–7.17 (4H, m, ArH), 7.18–7.25 (6H, m, ArH), 7.26–7.32 (3H, m, ArH); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ_C : 15.3 (C(2)CH₃), 40.5 (C(4)), 43.4 (NCH₂), 44.8 (C(2)), 45.8 (C(3)), 66.2 (OCH₂), 127.1 (ArCH), 127.3 (ArCH), 127.5 (ArCH), 128.1 (ArCH), 128.2 (ArCH), 128.48 (ArCH), 128.54 (ArCH), 135.7 (OCH₂ArC(1)), 137.9 (NCH₂ArC(1)), 141.1 (C(3)ArC(1)) 170.9 (C(5)), 174.6 (C(1)); *m/z* (NSI⁺) 424 ([M+Na]⁺, 33%), 402 ([M+H]⁺, 100%); HRMS (NSI⁺) C₂₆H₂₈O₃N₁ [M+H]⁺ found 402.2062, requires 402.2064 (–0.4 ppm).

(2*S*,3*S*)-*N*¹,*N*⁵-Dibenzyl-2-butyl-3-phenylpentanediamide (**25**). Following the general procedure, 1-oxohexan-2-yl 4-nitrobenzoate (80 mg, 0.30 mmol), (*E*)-1,1,1-trichloro-4-phenylbut-3-en-2-one **1** (50 mg, 0.20 mmol), NHC precatalyst **11** (7.4 mg, 0.020 mmol) and Et₃N (42 μ L, 0.30 mmol) in anhydrous THF (2.7 mL) at rt for 3 h gave a crude brown-green oil (>95:5 dr). The crude was stirred in anhydrous CH₂Cl₂ (6.6 mL) with benzylamine (6.6 mL, 60 mmol) at rt for 16 h to give a crude beige solid (>95:5 dr) that was triturated in Et₂O to give the title compound (78 mg, 89%) as a white solid. mp 205–207 °C; $[\alpha]_D^{20} -21.6$ (*c* 0.63, CHCl₃); Chiral HPLC AD-H (90:10 hexane : IPA, flow rate 1.0 mL·min⁻¹, 211 nm, 30 °C) *t*_R minor: 11.9 min, *t*_R major: 17.7 min, >99% ee; *v*_{max} (film, cm⁻¹) 3279 (N–H), 3252 (N–

H), 1636 (C=O), 1558 (N–C=O), 1495, 1454; ^1H NMR (400 MHz, CDCl_3) δ_{H} : 0.87 (3H, t, J 6.9, CH_3), 1.19–1.34 (4H, m, $\text{C}(2)\text{CH}_2(\text{CH}_2)_2$), 1.52–1.60 (2H, m, $\text{C}(2)\text{CH}_2$), 2.41–2.51 (2H, m, $\text{C}(2)\text{H}$ and $\text{C}(4)\text{H}^{\text{A}}\text{H}^{\text{B}}$), 2.89 (1H, dd, J 13.8, 7.0, $\text{C}(4)\text{H}^{\text{A}}\text{H}^{\text{B}}$), 3.38 (1H, q, J 8.0, $\text{C}(3)\text{H}$), 4.13 (1H, dd, J 14.7, 5.1, $\text{N}^1\text{CH}^{\text{A}}\text{H}^{\text{B}}$), 4.26 (1H, dd, J 14.8, 5.4, $\text{N}^5\text{CH}^{\text{A}}\text{H}^{\text{B}}$), 4.30 (1H, dd, J 14.8, 6.2, $\text{N}^1\text{CH}^{\text{A}}\text{H}^{\text{B}}$), 4.36 (1H, dd, J 14.8, 6.1, $\text{N}^5\text{CH}^{\text{A}}\text{H}^{\text{B}}$), 5.48 (1H, t, J 5.3, N^1H), 5.96 (1H, t, J 5.1, N^5H), 6.90–6.95 (2H, m, ArH), 6.98–7.03 (2H, m, ArH), 7.11–7.16 (2H, m, ArH), 7.19–7.26 (9H, m, ArH); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) 14.0 (CH_3), 22.7 (CH_2), 29.8 (CH_2), 30.2 ($\text{C}(2)\text{CH}_2$), 40.7 ($\text{C}(4)$), 43.3 (NCH_2), 43.5 (NCH_2), 45.3 ($\text{C}(3)$), 52.2 ($\text{C}(2)$), 127.0 (ArCH), 127.28 (ArCH), 127.32 (ArCH), 127.6 ($\text{ArCH} \times 2$), 127.8 ($\text{ArCH} \times 2$), 128.3 ($\text{ArCH} \times 2$), 128.50 ($\text{ArCH} \times 2$), 128.53 ($\text{ArCH} \times 2$), 128.6 ($\text{ArCH} \times 2$), 138.0 (NCH_2ArC), 138.1 (NCH_2ArC), 141.4 ($\text{C}(3)\text{ArC}(1)$), 171.4 ($\text{C}(5)$), 173.2 ($\text{C}(1)$); m/z (NSI^+) 443 ($[\text{M}+\text{H}]^+$, 100%); HRMS (NSI^+) $\text{C}_{29}\text{H}_{35}\text{O}_2\text{N}_2$ $[\text{M}+\text{H}]^+$ found 443.2692, requires 443.2653 (–0.2 ppm).

(2S,3S)-N¹,N⁵-Dibenzyl-3-(4-fluorophenyl)-2-(4-methoxybenzyl)pentanediamide **(26)**.

Following the general procedure, 1-(4-methoxyphenyl)-3-oxopropan-2-yl 4-nitrobenzoate (99 mg, 0.30 mmol), (*E*)-1,1,1-trichloro-4-(4-fluorophenyl)but-3-en-2-one (54 mg, 0.20 mmol), NHC precatalyst **11** (3.7 mg, 0.010 mmol) and Et_3N (42 μL , 0.30 mmol) in anhydrous CH_2Cl_2 (2.7 mL) at rt for 6 h gave a crude brown oil (>95:5 dr). The crude was stirred in anhydrous CH_2Cl_2 (6.6 mL) with benzylamine (6.6 mL, 60 mmol) at rt for 16 h to give a crude yellow solid (>95:5 dr) that was triturated in Et_2O to give the title compound (61 mg, 60%) as a beige solid. mp 221–223 °C; $[\alpha]_{\text{D}}^{20}$ –23.9 (c 0.41, DMSO); Chiral HPLC AD-H (90:10 hexane : IPA, flow rate 1.5 mL·min^{–1}, 211 nm, 40 °C) t_{R} major: 16.9 min, t_{R} minor: 21.2 min, 98% ee; ν_{max} (film, cm^{–1}) 3343 (N–H), 3296 (N–H), 1639 (C=O), 1553 (N–C=O), 1454, 1422, 1356; ^1H NMR (700 MHz, CDCl_3) δ_{H} : 2.52 (1H, dd, J 14.0, 8.5, $\text{C}(4)\text{H}^{\text{A}}\text{H}^{\text{B}}$), 2.71–2.78 (1H, m, $\text{C}(2)\text{H}$), 2.77–2.83 (1H, m, $\text{C}(2)\text{CH}^{\text{A}}\text{H}^{\text{B}}$), 2.85–2.93 (2H, m, $\text{C}(4)\text{H}^{\text{A}}\text{H}^{\text{B}}$ and $\text{C}(2)\text{CH}^{\text{A}}\text{H}^{\text{B}}$), 3.48 (1H, q, J 8.1, $\text{C}(3)\text{H}$), 3.79 (3H, s, OCH_3), 4.00 (1H, dd, J 14.8, 5.6,

$N^1CH^AH^B$), 4.12 (1H, dd, J 14.9, 6.0, $N^1CH^AH^B$), 4.28 (1H, dd, J 14.7, 5.5, $N^5CH^AH^B$), 4.38 (1H, dd, J 14.7, 6.0, $N^5CH^AH^B$), 5.41 (1H, t, J 5.6, N^1H), 5.78 (1H, t, J 5.1, N^5H), 6.67–6.71 (2H, m, ArH), 6.75–6.80 (2H, m, ArH), 6.89–6.95 (1H, m, ArH), 7.00–7.03 (1H, m, ArH), 7.03–7.06 (1H, m, ArH), 7.12–7.18 (4H, m, ArH), 7.24–7.28 (6H, m, ArH); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ_C : 35.7 (C(2)CH₂), 40.7 (C(4)), 43.0 (N^1CH_2), 43.5 (N^5CH_2), 44.4 (C(3)), 54.4 (C(2)), 55.2 (OCH₃), 113.9 (C(2)CH₂ArC(3,5)), 115.3 (d, J_{CF} 21.2, C(3)ArC(3,5)), 127.2 (NCH₂ArC(4)), 127.5 (NCH₂ArC(4) and N^1CH_2 ArC(2,6)), 127.6 (N^5CH_2 ArC(2,6)), 128.4 (NCH₂ArC(3,5)), 128.6 (NCH₂ArC(3,5)), 129.87 (C(2)ArC(2,6)), 129.93 (d, J_{CF} 7.8, C(3)ArC(2,6)), 131.1 (C(2)ArC(1)), 137.0 (d, J_{CF} 3.0, C(3)ArC(1)), 137.8 (NCH₂ArC), 137.9 (NCH₂ArC), 158.2 (C(2)CH₂ArC(4)), 161.9 (d, J_{CF} 245.3, C(3)ArC(4)), 170.9 (C(5)), 172.2 (C(1)); ^{19}F NMR (376 MHz, $CDCl_3$) δ_F : –115.57 (s, C(3)ArC(4)F); m/z (NSI⁺) 547 ([M+Na]⁺, 43%), 525 ([M+H]⁺, 100%); HRMS (NSI⁺) C₃₃H₃₄O₃N₂F [M+H]⁺ found 525.2554, requires 525.2548 (+1.1 ppm).

(2*S*,3*S*)-2-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-*N*¹,*N*⁵-dibenzyl-3-phenylpentanediamide (**27**).

Following the general procedure, 1-(benzo[*d*][1,3]dioxol-5-yl)-3-oxopropan-2-yl 4-nitrobenzoate (103 mg, 0.30 mmol), (*E*)-1,1,1-trichloro-4-phenylbut-3-en-2-one **1** (50 mg, 0.20 mmol), NHC precatalyst **11** (3.7 mg, 0.010 mmol) and Et₃N (42 μ L, 0.30 mmol) in anhydrous CH₂Cl₂ (2.7 mL) at rt for 27 h gave a crude brown oil (85:15 dr). The crude was stirred in anhydrous CH₂Cl₂ (6.6 mL) with benzylamine (6.6 mL, 60 mmol) at rt for 16 h to give a crude brown solid (80:20 dr) that was triturated in Et₂O to give the title compound (50 mg, 48%) as an off-white solid. mp 198 °C (*dec*); $[\alpha]_D^{20}$ –39.4 (*c* 0.18, CHCl₃); No ee could be determined by either chiral HPLC or chiral GC; ν_{max} (film, cm^{–1}) 3296 (N–H), 1643 (C=O), 1553 (N–C=O), 1499, 1487, 1354; 1H NMR (400 MHz, $CDCl_3$) δ_H : 2.57 (1H, dd, J 14.0, 8.3, C(4)*H*^A*H*^B), 2.74–2.84 (2H, m, C(2)*H* and C(2)*CH*^A*H*^B), 2.84–2.96 (2H, m, C(2)*H*^A*H*^B and C(4)*H*^A*H*^B), 3.43–3.52 (1H, m, C(3)*H*), 4.01–4.15 (2H, m, NCH₂), 4.26–4.40

(2H, m, NCH₂), 5.43 (1H, t, *J* 5.2, NH), 5.83 (1H, t, *J* 5.3, NH), 5.88–5.94 (2H, m, OCH₂O), 6.56–6.62 (1H, m, C(2)CH₂ArH), 6.62–6.70 (2H, m, C(2)CH₂ArH), 6.70–6.75 (2H, m, ArH), 6.99–7.05 (2H, m, ArH), 7.12–7.21 (5H, m, ArH), 7.22–7.25 (6H, m, ArH); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ_C: 36.2 (C(2)CH₂), 40.5 (C(4)), 43.0 (NCH₂), 43.5 (NCH₂), 45.2 (C(3)), 54.4 (C(2)), 100.8 (OCH₂O), 109.3 (C(2)CH₂ArCH), 121.9 (C(2)CH₂ArCH), 127.1 (ArCH × 2), 127.4 (ArCH), 127.5 (ArCH × 2), 127.6 (ArCH × 2), 128.3 (ArCH × 2), 128.4 (ArCH × 2), 128.6 (ArCH × 2), 128.6 (ArCH × 2), 133.1 (C(2)CH₂ArC(1)), 137.8 (NCH₂ArC(1)), 138.0 (NCH₂ArC(1)), 141.2 (C(3)ArC(1)), 146.0 (C(2)CH₂ArC(2a or 6a)), 147.6 (C(2)CH₂ArC(6a or 2a)), 171.2 (C=O), 172.2 (C=O); *m/z* (NSI⁺) 543 ([M+Na]⁺, 31%), 521 ([M+H]⁺, 100%); HRMS (NSI⁺) C₃₃H₃₃O₄N₂ [M+H]⁺ found 521.2440, requires 521.2435 (+1.0 ppm).

(2*S*,3*S*)-*N*¹,*N*⁵-Dibenzyl-3-(4-methoxyphenyl)-2-methylpentanediamide (**28**). Following the general procedure, 1-oxopropan-2-yl 4-nitrobenzoate **10** (67 mg, 0.30 mmol), (*E*)-1,1,1-trichloro-4-(4-methoxyphenyl)but-3-en-2-one (56 mg, 0.20 mmol), NHC precatalyst **11** (3.7 mg, 0.010 mmol) and Et₃N (42 μL, 0.30 mmol) in anhydrous CH₂Cl₂ (2.7 mL) at rt for 22 h gave a crude yellow solid (>95:5 dr). The crude was stirred in anhydrous CH₂Cl₂ (6.6 mL) with benzylamine (6.6 mL, 60 mmol) at rt for 16 h to give a crude light yellow solid (>95:5 dr) that was triturated in Et₂O to give the title compound (64 mg, 75%) as a white solid. mp 176–178 °C; [α]_D²⁰ –12.8 (*c* 0.56, CHCl₃); Chiral HPLC AD-H (90:10 hexane : IPA, flow rate 1.0 mL·min⁻¹, 211 nm, 30 °C) *t*_R minor: 18.1 min, *t*_R major: 24.8 min, >99% ee; *v*_{max} (film, cm⁻¹) 3273 (N–H), 1636 (C=O), 1558 (N–C=O), 1508, 1454, 1429, 1350, 1242; ¹H NMR (400 MHz, CDCl₃) δ_H: 1.22 (3H, d, *J* 6.9, C(2)CH₃), 2.46 (1H, dd, *J* 13.8, 8.8, C(4)H^AH^B), 2.64 (1H, p, *J* 6.9, C(2)H), 2.91 (1H, dd, *J* 13.8, 6.8, C(4)H^AH^B), 3.32 (1H, q, *J* 8.0, C(3)H), 3.81 (3H, s, OCH₃), 4.15 (1H, dd, *J* 14.7, 5.1, N¹CH^AH^B), 4.25 (1H, dd, *J* 14.9, 5.3, N⁵CH^AH^B), 4.37 (1H, dd, *J* 14.8, 6.4, N¹CH^AH^B), 4.42 (1H, dd, *J* 14.9, 6.3, N⁵CH^AH^B), 5.60

(1H, t, *J* 5.5, N¹H), 6.08 (1H, t, *J* 5.4, N⁵H), 6.74–6.82 (2H, m, C(3)ArC(3,5)*H*), 6.91–6.98 (2H, m, Ar*H*), 6.99–7.05 (2H, m, Ar*H*), 7.05–7.11 (2H, m, C(3)ArC(2,6)*H*), 7.21–7.28 (6H, m, Ar*H*); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ_C: 16.0 (C(2)CH₃), 40.8 (C(4)), 43.3 (N¹CH₂), 43.4 (N⁵CH₂), 45.6 (C(3)), 45.9 (C(2)), 55.2 (OCH₃), 113.9 (C(3)ArC(3,5)), 127.26 (ArCH), 127.33 (ArCH), 127.5 (ArCH), 127.7 (ArCH), 128.5 (ArCH), 129.2 (C(3)ArC(2,6)), 133.2 (C(3)ArC(1)), 137.9 (NCH₂ArC(1)), 138.1 (NCH₂ArC(1)), 158.6 (C(3)ArC(4)), 171.5 (C(5)), 174.1 (C(1)); *m/z* (NSI⁺) 883 ([2M+Na]⁺, 30%), 453 ([M+Na]⁺, 58%), 431 ([M+H]⁺, 100%); HRMS (NSI⁺) C₂₇H₃₁O₃N₂ [M+H]⁺ found 431.2328, requires 431.2329 (−0.3 ppm).

(2*S*,3*S*)-*N*¹,*N*⁵-Dibenzyl-2-methyl-3-(2-nitrophenyl)pentanediamide (**29**). Following the general procedure, 1-oxopropan-2-yl 4-nitrobenzoate **10** (67 mg, 0.30 mmol), (*E*)-1,1,1-trichloro-4-(2-nitrophenyl)but-3-en-2-one (59 mg, 0.20 mmol), NHC precatalyst **11** (3.7 mg, 0.010 mmol) and Et₃N (42 μL, 0.30 mmol) in anhydrous CH₂Cl₂ (2.7 mL) at rt for 2 h gave a crude brown oil (>95:5 dr). The crude was stirred in anhydrous CH₂Cl₂ (6.6 mL) with benzylamine (6.6 mL, 60 mmol) at rt for 16 h to give a crude light yellow solid (approx. 90:10 dr) that was triturated in Et₂O to give the title compound (60 mg, 68%) as a brown solid. mp 176 °C (*dec.*); [α]_D²⁰ −2.3 (*c* 0.61, CHCl₃); Chiral HPLC AD-H (95:5 hexane : IPA, flow rate 1.5 mL·min^{−1}, 211 nm, 30 °C) *t*_R major: 63.9 min, *t*_R minor: 70.9 min, 99% ee; *v*_{max} (film, cm^{−1}) 3292 (N–H), 1636 (C=O), 1558 (N–C=O), 1541 (N–C=O), 1522, 1456, 1354; ¹H NMR (400 MHz, CDCl₃) δ_H: 1.21 (3H, d, *J* 6.9, C(2)CH₃), 2.60 (1H, dd, *J* 15.0, 9.3, C(4)*H*^A*H*^B), 2.80 (1H, p, *J* 7.1, C(2)*H*), 2.87 (1H, dd, *J* 15.0, 5.9, C(4)*H*^A*H*^B), 3.94–4.04 (1H, m, C(3)*H*), 4.21–4.34 (4H, m, NCH₂ × 2), 6.06 (1H, t, *J* 4.9, NH), 6.31 (1H, t, *J* 5.4, NH), 6.98–7.08 (4H, m, Ar*H*), 7.18–7.25 (5H, m, Ar*H*), 7.2–7.36 (1H, m, C(3)ArC(5)*H*), 7.36–7.41 (1H, m, C(3)ArC(3)*H*), 7.42–7.49 (1H, m, C(3)ArC(4)*H*), 7.66 (2H, dd, *J* 8.1, 1.2, C(3)ArC(6)*H*); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ_C: 15.1 (C(2)CH₃), 38.6 (C(4)), 43.4 (NCH₂), 43.5 (NCH₂), 45.2 (C(2)), 124.6 (C(3)ArC(6)), 127.3 (ArCH), 127.4 (ArCH), 127.6

(ArCH), 127.6 (ArCH), 128.6 (ArCH), 132.6 (C(3)ArC(4)), 135.9 (C(3)ArC(1)), 137.9 (NCH₂ArC(1)), 138.1 (NCH₂ArC(1)), 150.3 (C(3)ArC(2)), 170.4 (C(5)), 173.8 (C(1)), C(3) and C(3)ArC(3) not observed; m/z (NSI⁺) 468 ([M+Na]⁺, 33%), 446 ([M+H]⁺, 100%); HRMS (NSI⁺) found C₂₆H₂₈O₄N₃ found 446.2072, requires 446.2074 (−0.5 ppm).

(2*S*,3*S*)-*N*¹,*N*⁵-Dibenzyl-3-(4-fluorophenyl)-2-methylpentanediamide (**30**). Following the general procedure, 1-oxopropan-2-yl 4-nitrobenzoate **10** (67 mg, 0.30 mmol), (*E*)-1,1,1-trichloro-4-(4-fluorophenyl)but-3-en-2-one (54 mg, 0.20 mmol), NHC precatalyst **11** (3.7 mg, 0.010 mmol) and Et₃N (42 μL, 0.30 mmol) in anhydrous CH₂Cl₂ (2.7 mL) at rt for 3 h gave a crude brown oil (>95:5 dr). The crude was stirred in anhydrous CH₂Cl₂ (6.6 mL) with benzylamine (6.6 mL, 60 mmol) at rt for 16 h to give a crude beige solid (>95:5 dr) that was triturated in Et₂O to give the title compound (76 mg, 90%) as a white solid. mp 204–206 °C; $[\alpha]_D^{20}$ −2.5 (*c* 0.52, DMSO); Chiral HPLC AD-H (90:10 hexane : IPA, flow rate 1.0 mL·min^{−1}, 211 nm, 30 °C) *t*_R minor: 12.8 min, *t*_R major: 19.1 min, >99% ee; $\nu_{\max}$ (film, cm^{−1}) 3292 (N–H), 1645 (C=O), 1541 (N–C=O), 1508, 1495, 1456, 1219; ¹H NMR (400 MHz, CDCl₃) δ_H : 1.22 (3H, d, *J* 6.9, C(2)CH₃), 2.45 (1H, dd, *J* 13.8, 8.7, C(4)*H*^A*H*^B), 2.65 (1H, p, *J* 7.0, C(2)*H*), 2.91 (1H, dd, *J* 13.8, 6.8, C(4)*H*^A*H*^B), 3.38 (1H, q, *J* 8.0, C(3)H), 4.16 (1H, dd, *J* 14.7, 5.1, N¹CH^A*H*^B), 4.26 (1H, dd, *J* 14.7, 5.3, N⁵CH^A*H*^B), 4.37 (1H, dd, *J* 15.1, 6.8, N¹CH^A*H*^B), 4.42 (1H, dd, *J* 14.9, 6.4, N⁵CH^A*H*^B), 5.61 (1H, t, *J* 5.5, N¹*H*), 6.01 (1H, t, *J* 5.5, N⁵*H*), 6.88–6.94 (1H, m, C(3)ArC(3)*H*), 6.94–6.98 (2H, m, Ar*H* ×1 and C(3)ArC(5)*H*), 7.00–7.06 (2H, m, Ar*H*), 7.09–7.16 (2H, m, C(3)ArC(2,6)*H*), 7.23–7.28 (7H, m, Ar*H*); ¹³C{¹H} NMR (126 MHz, CDCl₃) δ_C : 16.1 (C(2)CH₃), 40.7 (C(4)), 43.3 (NCH₂), 43.5 (NCH₂), 45.7 (C(2)), 45.7 (C(3)), 115.3 (d, *J*_{CF} 21.1, C(2)ArC(3,5)), 127.4 (NCH₂ArC(4)), 127.5 (NCH₂ArC(4)), 127.6 (ArCH × 2), 127.7 (ArCH × 2), 128.6 (ArCH × 4), 129.8 (d, *J*_{CF} 7.9, C(3)ArC(2,6)), 136.9 (d, *J*_{CF} 3.1, C(3)ArC(1)), 137.8 (NCH₂ArC(1)), 138.0 (NCH₂ArC(1)), 161.9 (d, *J*_{CF} 245.3, C(3)ArC(4)), 171.2 (C(5)), 173.8 (C(1)); ¹⁹F (376 MHz,

CDCl_3) δ_{F} : -115.60 (s, C(3)ArC(4)F); m/z (NSI^+) 441 ($[\text{M}+\text{Na}]^+$, 51%), 419 ($[\text{M}+\text{H}]^+$, 100%); HRMS (NSI^+) $[\text{M}+\text{H}]^+$ $\text{C}_{26}\text{H}_{28}\text{O}_2\text{N}_2\text{F}$ found 419.2129, requires 419.2129 (-0.1 ppm).

(2*S*,3*S*)-*N*¹,*N*⁵-Dibenzyl-3-(furan-2-yl)-2-methylpentanediamide (**31**). Following the general procedure, 1-oxopropan-2-yl 4-nitrobenzoate **10** (67 mg, 0.30 mmol), (*E*)-1,1,1-trichloro-4-(furan-2-yl)but-3-en-2-one (48 mg, 0.20 mmol), NHC precatalyst **11** (3.7 mg, 0.010 mmol) and Et_3N (42 μL , 0.30 mmol) in anhydrous CH_2Cl_2 (2.7 mL) at rt for 3 h gave a crude brown crystallised oil (95:5 dr). The crude was stirred in anhydrous CH_2Cl_2 (6.6 mL) with benzylamine (6.6 mL, 60 mmol) at rt for 16 h to give a crude beige solid ($>95:5$ dr) that was triturated in Et_2O to give the title compound (58 mg, 75%) as a beige solid. mp $192\text{--}194$ $^\circ\text{C}$; $[\alpha]_{\text{D}}^{20}$ -1.4 (c 0.50, CHCl_3); Chiral HPLC AD-H (90:10 hexane : IPA, flow rate $1.0\text{ mL}\cdot\text{min}^{-1}$, 211 nm, 30 $^\circ\text{C}$) t_{R} major: 19.8 min, t_{R} minor: 27.6 min, $>99\%$ ee; ν_{max} (film, cm^{-1}) 3279 (N–H), 1645 (C=O), 1562 (N–C=O), 1541 (N–C=O), 1506, 1456; ^1H NMR (400 MHz, CDCl_3) δ_{H} : 1.19 (3H, d, J 7.0, C(2) CH_3), 2.53 (1H, dd, J 13.9, 8.5, C(4) $\text{H}^{\text{A}}\text{H}^{\text{B}}$), 2.71 (1H, p, J 7.0, C(2) H), 2.80 (1H, dd, J 13.9, 6.7, C(4) $\text{H}^{\text{A}}\text{H}^{\text{B}}$), 3.49–3.58 (1H, m, C(3) H), 4.25–4.36 (3H, m, N^1CH_2 and $\text{N}^5\text{CH}^{\text{A}}\text{H}^{\text{B}}$), 4.41 (1H, dd, J 14.8, 6.0, $\text{N}^5\text{CH}^{\text{A}}\text{H}^{\text{B}}$), 5.76 (1H, t, J 5.2, N^1H), 6.06–6.10 (1H, m, C(3)ArC(5) H), 6.15 (1H, t, J 4.9, N^5H), 6.25 (1H, dd, J 3.2, 1.9, C(3)ArC(4) H), 7.10–7.18 (4H, m, Ar H), 7.22 (1H, dd, J 1.8, 0.8, C(3)ArC(3) H), 7.23–7.32 (6H, m, Ar H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ_{C} : 15.2 (C(2) CH_3), 38.2 (C(4)), 39.8 (C(3)), 45.54 (NCH_2Ph), 45.55 (NCH_2Ph), 43.9 (C(2)), 107.3 (C(3)ArC(5)), 110.3 (C(3)ArC(4)), 127.4 (ArCH), 127.5 (ArCH), 127.7 (ArCH), 127.9 (ArCH), 128.60 (ArCH), 128.61 (ArCH), 138.0 ($\text{NCH}_2\text{ArC}(1)$), 138.2 ($\text{NCH}_2\text{ArC}(1)$), 141.4 (C(3)ArC(3)), 154.6 (C(3)ArC(1)), 171.1 (C(5)), 173.9 (C(1)); m/z (NSI^+) 413 ($[\text{M}+\text{Na}]^+$, 41%), 391 ($[\text{M}+\text{H}]^+$, 100%); HRMS (NSI^+) $\text{C}_{24}\text{H}_{27}\text{O}_3\text{N}_2$ $[\text{M}+\text{H}]^+$ found 391.2016, requires 391.2016 ($+0.0$ ppm).

(2*S*,3*S*)-*N*¹,*N*⁵,2-Tribenzyl-3-(furan-2-yl)pentanediamide (**32**). Following the general procedure, 1-oxo-3-phenylpropan-2-yl 4-nitrobenzoate (90 mg, 0.30 mmol), (*E*)-1,1,1-

trichloro-4-(furan-2-yl)but-3-en-2-one (48 mg, 0.20 mmol), NHC precatalyst **11** (3.7 mg, 0.010 mmol) and Et₃N (42 µL, 0.30 mmol) in anhydrous THF (2.7 mL) at rt for 4 h gave a crude brown oil (>95:5 dr). The crude was stirred in anhydrous CH₂Cl₂ (6.6 mL) with benzylamine (6.6 mL, 60 mmol) at rt for 16 h to give a crude orange solid (>95:5 dr) that was triturated in Et₂O to give the title compound (36 mg, 39%) as a off-white solid. mp 192–194 °C; $[\alpha]_{\text{D}}^{20}$ –17.3 (*c* 0.48, CHCl₃); Chiral HPLC AD-H (80:20 hexane : IPA, flow rate 1.5 mL·min^{–1}, 211 nm, 40 °C) *t*_R major: 5.6 min, *t*_R minor: 13.0 min, >99% ee; *v*_{max} (film, cm^{–1}) 3275 (N–H), 1638 (C=O), 1560 (N–C=O), 1533, 1495, 1452; ¹H NMR (400 MHz, CDCl₃) δ_{H} : 2.61 (1H, dd, *J* 14.0, 8.3, C(4)*H*^A*H*^B), 2.83–2.99 (4H, m, C(4)*H*^A*H*^B, C(2)*H*, C(2)CH₂), 3.59–3.68 (1H, m, C(3)*H*), 4.14 (1H, dd, *J* 14.8, 5.6, N¹CH^A*H*^B), 4.21 (1H, dd, *J* 14.8, 5.9, N¹CH^A*H*^B), 4.31–4.42 (2H, m, N⁵CH₂), 5.62 (1H, t, *J* 5.5, N¹*H*), 5.98 (1H, t, *J* 5.5, N⁵*H*), 6.12–6.17 (1H, m, C(3)ArC(5)*H*), 6.29 (1H, dd, *J* 3.2, 1.9, C(3)ArC(4)*H*), 6.84–6.90 (2H, m, Ar*H*), 7.10–7.17 (4H, m, Ar*H*), 7.17–7.21 (4H, m, Ar*H*), 7.21–7.25 (3H, m, Ar*H*), 7.26–7.33 (3H, m, Ar*H*); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ_{C} : 35.8 (C(2)CH₂), 38.2 (C(4)), 38.6 (C(3)), 43.3 (N¹CH₂), 43.6 (N⁵CH₂), 52.1 (C(2)), 107.5 (C(3)ArC(4)), 110.4 (C(3)ArC(5)), 126.4 (ArCH), 127.2 (ArCH), 127.4 (ArCH), 127.6 (ArCH × 2), 127.8 (ArCH × 2), 128.4 (ArCH × 2), 128.5 (ArCH × 2), 128.6 (ArCH × 2), 128.9 (ArCH × 2), 137.9 (NCH₂ArC(1)), 138.1 (NCH₂ArC(1)), 139.3 (C(2)CH₂ArC(1)), 141.4 (C(3)ArC(3)), 154.4 (C(3)ArC(1)), 170.9 (C(5)), 172.2 (C(1)); *m/z* (NSI⁺) 489 ([M+Na]⁺, 34%), 467 ([M+H]⁺, 100%); HRMS (NSI⁺) C₃₀H₃₁O₃N₂ [M+H]⁺ found 467.2326, requires 467.2329 (–0.7 ppm).

(2*S*,3*S*)-*N*¹,*N*⁵-Dibenzyl-2-methyl-3-pentylpentanediamide (**33**). Following the general procedure, 1-oxopropan-2-yl 4-nitrobenzoate **10** (67 mg, 0.30 mmol), (*E*)-1,1,1-trichloronon-3-en-2-one (56 mg, 0.20 mmol), NHC precatalyst **11** (7.4 mg, 0.020 mmol) and Et₃N (42 µL, 0.30 mmol) in anhydrous CH₂Cl₂ (2.7 mL) at rt for 24 h gave a crude brown oil (>95:5 dr). The crude was stirred in anhydrous CH₂Cl₂ (6.6 mL) with benzylamine (6.6 mL, 60 mmol) at

rt for 16 h to give a crude orange paste (>95:5 dr) that was triturated in Et₂O to give the title compound (21 mg, 26%) as a white solid. mp 168–170°C; $[\alpha]_D^{20} +15.0$ (c 0.40, CHCl₃); Chiral HPLC AD-H (90:10 hexane : IPA, flow rate 1.0 mL·min⁻¹, 211 nm, 40 °C) *t*_R minor: 5.3 min, *t*_R major: 5.8 min, >99% ee; *v*_{max} (film, cm⁻¹) 3287 (N–H), 1636 (C=O), 1541 (N–C=O), 1535 (N–C=O), 1454; ¹H NMR (400 MHz, CDCl₃) δ_H : 0.86 (3H, t, *J* 6.8, CH₃), 1.12 (3H, d, *J* 7.0, C(2)CH₃), 1.16–1.36 (7H, m, CH₃(CH₂)₃ and C(3)CH^AH^B), 1.43–1.53 (1H, m, C(3)CH^AH^B), 1.95–2.07 (1H, m, C(3)H), 2.22 (1H, dd, *J* 13.9, 6.1, C(4)H^AH^B), 2.29 (1H, dd, *J* 13.9, 8.0, C(4)H^AH^B), 2.50–2.59 (1H, m, C(2)H), 4.39–4.44 (4H, m, NCH₂ × 2), 6.14 (1H, t, *J* 4.8, N⁵H), 6.48 (1H, t, *J* 5.1, N¹H), 7.23–7.35 (10H, m, ArH); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ_C : 14.0 (C(2)CH₃), 14.1 (CH₃), 22.6 (CH₃CH₂), 27.3 (CH₃(CH₂)₂CH₂), 31.1 (C(3)CH₂), 31.9 (CH₃CH₂CH₂), 38.7 (C(4)), 40.0 (C(3)), 42.1 (C(2)), 43.4 (NCH₂), 43.5 (NCH₂), 127.4 (ArCH), 127.5 (ArCH), 127.7 (ArCH), 127.8 (ArCH), 128.7 (ArCH), 128.7 (ArCH), 138.4 (NCH₂ArC(1)), 138.6 (NCH₂ArC(1)), 172.9 (C(5)), 174.7 (C(1)); *m/z* (NSI⁺) ([2M+Na]⁺, 34%), 395 ([M+H]⁺, 100%); HRMS (NSI⁺) C₂₅H₃₅O₂N₂ [M+H]⁺ found 395.2690, requires 395.2693.

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Supporting Information: ¹H and ¹³C{¹H} NMR spectra and HPLC traces of all novel compounds. CIF file giving X-ray crystallographic data for **28**. This material is available free of charge *via* the Internet at <http://pubs.acs.org>.

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