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Supporting Information Placeholder

ABSTRACT: In this communication, we report the first example of dynamic kinetic asymmetric [3+2] annulation reaction of aminocyclopropanes with both enol ethers and aldehydes. Using a copper catalyst and a commercially available bisoxazoline ligand, cyclopentyl- and tetrahydrofuryl- amines were obtained in 69-97% yield and up to a 98:2 enantiomeric ratio using the same reaction conditions. The method gives access to important enantioc-enriched nitrogen building blocks for the synthesis of bioactive compounds.

The combination of nitrogen functionalities and cyclic structures is omnipresent in bioactive compounds. From the ten most sold pharmaceutical products based on small molecules in 2009, nine contain nitrogen atoms embedded in ring systems. Among the multitude of reported nitrogen-rich cyclic scaffolds, tetrahydrofurylamines and cyclopentylamines occupy a privileged position (Figure 1). Tetrahydrofurylamines are especially important in the form of aminosugars, such as aminodeoxyriboses 1, which are at the core of DNA and many bioactive synthetic nucleoside analogues. Cyclopentylamines are well-represented in bioactive compounds, such as the bicyclic drug Ramipril (2) used to treat hypertension and heart diseases.1 They are also at the core of numerous bioactive natural products, such as the antibiotic Pacytactamycin (3).2 A stereoselective synthetic access to tetrahydrofuranyl- and cyclopentylamines would be consequently highly valuable in order to discover new bioactive compounds.

Figure 1: Biomolecules and bioactive compounds containing an amino- tetrahydrofuran or cyclopentane ring.

Since 2010, our group has examined the use of donor-acceptor substituted aminocyclopropanes and aminocyclobutanes for the synthesis of nitrogen-rich molecules (Scheme 1, A).3 This approach is particularly attractive as the nitrogen atom plays a dual role: it is not only an essential structural element of the product, but also a steering group to control regioselective ring opening upon release of ring strain. Despite important progress in the use of donor-acceptor substituted cyclopropanes,4 only few examples on the use of aminocyclopropanes had been reported prior to our own work.5 In our hands, the ring-opening of aminocyclopropanes was highly successful for the inter- and intramolecular addition of nucleophiles,3a-c and the development of new annulation reactions, in particular for the synthesis of cyclopentyl- and tetrahydrofuryl- amines ((1) in Scheme 1, B).3d-e The reaction of enol ethers and ketones using a tin catalyst was enantiospecific, whereas the iron-catalyzed annulation of aldehydes gave racemic products.

Scheme 1: General strategy (A), previous work (B) and current work (C) to access nitrogen-rich building blocks.

An approach allowing the complete conversion of easily accessible racemic aminocyclopropanes into enantiopure cyclopentylamines—a dynamic kinetic asymmetric transformation (DYKAT)-6 would be much more straightforward. Such reactions have been realized for other classes of donor-acceptor cyclopro-
panes in the past,\textsuperscript{7} but have never been reported in the case of aminocyclopropanes (2) in Scheme 1, B). Furthermore, each class of substrates asked for the development of a unique catalytic system. The synthesis of cyclopentanes has been especially challenging. Success has been limited to the use of cyclic silyl enol ethers\textsuperscript{6} and indoles\textsuperscript{7\textdagger} as substrates by Tang and co-workers using a copper catalyst with specifically designed bisoxazoline ligands.

Herein, we would like to report the first successful dynamic kinetic asymmetric annulation of aminocyclopropanes with enol ethers and aldehydes (Scheme 1, C). Enantiomeric ratios up to 98:2 could be achieved with complete conversion of the aminocyclopropane starting materials using a simple commercially available bisoxazoline catalyst. In contrast to the only previously reported method for silyl enol ethers,\textsuperscript{7\textdagger} the transformation was especially successful for non-cyclic alkyl enol ethers. The same catalytic system could then be extended to the reaction of aminocyclopropanes with aldehydes to give tetrahydrofuranlamines with up to a 96:4 enantiomeric ratio. To the best of our knowledge, this is the first report of an enantioselective catalytic system working for the synthesis of both cyclopentanes and tetrahydrofurans. The obtained enantiopure chiral building blocks will be highly useful for the synthesis of new nitrogen-rich bioactive compounds.

We started our investigations by studying the annulation reaction between phthalimido-substituted dimethyl ester cyclopropane 4a and silyl enol ether 5a, as this transformation had already been studied in our previous work involving enantiospecific reactions (Scheme 2).\textsuperscript{3,4,8} The catalytic system used in this work (SnCl\textsubscript{4} at -78 °C) was not well suited for the development of a dynamic kinetic asymmetric transformation, as it was highly enantiospecific at low temperature and led to decomposition at higher temperature. Consequently, a broad range of other catalysts and chiral ligands were examined. From these studies, copper bisoxazoline complex 7a emerged as the most promising catalyst, leading to complete conversion of cyclopropane 4a and formation of the cyclopentylamine 6a in a 76:24 er and a very good diastereoselectivity (Scheme 2, A). Nevertheless, the enantioselectivity observed was still not satisfactory and the yield of the isolated product remained low and variable (0-50%) due to the formation of ring-opening side products resulting from a retro-alold reaction.

To address these shortcomings, extensive optimization of the reaction conditions, cyclopropane and enol ethers substrates, as well as the catalyst structure was performed (Scheme 2, B and C).\textsuperscript{9} No significant improvement could be obtained by changing solvent, temperature, concentration or catalyst loading. In contrast to what has been observed by Tang and co-workers,\textsuperscript{7\textdagger} modification of the diester substrates was also not successful. Finally, four parameters were found to be crucial to increase the selectivity and the efficiency of the reaction:

1) Replacing the silyl group on the enol ether by an alkyl group (benzyl) allowed for a significant increase in yield and reproducibility. The higher stability of the carbon-oxygen bond was probably essential to prevent ring-opening side reactions.

2) The structure of the substituents on the nitrogen was essential to achieve high enantioinduction. The enantiomeric ratio was lower with an electron-donating methoxy substituent on the phthalimide (74:26, cyclopropane 4e), but increased significantly to 92:8 with a nitro substituent (cyclopropane 4d). However, this increase of enantioselectivity came at the cost of a lower diastereoselectivity (4:1). On the other hand, replacing the phthalimide group by a succinimide led to the highest enantiomeric ratio (95:5) without compromising the diastereoselectivity.

3) Steric hindrance of the substituent on the ligand was another important factor. Best results were obtained with the commercially available bisoxazoline ligand bearing a bulky tert-butyl group.

4) Finally, a strong counteranion effect was observed. The highest enantioinduction was obtained with perchlorate, whereas hexafluorostannate led to the highest diastereoselectivity. To obtain high enantioselectivity, it was important to exclude moisture, as the blue copper aqua complex gave lower enantioinduction than the anhydrous green catalyst.

Under the optimized conditions, the desired cyclopentylamine 6b could finally be obtained in 94% yield and a 95:5 er with good diastereoselectivity (10:1), setting the stage for the investigation of the scope of the reaction (Scheme 1, B).

Scheme 2: Lead result (A), optimized reaction conditions (B) and key parameters influencing yield and selectivity of the reaction.

On preparative scale, cyclopentylamine 6b could be obtained in quantitative yield with a 96:4 er and a 7:1 dr (Table 1, entry 1). Variation of the oxygen substituent was examined first: A methyl enol ether (entry 2) and a more electron-withdrawing trifluoroethyl group (entry 3) both worked in the annulation reaction, but for the latter the diastereoselectivity of the reaction was lost. Variation of the aromatic substituent on the olefin gave comparable enantioinduction for both a meta methyl-substituted phenyl ring (entry 4) and a thiophene heterocycle (entry 5). The annulation reaction was not limited to the synthesis of tertiary ethers: unsubstituted benzyl ethers 5g-i also gave the desired products with useful selectivity (entries 6-8). On a 1 mmol scale, product 6g was obtained in 80% yield and a 95.5:4.5 er (entry 6).

Achieving high selectivity in DYKAT processes is challenging and the catalytic system often has to be optimized for each class of substrates. Nevertheless, when benzaldehyde (8a) was used in the [3+2] annulation process with aminocyclopropane 4b, the DYKAT process was successful and gave the desired tetrahydrofurylamine 9a with a 92:8 er and a 13:1 dr (Table 2, entry 1). The annulation reaction was successful for both electron-rich (entries...
2 and 3) and electron-poor (entry 4) aromatic aldehydes, as well as for thiophene carboxaldehyde (8e) (entry 5). The best enantiomeric ratio (96:4) was observed for the para-methoxy substituted benzene ring (entry 2). The reaction was not limited to aromatic aldehydes: both cinnamaldehyde (8f) (entry 6) and aliphatic aldehyde 8g (entry 7) could be used.

Table 1. Scope of the annulation reaction with enol ethers.

| Entry | Enol Ether | Product | Yield \%/er/dr | \n | \n |
|-------|------------|---------|----------------|
| 1     | \(\text{BnO} - \text{Ph}\) | \(\text{5b}\) | 97\% 96:4 er 7:1 dr |
| 2     | \(\text{MeO} - \text{Me}\) | \(\text{5c}\) | 95\% 94.5:5.5 er 2:1 dr |
| 3     | \(\text{F}_{2} \text{C} - \text{O} - \text{Ph}\) | \(\text{5d}\) | 88\% 95.5:4.5 er 1.5:1 dr |
| 4     | \(\text{BnO} - \text{Ph}\) | \(\text{5e}\) | 94\% 94:6 er 8:1 dr |
| 5     | \(\text{BnO} - \text{S}\) | \(\text{5f}\) | 96\% (80\%) | 96.5:3.5 (95.5:4.5) er 4:1 (4:1) dr |
| 6     | \(\text{BnO} - \text{Bn}\) | \(\text{5g}\) | 73\% | |
| 7     | \(\text{4-BrNo} - \text{Ph}\) | \(\text{5h}\) | 94.5:5.5 er 5:1 dr |
| 8     | \(\text{4-NO}_{2} \text{BnO} - \text{Ph}\) | \(\text{5i}\) | 82\% 98.2 er 5:1 dr |

\footnote{Reaction conditions: 0.20 mmol cyclopropane 4b, 0.40 mmol enol ether 5, 0.02 mmol catalyst 7b, 3Å MS in dichloromethane at room temperature, under argon. \textsuperscript{5}Yield after purification by column chromatography. \textsuperscript{6}Determined by chiral phase HPLC. \textsuperscript{7}Determined by analysis of crude \textsuperscript{1}H NMR. \textsuperscript{8}Value for major \textit{anti} diastereoisomer, \textit{syn} diastereoisomer: er = 96.5:3.5. \textsuperscript{9}Values in brackets correspond to the results on 1 mmol scale.}

Table 2. Scope of the annulation reaction with aldehydes.

| Entry | aldehyde | Product | Yield \%/er/dr | \n | \n |
|-------|----------|---------|----------------|
| 1     | \(\text{Ph}\) | \(\text{8a}\) | 82\% 92.8 er 13:1 dr |
| 2     | \(\text{4-MeOPh}\) | \(\text{8b}\) | 69\% 96:4 er >20:1 dr |
| 3     | \(\text{3-MeOPh}\) | \(\text{8c}\) | 84\% 93:7 er 10:1 dr |
| 4     | \(\text{4-CPH}\) | \(\text{8d}\) | 90\% 91:9 er 14:1 dr |
| 5     | \(\text{Ph}\) | \(\text{8e}\) | 97\% 94:6 er >20:1 dr |
| 6     | \(\text{Ph}\) | \(\text{8f}\) | 96\% 94:6 er 14:1 dr |
| 7     | \(\text{Ph}\) | \(\text{8g}\) | 85\% 91.5:8.5 er 13:1 dr |

\footnote{Reaction conditions: 0.20 mmol cyclopropane 4b, 0.40 mmol aldehyde 8, 0.02 mmol catalyst 7b, 3Å MS in dichloromethane at room temperature, under argon. \textsuperscript{5}Yield after purification by column chromatography. \textsuperscript{6}Determined by chiral phase HPLC. \textsuperscript{7}Determined by analysis of crude \textsuperscript{1}H NMR.}

Figure 2: X-ray structure of compound 6g.\textsuperscript{11}
In summary, we have reported the first example of dynamic kinetic asymmetric [3+2] annulation reaction of aminocyclopropanes. The reaction proceeded with high enantioselectivity and diastereoselectivity with a broad range of acyclic alkyld enol ethers and aldehydes using a copper catalyst with a commercially available bisoxazoline ligand. Importantly, the developed catalytic system could be used for both classes of substrates without re-optimization. The method is expected to be highly useful for the asymmetric synthesis of nitrogen-rich small organic molecules.

Scheme 3: Stereochemical model for the reaction and X-ray structure of complex 7b•(H$_2$O)$_2$.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes
The authors declare no competing financial interests.

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REFERENCES


(9) For easier comparison, the values given in Scheme 2, C have been limited to those obtained when changing a single parameter from the optimized conditions given in Scheme 2, B. For the optimization studies, the yields and diastereoselectivities were calculated by NMR and the er by chiral HPLC, see Supporting Information for further details.

(10) (a) Evans, D. A.; Rovis, T.; Kozlowski, M. C.; Tedrow, J. S. J. Am. Chem. Soc. 1999, 121, 1994. (b) Desimoni, G.; Faita, G.; Jørgensen, K. A. Chem. Rev. 2011, 111, PR284. See also Figure S1 in Supporting Information for a simplified stereochemical model with different complex geometries.

(11) The different atom locations in the benzene region result from the presence of two conformations in the crystal structure.

(12) The hydrogen atoms are omitted for clarity.
Supporting Information for

**Dynamic Kinetic Asymmetric [3+2] Annulation Reactions of Aminocyclopropanes.**

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95 pages
Synthesis of cyclopentylamines and tetrahydrofurylamines:

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Figure S1:

X-ray structure of compound 6g. The different atom locations in the benzene region result from the presence of two conformations in the crystal structure. As the region containing the stereocenters is well-defined, the assignment of the configuration is not disturbed.
**Figure S2:**
Simplified stereochemical model for nucleophilic attack on aminocyclopropanes in dependence of the complex geometry. Only the CH$_2$-CHN bond of the cyclopropane is drawn. The grey quadrants are blocked by the two tert-butyl groups of the ligand.
**General Methods**

All reactions were carried out in oven-dried glassware under nitrogen or argon atmosphere with magnetic stirring, unless stated otherwise. THF, Et$_2$O, CH$_3$CN, toluene, hexane and dichloromethane were dried by passage over activated alumina under nitrogen atmosphere (water content < 30 ppm, Karl-Fischer titration) on an Innovative Technology Solvent Delivery System. All chemicals were purchased from Strem, Acros, Aldrich, Fluka, VWR, Aplichem or Merck and used as such unless stated otherwise. Chromatographic purification was performed as flash chromatography using Macherey-Nagel silica 40-63, 60 Å or using aluminium oxide, basic, Brockmann I purchased from Acros, using the solvents indicated as eluent with 0.1-0.5 bar pressure. For flash chromatography, previously distilled technical grade solvents were used. TLC was performed on Merck silica gel 60 F254 TLC glass plates or aluminium plates and visualized with UV light, and by permanganate stain, CAN stain or p-anisaldehyde stain followed by heating. Melting points were measured on a calibrated Büchi B-540 melting point apparatus using open glass capillaries. $^1$H- NMR spectra were recorded on a Brucker DPX-400 400 MHz spectrometer in CDCl$_3$, DMSO- d$_6$, CD$_2$Cl$_2$ or CD$_3$OD, all signals are reported in ppm with the internal chloroform signal at 7.26 ppm, the internal DMSO signal at 2.50 ppm, the internal CD$_2$Cl$_2$ signal at 5.31 ppm, or the internal MeOD signal at 3.30 ppm as standard. The data are reported as follows: (s = singlet, d = doublet, t = triplet, q = quadruplet, qi = quintet, m = multiplet or unresolved, br = broad signal, coupling constant(s) in Hz, integration, interpretation). $^{13}$C-NMR spectra were recorded with $^1$H-decoupling on a Brucker DPX- 400 100 MHz spectrometer in CDCl$_3$, DMSO-d$_6$, CD$_2$Cl$_2$ or CD$_3$OD, all signals are reported in ppm with the internal chloroform signal at 77.0 ppm, the internal DMSO signal at 39.5 ppm, the internal CD$_2$Cl$_2$ signal at 53.5 ppm or the internal MeOD signal at 49.0 ppm as standard. Infrared spectra were recorded on a JASCO FT-IR B4100 spectrophotometer with an ATR PRO410-S and a ZnSe prisma and are reported as cm$^{-1}$ (w = weak, m = medium, s = strong, sh = shoulder). High resolution mass spectrometry measurements were performed by the mass spectrometry service of ISIC at the EPFL on a MICROMASS (ESI) Q-TOF Ultima API. HPLC measurements were done on a JASCO HPLC system with an AS2055 Autosampler, a PU 2089 Pump, a UV 2075 detector using a CHIRALPAK IC, IB, IF or IA column from DAICEL Chemical. Optical rotations were measured on a polarimeter using a 10 cm cell with a Na 589 nm filter. The specific solvents and concentrations (in g/100 mL) are indicated.
Synthesis of Dimethyl-2-diazomalonate (12)

Following a modified procedure, dimethylmalonate (10) (7.93 mL, 69.7 mmol, 1.00 eq), triethylamine (10.6 mL, 76.6 mmol, 1.10 eq) and tosyl azide (11) (15.1 g, 76.6 mmol, 1.10 eq) were dissolved in acetonitrile (100 mL). The solution was stirred at room temperature for 24 hours. The solution was concentrated under reduced pressure and partitioned between dichloromethane (30 mL) and water (30 mL), the layers were separated and the aqueous layer was extracted with dichloromethane (1 x 20 mL). The organic layers were combined and dried over MgSO₄. The crude was first filtered over a plug of silica gel (Hexane/Et₂O 1:1) to remove most of the tosylamide formed during the reaction. Purification by column chromatography (Hexane/Et₂O 90:10 to 80:20) afforded dimethyl-2-diazomalonate (12) as yellow oil which solidified under storage at 4 °C (10.4 g, 65.5 mmol, 94 % yield).

R₁ 0.32 (1:1 PET/Et2O).

1H NMR (400 MHz, CDCl₃) δ: 3.87 (s, 1H, OCH₃).

13C NMR (101 MHz, CDCl₃) δ: 161.2, 52.4

The characterization data for 12 correspond to the reported values.¹

Synthesis of N-vinyl-imides

5-Methoxyisobenzofuran-1,3-dione (14)

Following a modified procedure,³ a solution of 4-hydroxyphthalic acid (13) (2.00 g, 11.0 mmol, 1.00 eq), catalytic sulfuric acid (0.10 mL, 1.9 mmol, 0.17 eq) and MeOH (20.0 mL), was stirred at reflux for 7 hours. under air. The solvent was removed under reduced pressure to afford crude dimethyl 4-hydroxyphthalate. The crude diester was dissolved in acetone (70 mL) and reacted with potassium carbonate (7.40 g, 53.5 mmol, 5.00 eq) at 50 °C for 20 min. Iodomethane (1.47 mL, 23.6 mmol, 2.20 eq) was added, and the mixture was stirred at reflux overnight. K₂CO₃ was removed by filtration and the solvent was removed under reduced pressure to afford a colorless oil.

The crude was dissolved in acetone (16.0 mL) and a 11 M solution of sodium hydroxide, (6.00 mL, 66.0 mmol, 6.20 eq) was added, and the solution was stirred for 6 hours. under air at rt. The solution was then acidified with 2 M HCl to pH 3, and concentrated under reduced

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² The diazo carbon could not be detected.
pressure. Then, the crude 4-methoxyphthalic acid was dissolved into acetone (50 mL) and dried over MgSO₄, filtered through a plug of cotton wool, and the solvent was removed in vacuo. The crude diacid was partitioned between 2 M NaOH (50 mL) and DCM (50 mL). The organic layer was extracted with NaOH 2 M (50 mL). The combined aqueous phase was cooled down to 0 °C and acidified with 37% HCl % to pH 3. The aqueous layer was then extracted five times with AcOEt (50 mL). The combined organic layers were dried over MgSO₄ and concentrated under reduced pressure to afford the crude diacid as a light brown solid (1.82 g).

A solution of crude 4-methoxyphthalic acid (1.82 g, 9.28 mmol, 1.00 eq) in acetic anhydride (25.0 mL, 266 mmol, 28.7 eq) was stirred at reflux for 21 hours. Volatiles were removed in vacuo and the crude diacid was dissolved in DCM (50 mL) and filtered through fritted glass to remove solid impurities. The solution was concentrated under reduced pressure and dried in vacuo to afford the anhydride 14 as a light brown solid (1.62 g, 9.08 mmol, 83% yield over 4 steps)

\( ^1H \) NMR (400 MHz, CDCl₃) δ 7.90 (dd, 1 H, J = 8.5, 0.4 Hz, Ar), 7.41 (d, 1 H, J = 2.2 Hz, Ar), 7.35 (dd, 1 H, J = 8.5, 2.3 Hz, Ar), 3.98 (s, 3 H, OMe).

HRMS (ESI) calcd for C₉H₇O₄⁺ [M+H]⁺ 179.0339; found 179.0349.

The \( ^1H \) NMR data for 14 corresponded to the reported values.⁴

5-Methoxyisoindoline-1,3-dione (16)

Following a modified procedure,⁵ 5-methoxyisobenzofuran-1,3-dione (14) (1.58 g, 8.84 mmol, 1.00 eq) and formamide (15) (35.0 mL, 880 mmol, 100 eq) were divided between four 20 mL microwave vials sealed with a microwave cap. The mixture was stirred at rt until the product was completely dissolved, then heated 2 times at 200 °C for 30 sec with 10 sec pre-stirring, using Biotage Initiator 2.0 microwave reactor. The mixture was cooled to 0 °C to induce crystallization and cold water (10 mL) was added into each vial. The obtained solid was filtrated over filter paper, washed with water (15 mL) and hexanes (20 mL) and dried under reduced pressure to afford 5-methoxyisoindoline-1,3-dione (16) as a beige solid (982 mg, 5.54 mmol, 63% yield) which was used without further purification.

\( ^1H \) NMR (400 MHz, CDCl₃) δ 7.77 (dd, 1 H, J = 8.3, 0.4 Hz, Ar), 7.59 (br s, 1 H, NH), 7.33 (d, 1 H, J = 2.2 Hz, Ar), 7.20 (dd, 1 H, J = 8.3, 2.3 Hz, Ar), 3.94 (s, 3 H, OMe).

\( ^13C \) NMR (101 MHz, CDCl₃) δ 167.8, 167.7, 165.0, 135.2, 125.4, 124.5, 120.4, 108.1, 56.2.

HRMS (ESI) calcd for C₉H₈NO₃⁺ [M+H]⁺ 178.0499; found 178.0497.

5-Methoxy-2-vinylisoindoline-1,3-dione (18)

Following a modified procedure, 6 5-methoxyisoindoline-1,3-dione (16) (980 mg, 5.53 mmol, 1.00 eq), PdCl₂ (98.0 mg, 0.553 mmol, 0.100 eq), LiCl (235 mg, 5.53 mmol, 1.00 eq, weighted in a glovebox) and vinyl acetate (17) (13.7 mL, 148 mmol, 26.8 eq) were heated under reflux for 24 hours. The mixture was cooled down to room temperature and diluted with DCM/MeOH 4:1 (20 mL). Activated charcoal was added and the resulting suspension was filtered through a pad of Celite (DCM/MeOH 4:1 100 mL) and concentrated under reduced pressure. Purification by silica gel chromatography (pentane/AcOEt 90:10 to 75:25) afforded 5-methoxy-2-vinylisoindoline-1,3-dione (18) as a colorless solid (828 mg, 4.08 mmol, 74% yield).

Rᶠ 0.56 (6:4 Hexane/AcOEt).
M.p. 102.2 - 105.1 °C.
¹H NMR (400 MHz, CDCl₃) δ 7.76 (d, 1 H, J = 8.3 Hz, Ar), 7.32 (d, 1 H, J = 2.2 Hz, Ar), 7.17 (dd, 1 H, J = 8.3, 2.2 Hz, Ar), 6.83 (dd, 1 H, J = 16.4, 9.9 Hz, =CH), 6.03 (d, 1 H, J = 16.4 Hz, =CH), 4.99 (d, 1 H, J = 9.9 Hz, =CH), 3.93 (s, 3 H, OMe).
¹³C NMR (101 MHz, CDCl₃) δ 166.5, 166.3, 165.1, 134.4, 125.5, 124.0, 123.5, 120.6, 108.2, 104.0, 56.3.
IR 1779 (w), 1720 (s), 1639 (w), 1493 (w), 1386 (s), 1307 (w), 1295 (w), 1021 (w). HRMS (ESI) calcd for C₁₁H₁₀NO₃⁺ [M+H]⁺ 204.0655; found 204.0662.

1-Vinylpyrrolidin-2,5-dione (20)

Following a modified procedure, 6 succinimide (19) (1.00 g, 10.1 mmol, 1.00 eq), vinyl acetate (17) (25.0 mL, 270 mmol, 26.8 eq) and Na₂PdCl₄ (59.0 mg, 0.202 mmol, 2.00 mol%) were heated under reflux for 72 hours. After solvent evaporation, the crude was purified by Biotage SNAP Cartridge KP-Sil 50 g, 7.3 Hexane/AcOEt to obtain (20) as a yellow solid (1.22 g, 9.78 mmol, 97% yield).

Rᶠ 0.17 (8:2 Hexane/AcOEt). m.p. 47.6 – 48.9 °C.
¹H NMR (400 MHz, CDCl₃) δ 6.86 (d, 1 H, J = 16.4, 9.9 Hz, =CH), 5.06 (d, 1 H, J = 9.9 Hz, =CH), 2.72 (s, 4 H, CH₂).
¹³C NMR (101 MHz, CDCl₃) δ 175.4, 124.3, 106.6, 27.8.
IR 2946 (w), 1707 (s), 1382 (s), 1307 (m), 1222 (s), 1113 (s), 974 (m), 906 (m), 821 (w). HRMS (ESI) calcd for C₆H₈NO₂⁺ [M+H]⁺ 126.0550; found 126.0621.

5-Nitro-2-vinylisoindoline-1,3-dione (22)

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S10
Following a modified procedure, 5-nitrosoindoline-1,3-dione (21) (1.00 g, 5.20 mmol, 1.00 eq), PdCl$_2$ (92.0 mg, 0.520 mmol, 0.100 eq), LiCl (0.221 mg, 5.20 mmol, 1.00 eq, weighted in a glovebox) and vinyl acetate (17) (12.9 mL, 139 mmol, 26.8 eq) were heated under reflux for 20 hours. The mixture was cooled down to room temperature and the solvent was evaporated under reduced pressure. The crude was purified by column chromatography using silica gel (Hexane/AcOEt 8:2 to 5:5) to afford 5-nitro-2-vinylisoindoline-1,3-dione (22) as a bright yellow solid (1.14 g, 5.23 mmol, quantitative yield).

R$_f$ 0.32 (9:1 Pentane/AcOEt).
M.p. 144.3 - 148.6 °C.
$^1$H NMR (400 MHz, CDCl$_3$) δ 8.68 (dd, 1 H, $J = 2.0, 0.5$ Hz, Ar), 8.63 (dd, 1 H, $J = 8.1, 2.0$ Hz, Ar), 8.08 (m, 1 H, Ar), 6.88 (dd, 1 H, $J = 16.4, 9.8$ Hz, $CH-N$), 6.14 (dd, 1 H, $J = 16.4, 0.5$ Hz, =CH$_2$), 5.16 (dd, 1 H, $J = 9.8, 0.4$ Hz, =CH$_2$).
$^{13}$C NMR (101 MHz, CDCl$_3$) δ 164.5, 164.2, 152.1, 136.1, 133.1, 129.8, 125.0, 123.6, 119.2, 106.3.
IR 3101 (w), 3074 (w), 2924 (w), 1709 (s), 1533 (s), 1383 (s), 1341 (s), 1307 (s), 1062 (m), 1024 (s), 915 (s). HRMS (ESI) calcd for C$_{10}$H$_6$N$_2$O$_4$ [M$^+$] 218.0328; found 218.0355.
Synthesis of Aminocyclopropanes

General Procedure for the of Synthesis of Aminocyclopropanes

Following a modified procedure, the corresponding N-vinyl-imide (1.00 eq) was dissolved in dry dichloromethane (10.0 mL) and the solution was cooled down to 0 °C with an ice/water bath. Then, bis[rhodium(α,α,α’, α'-tetramethyl-1,3-benzenedipropionic acid)] (0.1 mol%) was added in one portion. A solution in dichloromethane (2.0 mL) of dimethyl diazomalate (12) (1.20 eq) was added dropwise over 5 min. After the addition, the mixture was allowed to warm to room temperature and stirred overnight. The solvent is then removed under reduced pressure and the crude is directly purified by column chromatography.

Dimethyl 2-(1,3-dioxoisindolin-2-yl)cyclopropane-1,1-dicarboxylate (4a)

Following the general procedure, 4a was synthesized starting from N-vinyl-phthlimide (2.50 g, 14.4 mmol, 1.00 eq), dimethyl diazomalate (12) (2.74 g, 17.3 mmol, 1.20 eq) and bis[rhodium(α,α,α’, α'-tetramethyl-1,3-benzenedipropionic acid)] (14.0 mg, 0.0144 mmol, 0.100 mol%). After solvent evaporation, the residue was purified by column chromatography using silica gel (from 8:2 to 6:4 Hexane/ACOEt), to obtain dimethyl 2-(1,3-dioxoisindolin-2-yl)cyclopropane-1,1-dicarboxylate (4a) as a colorless solid (4.03 g, 13.3 mmol, 92% yield).

Rt 0.34 (6:4 Hexane/ACOEt).
M.p. 131.8 – 133.9 °C.

1H NMR (400 MHz, CDCl3) δ 7.86 (m, 2 H, Phth), 7.75 (m, 2 H, Phth), 3.85 (s, 3 H, OMe), 3.72 (dd, 1 H, J = 8.5, 6.6 Hz, N-CH), 3.64 (s, 3 H, OMe), 2.73 (dd, 1 H, J = 6.5, 6.5 Hz, CH2), 2.06 (dd, 1 H, J = 8.5, 6.4 Hz, CH2).

13C NMR (101 MHz, CDCl3) δ 168.5, 167.8, 166.9, 134.3, 131.4, 123.5, 53.1, 53.0, 34.9, 33.1, 19.6.
IR 2956 (w), 1783 (w), 1727 (s), 1468 (w), 1439 (w), 1399 (m), 1329 (m), 1294 (m), 1222 (m), 1134 (w), 909 (w), 876 (w), 720 (m).
HRMS (ESI) calcd for C15H14NO6 [M+H]+ 304.0816; found 304.0811.
The 1H NMR data for 4a corresponded to the reported values.

Dimethyl 2-(2,5-dioxopyrrrolidin-1-yl)cyclopropane-1,1-dicarboxylate (4b)

Following the general procedure, compound 4b was synthesized starting from N-vinylsuccinimide (20) (500 mg, 4.00 mmol, 1.00 eq), dimethyl diazomalonate (12) (300 mg, 4.80 mmol, 1.20 eq) and bis[rhodium(α,α,α',α'-tetramethyl-1,3-benzenedipropionic acid)] (3.0 mg, 4.0 μmol, 0.10 mol%). After solvent evaporation, the residue was purified by Biotage (SNAP Cartridge KP-Sil 50 g, 5:5 Hexane/AcOEt), to obtain dimethyl 2-(2,5-dioxopyrrolidin-1-yl)cyclopropane-1,1-dicarboxylate (4b) as a yellow solid (801 mg, 3.14 mmol, 79% yield).

**Protocol for the synthesis of enantioenriched 4b:**

Following the general procedure, dimethyl 2-(2,5-dioxopyrrolidin-1-yl)cyclopropane-1,1-dicarboxylate (4b) was synthesized starting from N-vinylsuccinimide (100 mg, 0.800 mmol, 1.00 eq), dimethyldiazomalonate (152 mg, 0.960 mmol, 1.20 eq) using tetrakis[(S)-(S)-N-(p-dodecylphenylsulfonyl)prolinato]dirhodium(II) (0.8 mg, 8 μmol, 1 mol%). After solvent evaporation, the residue was purified by flash column chromatography on silica gel (1:1 to 3:7 Pentane/AcOEt) to obtain a yellow solid, which was washed two times with MeOH to afford dimethyl 2-(2,5-dioxopyrrolidin-1-yl)cyclopropane-1,1-dicarboxylate as a white solid (20 mg, 0.078 mmol, 10% yield).

$er = 58:42$, Chiralcel IA Hexane/iPrOH 80:20, 1 mL/min, $\lambda = 210$ nm, tr1 = 23.2 min; tr2 = 25.8 min.

Rf 0.39 (5:5 Hexane/AcOEt).

M.p. 81.9 – 85.3 °C.

$^1$H NMR (400 MHz, CDCl3) δ 3.78 (s, 3 H, OMe), 3.68 (s, 3 H, OMe), 3.45 (dd, 1 H, $J = 8.5$, 6.5 Hz, N-CH), 2.73-2.58 (m, 4 H, O=C-CH$_2$), 2.45 (t, 1 H, $J = 6.5$ Hz, CH$_2$), 1.93 (dd, 1 H, $J = 8.5$, 6.5 Hz, CH$_2$).

$^{13}$C NMR (101 MHz, CDCl3) δ 176.9, 168.4, 167.2, 53.2, 53.1, 35.1, 32.7, 28.1, 19.7.

IR 2955 (w), 1717 (s), 1439 (w), 1406 (m), 1332 (m), 1296 (m), 1216 (s), 1132 (m), 1079 (w), 910 (s).

HRMS (ESI) calcd for C$_{11}$H$_{14}$NO$_6^+$ [M+H]$^+$ 256.0816; found 256.0822.

**Dicarboxylate dimethyl 2-(5-methoxy-1,3-dioxoisoinolin-2-yl)cyclopropane-1,1-dicarboxylate (4c)**

Following the general procedure, compound 4c was synthesized starting from 5-methoxy-2-vinylisooindoline-1,3-dione (18) (0.130 g, 0.640 mmol, 1.00 eq), dimethyl diazomalonate (12) (0.121 g, 0.768 mmol, 1.20 eq) and bis[rhodium(α,α,α',α'-tetramethyl-1,3-benzenedipropionic acid)] (0.5 mg, 0.6 μmol, 0.1 mol%). After solvent evaporation, the crude was purified by
Biotage (SNAP Cartridge KP-Sil 10 g, 6:4 Hexane/AcOEt), to obtain dicarboxylate dimethyl 2-(5-methoxy-1,3-dioxoisoindolin-2-yl)cyclopropane-1,1-dicarboxylate (4e) as a colorless solid (176 mg, 0.528 mmol, 83% yield).

Rf 0.15 (8:2 Pentane/AcOEt).
M.p. 113.5 – 117.8 °C.

1H NMR (400 MHz, CDCl3) δ 7.71 (d, 1 H, J = 8.3 Hz, Phth), 7.27 (d, 1 H, J = 2.2 Hz, Phth), 7.14 (dd, 1 H, J = 8.3, 2.3 Hz, Phth), 3.90 (s, 3 H, OMe), 3.80 (s, 3 H, OMe-C=O), 3.66 (dd, 1 H, J = 8.5, 6.6 Hz, N-CH), 3.59 (s, 3 H, OMe-C=O), 2.68 (t, 1 H, J = 6.5 Hz, CH2), 1.99 (dd, 1 H, J = 8.5, 6.4 Hz, CH2).

13C NMR (101 MHz, CDCl3) δ 168.7, 167.8, 167.6, 167.0, 165.0, 134.1, 125.3, 123.4, 120.4, 108.1, 56.2, 35.0, 35.0, 33.2, 19.7.

IR 2955 (w), 1720 (s), 1178 (m), 1158 (m), 1018 (s), 1016 (w).

HRMS (ESI) calcd for C16H16NO6+ [M+H]+ 334.0921; found 334.0915.

Dimethyl 2-(5-nitro-1,3-dioxoisoindolin-2-yl)cyclopropane-1,1-dicarboxylate (4d)

Following the general procedure, compound 4d was synthesized starting from 5-nitro-2-vinylisoindoline-1,3-dione (22) (0.500 g, 2.29 mmol, 1.00 eq), dimethyl diazomalonate (12) (0.544 g, 2.75 mmol, 1.20 eq) and bis[rhodium(α,α,α′,α′-tetramethyl-1,3-benzenedipropionic acid)] (1.7 mg, 2.3 µmol, 0.10 mol%). After solvent evaporation, the crude was purified by Biotage (SNAP Cartridge KP-Sil 50 g, 7:3 Hexane/AcOEt), to obtain Dimethyl 2-(5-nitro-1,3-dioxoisoindolin-2-yl)cyclopropane-1,1-dicarboxylate (4d) as a colorless solid (712 mg, 2.04 mmol, 89% yield).

Rf 0.19 (8:2 Pentane/AcOEt).
M.p. 113.0 – 115.8 °C.

1H NMR (400 MHz, CDCl3) δ 8.61 (m, 2 H, Ar), 8.03 (d, 1 H, J = 8.1 Hz, Ar), 3.83 (s, 3 H, OMe), 3.70 (m, 1 H, CH-N), 3.62 (s, 3 H, OMe), 2.63 (m, 1 H, CH2), 2.07 (m, 1 H, CH2).

13C NMR (101 MHz, CDCl3) δ 168.2, 167.1, 165.9, 165.6, 152.0, 135.9, 132.9, 129.6, 124.9, 119.0, 53.3, 53.2, 35.0, 33.1, 19.7.

IR 3110 (w), 2956 (w), 2926 (w), 2853 (w), 1726 (s), 1541 (m), 1400 (m), 1344 (s), 1222 (s), 1130 (m).

HRMS (ESI) calcd for C15H13N2O8+ [M+H]+ 349.0666; found 349.0664.
Synthesis of Esters

2,2,2-Trifluoroethyl benzoate (24)

In a 250 mL round bottom flask equipped with a stirring bar, 2,2,2-trifluoroethanol (2.33 mL, 32.3 mmol, 1.00 eq), DMAP (39.5 mg, 0.323 mmol, 0.01 eq) and pyridine (3.14 mL, 38.8 mmol, 1.20 eq) were dissolved in diethyl ether (150 mL) while stirring. A solution of benzoyl chloride (23) (5.00 g, 35.6 mmol, 1.10 eq) in diethyl ether (10 mL) was added dropwise to the reaction mixture and the reaction was stirred at room temperature for 12 hours. A saturated NaHCO₃ solution (100 mL) was added to the crude mixture. The two layers were separated and the organic layer washed with water (50 mL x 3), dried over MgSO₄ and the solvent removed under reduced pressure. 2,2,2-trifluoroethyl benzoate (24) was purified by flash column chromatography on silica gel (9:1 to 8:2 Pentane/AcOEt) to obtain a colourless oil (3.50 g, 17.1 mmol, 53 % yield).

Rf 0.8 (9:1 Pentane/Et₂O).

³¹H NMR (400 MHz, CDCl₃) δ 8.09 - 8.07 (m, 2 H, Ar), 7.64 - 7.60 (m, 1 H, Ar), 7.50 - 7.46 (m, 2 H, Ar), 4.71 (q, 2 H, J₁-H = 8.4 Hz, CH₂-CF₃).

³¹C NMR (101 MHz, CDCl₃) δ 165.1, 134.0, 130.2, 128.8, 128.5, 123.3 (q, J₁-C = 277 Hz), 60.9 (q, J₁-C = 37 Hz).

The characterization data for 24 correspond to the reported values.

General Procedure for the Synthesis of Benzyl Esters

In a 250 mL round bottom flask equipped with a stirring bar and a condenser, benzyl alcohol (25) (1.00 eq), DMAP (0.01 eq) and triethylamine (1.10 eq) were dissolved in diethyl ether (90 mL) while stirring. A solution of the corresponding acyl chloride (1.20 eq) in diethyl ether (10 mL) was added dropwise to the reaction mixture and the reaction was stirred at reflux for 12 hours. A saturated NaHCO₃ solution (100 mL) was added to the crude mixture and stirred for 15 min at room temperature. The two layers were separated and the organic layer was washed with water (50 mL x 3), dried over Na₂SO₄ and the solvent removed under reduced pressure. The esters were purified by flash column chromatography on silica gel (9:1 to 8:2 Pentane/AcOEt).

Benzyl 3-methylbenzoate (26)

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Following the general procedure, compound 26 was synthesized starting from benzyl alcohol (25) (1.17 g, 10.8 mmol, 1.00 eq), DMAP (13.0 mg, 0.108 mmol, 0.01 eq), triethylamine (1.66 mL, 11.9 mmol, 1.10 eq) and 3-methylbenzoyl chloride (2.01 g, 13.0 mmol, 1.20 eq). Compound 26 was obtained as a colorless oil (2.37 g, 10.5 mmol, 97% yield).

\[ RF \ 0.55 \ (9:1 \ Hexane/AcOEt) \]

\(^1H\) NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.90 – 7.88 (m, 2 H, Ph), 7.47 – 7.45 (m, 2 H, Ph), 7.42 – 7.31 (m, 5 H, Ph), 5.37 (s, 2 H, CH\(_2\)), 2.40 (s, 3 H, Me).

\(^13C\) NMR (101 MHz, CDCl\(_3\)) \(\delta\) 166.7, 138.3, 136.3, 133.9, 130.3, 130.2, 128.7, 128.4, 128.3, 128.3, 127.0, 66.8, 21.4.

The characterization data for 26 correspond to the reported values.\(^{10}\)

**Benzyl thiophene-2-carboxylate (27)**

Following the general procedure, compound 27 was synthesized starting from benzyl alcohol (25) (1.08 g, 10.0 mmol, 1.00 eq), DMAP (12.2 mg, 0.100 mmol, 0.01 eq), triethylamine (1.54 mL, 11.0 mmol, 1.10 eq) and thiophene-2-carbonyl chloride (1.76 g, 12.0 mmol, 1.20 eq), compound 27 was obtained as a colorless oil (2.09 g, 9.58 mmol, 96% yield).

\[ RF \ 0.48 \ (9:1 \ Hexane/AcOEt) \]

\(^1H\) NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.85 - 7.84 (m, 1 H, Thiophene), 7.56 (dd, 1 H, J = 5.0, 1.2 Hz, Thiophene), 7.46 - 7.44 (m, 2 H, Ph), 7.42 - 7.33 (m, 3 H, Ph), 7.10 (dd, 1 H, J = 4.9, 3.8 Hz, Thiophene), 5.36 (s, 2 H, CH\(_2\)-Ph).

\(^13C\) NMR (101 MHz, CDCl\(_3\)) \(\delta\) 162.1, 135.9, 133.7, 133.7, 132.6, 128.7, 128.4, 128.3, 127.9, 66.8.

The characterization data for 27 correspond to the reported values.\(^{11}\)


Synthesis of Enol ethers

Triisopropyl((1-phenylvinyl)oxy)silane (5a)

In an oven-dried flask sealed with a septum and under \( \text{N}_2 \) atmosphere, acetophenone (28) (2.06 g, 17.1 mmol, 1.00 eq) in anhydrous THF (20 mL) is cooled down to -78 °C and a 1.9 M solution of NaHMDS (10.8 mL, 20.5 mmol, 1.20 eq) is added dropwise. The cold bath is removed and the pale yellow solution is stirred for 1 hour at room temperature. The reaction is cooled again to 0 °C and triisopropylsilyle chloride (3.96 g, 20.5 mmol, 1.20 eq) is added dropwise. The reaction is stirred at room temperature for 5 hours and the solvent is directly removed under reduced pressure. The resulting orange oil is purified by plug or by column chromatography on triethylamine-deactivated silica (99% Hexane, 1% Et\(_3\)N) to obtain Triisopropyl((1-phenylvinyl)oxy)silane 5a as a colorless oil (4.7 g, 17 mmol, 99% yield).

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.69-7.65 (m, 2 H, \( \text{Ar} \)), 7.38-7.29 (m, 3 H, \( \text{Ar} \)), 4.85 (d, 1 H, \( J = 1.8 \) Hz, C=CH\(_2\)), 4.41 (d, 1 H, \( J = 1.8 \) Hz, C=CH\(_2\)), 1.39-1.27 (m, 3 H, SiCH(CH\(_3\))\(_2\)), 1.19-1.13 (m, 18 H, SiCH(CH\(_3\))\(_2\)).

\(^1\)C NMR (101 MHz, CDCl\(_3\)) \( \delta \) 156.2, 138.0, 128.2, 128.1, 125.4, 90.0, 18.2, 12.9.

The characterization data for 5a corresponded to the reported values.\(^1\)

General procedure for the Synthesis of disubstituted Enol Ethers.

Following a slightly modified procedure,\(^2\) a round-bottom flask equipped with a magnetic stirrer was charged with a solution (10 to 15% in toluene) of di(cyclopenta-1,3-dien-1-yl)dimethyltitanium (2.0 eq) in toluene,\(^3\) di(cyclopenta-1,3-dien-1-yl)titanium(IV) chloride (0.060 eq) and the corresponding ester (1.00 eq) under inert atmosphere. The red/orange mixture was heated in the dark to 80 °C for 16 hours, and then cooled to room temperature. Pentane (50 mL) was added to the mixture and the precipitated solids were removed by filtration through a basic alumina plug (Pentane/diethyl ether 9:1, 3% \( \text{Et}_3\)N) to afford a yellow oil. The benzyl enol ethers were purified right before use by flash column chromatography using basic alumina (Pentane, 3% \( \text{Et}_3\)N).

(1-(Benzyloxy)vinyl)benzene (5b)


Following the general procedure, compound 5b was synthesized starting from di(cyclopenta-1,3-dien-yl)dimethyltitanium (19.1 g of a 10.8% solution in toluene, 9.90 mmol, 2.20 eq), di(cyclopenta-1,3-dien-1-yl)titanium(IV) chloride (67.2 mg, 0.270 mmol, 0.060 eq) and benzyl benzoate (0.955 g, 4.50 mmol, 1.00 eq) to obtain (1-(benzyloxy)vinyl)benzene (5b) as a colorless oil (545 mg, 2.59 mmol, 58% yield).

R<sub>f</sub> 0.8 (9:1 Hexane/Et<sub>2</sub>O).

<sup>1</sup>H NMR (400 MHz CDCl<sub>3</sub>) δ 7.72 (ddd, J = 7.5, 3.3, 1.7 Hz, 2 H, Ar), 7.59 – 7.29 (m, 8 H, Ar), 5.00 (d, J = 2.1 Hz, 2 H, O-CH<sub>2</sub>-Ar), 4.79 (t, J = 2.8 Hz, 1 H, CH=C), 4.36 (t, J = 2.5 Hz, 1 H, CH=C).

<sup>1</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 159.8, 137.3, 136.5, 128.6, 128.6, 128.3, 127.9, 127.5, 125.6, 83.3, 69.9.

IR 2432 (w), 2407 (w), 1361 (m), 1336 (s), 1161 (m), 1064 (s), 994 (s), 862 (s), 782 (m).

HRMS (ESI) calcd for C<sub>15</sub>H<sub>14</sub>AgO<sup>+</sup> [M+Ag]<sup>+</sup> 317.0090; found 317.0102.

1-(1-Methoxyvinyl)-4-methylbenzene (5c)

Following the general procedure, compound 5c was synthesized starting from di(cyclopenta-1,3-dien-1-yl)dimethyltitanium (24.2 g of a 12.6% solution in toluene, 14.7 mmol, 2.20 eq), di(cyclopenta-1,3-dien-1-yl)titanium(IV) chloride (99.0 mg, 0.400 mmol, 0.060 eq) and 2,2,2-trifluoroethyl benzoate (1.00 g, 6.66 mmol, 1.00 eq) to obtain 1-(1-methoxyvinyl)-4-methylbenzene (5c) as a colorless oil (537 mg, 3.63 mmol, 54% yield).

R<sub>f</sub> 0.9 (9:1 Hexane/Et<sub>2</sub>O).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.78 – 7.45 (m, 2 H, Ar), 7.17 (d, J = 8.0 Hz, 2 H, Ar), 4.64 (dd, J = 2.7, 1.0 Hz, 1 H, C=CH<sub>2</sub>), 4.20 (d, J = 2.7 Hz, 1 H, C=CH<sub>2</sub>), 3.76 (s, 3 H, OMe), 2.38 (s, 3 H, CH<sub>3</sub>Ar).

<sup>1</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 161.0, 138.3, 133.7, 128.9, 128.8, 128.8, 125.3, 125.3, 125.3, 81.0, 55.2, 21.2.

IR 2953 (w), 1743 (w), 1706 (w), 1644 (w), 1514 (m), 1303 (s) 1127 (s), 1047 (s), 903 (m), 796 (s).

HRMS (ESI) calcd for C<sub>10</sub>H<sub>14</sub>AgO<sup>+</sup> [M+Ag]<sup>+</sup> 254.9934; found 254.9898.

(1-(2,2,2-Trifluoroethoxy)vinyl)benzene (5d)
Following the general procedure, compound 5d was synthesized starting from di(cyclopenta-1,3-dien-1-yl)dimethyltitanium (18.2 g of a 12.6% solution in toluene, 11.0 mmol, 2.20 eq), di(cyclopenta-1,3-dien-1-yl)titanium(IV) chloride (75.0 mg, 0.300 mmol, 0.060 eq) and 2,2,2-trifluoroethyl benzoate (1.02 g, 5.00 mmol, 1.00 eq) to obtain (1-(2,2,2-trifluoroethoxy)vinyl)benzene (5d) as a colorless oil (621 mg, 3.07 mmol, 61% yield).

\[ \text{RF} = 0.9 \ (9:1 \ \text{Hexane/Et}_2\text{O}). \]

\[ ^1\text{H NMR} \ (400 \text{ MHz CDCl}_3) \ \delta = 7.65 - 7.61 \ (m, 2 \text{ H, Ar}), 7.39 - 7.36 \ (m, 3 \text{ H, Ar}), 4.82 \ (d, J = 3.7 \text{ Hz}, 1 \text{ H, CH}=C), 4.31 - 4.19 \ (m, 3 \text{ H, CH}=C, \text{CH}_2\text{-CF}_3). \]

\[ ^{13}\text{C NMR} \ (101 \text{ MHz CDCl}_3) \ \delta = 159.1, 135.0, 129.2, 128.4, 125.6, 123.6 \ (q, J = 277 \text{ Hz}). \]

IR 2374 \ (w), 1331 \ (m), 69.9 \ (s), 818 \ (m), 801 \ (m), 656 \ (s).

HRMS (ESI) calcd for C_{10}F_3H_{10}O^+ [M+H]^+ 203.0678; found 203.0678.
The NMR data for (XX) corresponded to the reported values.\(^\text{15}\)

1-(1-(Benzyloxy)vinyl)-3-methylbenzene (5e)

Following the general procedure, compound 5e was synthesized starting from di(cyclopenta-1,3-dien-1-yl)dimethyltitanium (17.1 g of a 10.7% solution in toluene, 8.80 mmol, 2.20 eq), di(cyclopenta-1,3-dien-1-yl)titanium(IV) chloride (60.0 mg, 0.240 mmol, 0.060 eq) and benzyl 3-methylbenzoate (0.905 g, 4.00 mmol, 1.00 eq) to obtain 1-(1-(benzyloxy)vinyl)-3-methylbenzene (5e) as a colorless oil (450 mg, 2.01 mmol, 45% yield).

\[ \text{RF} = 0.9 \ (9:1 \ \text{Hexane/Et}_2\text{O}). \]

\[ ^1\text{H NMR} \ (400 \text{ MHz CDCl}_3) \ \delta = 7.44 - 7.35 \ (m, 4 \text{ H, Ph}), 7.31 \ (t, J = 7.5 \text{ Hz}, 2 \text{ H, ArMe}), 7.28 - 7.21 \ (m, 1 \text{ H, Ph}), 7.15 \ (\text{ddd, } J = 8.3, 6.1, 1.5 \text{ Hz}, 1 \text{ H, ArMe}), 7.05 \ (d, J = 7.5 \text{ Hz}, 1 \text{ H, ArMe}), 4.88 \ (s, 2 \text{ H, CH}_2\text{-Ph}), 4.64 \ (d, J = 2.8 \text{ Hz}, 1 \text{ H, CH}_2\text{=C}), 4.22 \ (d, J = 2.8 \text{ Hz}, 1 \text{ H, CH}_2\text{=C}), 2.28 \ (s, 3 \text{ H, Me}). \]

\[ ^{13}\text{C NMR} \ (101 \text{ MHz CDCl}_3) \ \delta = 160.1, 137.8, 137.3, 136.5, 129.4, 128.6, 128.2, 127.9, 127.6, 126.3, 122.8, 83.2, 69.9, 21.7. \]

HRMS (ESI) calcd for C_{16}H_{17}O^+ [M+H]^+ 225.1274; found 225.1282.

2-(1-(Benzyloxy)vinyl)thiophene (5f)

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S19
Following the general procedure, compound 5f was synthesized starting from di(cyclopenta-1,3-dien-1-yl)dimethyltitanium (17.1 g of a 10.7% solution in toluene, 8.80 mmol, 2.20 eq), di(cyclopenta-1,3-dien-1-yl)titanium(IV) chloride (60.0 mg, 0.240 mmol, 0.060 eq) and benzyl thiophene-2-carboxylate (0.873 g, 4.00 mmol, 1.00 eq) to obtain 2-(1-(benzyloxy)vinyl)thiophene (5f) (0.500 g, 4.00 mmol, 58%) as a colorless oil. Impurities are present in the NMR sample due to degradation of the product during analysis.

Rf 0.8 (9:1 Hexane/Et2O).

\[ ^1H \text{ NMR} (400 \text{ MHz, CDCl}_3) \delta 7.58 – 7.35 (m, 6 \text{ H, Ar}), 7.30 (d, J = 5.0 \text{ Hz, 1 H, Ar}), 7.07 \text{ (dd, } J = 5.0, 3.7 \text{ Hz, 1 H, Ar}), 5.05 (s, 2 \text{ H, Benzyl}), 4.81 (d, J = 2.9 \text{ Hz, 1 H, C=CH}), 4.35 (d, J = 3.1 \text{ Hz, 1 H, C=CH}). \]

\[ ^13C \text{ NMR} (101 \text{ MHz, CDCl}_3) \delta 155.0, 140.4, 136.9, 128.6, 127.9, 127.3, 127.3, 125.2, 124.0, 82.7, 69.8. \]

HRMS (ESI) calcd for C_{13}H_{13}OS^+ [M+H]^+ 217.0682; found 217.0688.

**General Procedure for the Synthesis of Monosubstituted Enol Ethers**

\[
\begin{align*}
\text{PhOH} & \quad + \quad \text{29} \quad \xrightarrow{\text{Pd(TFA)}_2 \text{ dppp \ Et}_3\text{N}} \quad \text{PhO} \quad \text{C=C} \\
\end{align*}
\]

Following a slightly modified procedure,\(^1\) palladium(II) trifluoroacetate (0.500 mol%) and 4,7-diphenyl-1,10-phenanthroline (0.500 mol%) were dissolved in 1-(vinyloxy)butane (29) (20.0 eq) in an oven-dried 20 mL vial equipped with a stirring bar to obtain a yellow solution. The corresponding alcohol (1.00 eq) and triethylamine (0.0750 eq) were then added to the solution. The flask was sealed with a microwave cap and stirred at 75 °C for 24 hours. The reaction was cooled to room temperature and filtrated through a plug of activated charcoal and eluted with hexane. The solvent was evaporated under reduced pressure to obtain the crude oils that were purified by a short column chromatography using deactivated silica gel (3 % Et,N) or basic alumina and hexane as eluent.

**((Vinyloxy)methyl)benzene (5g)**

\[
\begin{align*}
\text{H} & \quad \text{O} \quad \text{Ph} \\
\end{align*}
\]

Following the general procedure, compound 5g was synthesized starting from 1-(vinyloxy)butane (29) (12.0 mL, 92.0 mmol, 20.0 eq) and phenylmethanol (500 mg, 4.62 mmol, 1.00 eq) with palladium(II) trifluoroacetate (7.70 mg, 23.0 µmol, 0.500 mol%), 4,7-diphenyl-1,10-phenanthroline (7.70 mg, 23.0 µmol, 0.500 mol%), and triethylamine (35.0 mg, 0.350 mmol, 0.0750 eq). The crude product was purified by a short column chromatography.

using deactivated silica gel (3 % Et3N) and hexane as eluent to obtain ((vinyloxy)methyl)benzene (5g) as a colorless oil (421 mg, 3.14 mmol, 63% yield).

Rf 0.9 (100 Hexane).

1H NMR (400 MHz, CDCl3) δ 7.40-7.30 (m, 5 H, Ph), 6.57 (dd, 1 H, J = 14.3, 6.8 Hz, CH2=CH-O), 4.77 (s, 2 H, CH2Ph), 4.31 (dd, 1 H, J = 14.3, 1.7 Hz, CH2=CH-O), 4.09 (m, 1 H, CH2=CH-O).

13C NMR (101 MHz, CDCl3) δ 151.7, 136.9, 128.5, 128.0, 127.6, 87.4, 70.1.

The characterization data for 5g corresponded to the reported values.17

1-Bromo-4-((vinyloxy)methyl)benzene (5h)

Following the procedure described above, compound 5h was synthesized starting from 1-(vinyloxy)butane (29) (14.0 mL, 107 mmol, 20.0 eq) and (4-bromophenyl)methanol (1.00 g, 5.35 mmol, 1.00 eq) with palladium(II) trifluoroacetate (8.9 mg, 27.0 μmol, 0.500 mol%), 4,7-diphenyl-1,10-phenanthroline (8.9 mg, 27.0 μmol, 0.500 mol%), and triethylamine (56.0 μL, 0.401 mmol, 0.075 eq). The crude product was purified by a short column chromatography using basic alumina and hexane as eluent to obtain 1-bromo-4-((vinyloxy)methyl)benzene (5h) as a colorless oil (915 mg, 4.29 mmol, 80% yield).

Rf 0.9 (9:1 Hexane/Et2O).

1H NMR (400 MHz, CDCl3) δ 7.49 (d, J = 8.4 Hz, 2 H, Ar), 7.23 (d, J = 8.3 Hz, 2 H, Ar), 6.54 (dd, J = 14.3, 6.8 Hz, 1 H, CH2=CH-O), 4.71 (s, 2 H, CH2Ar), 4.29 (dd, J = 14.3, 2.3 Hz, 1 H, CH2=CH-O), 4.10 (dd, J = 6.8, 2.3 Hz, 1 H, CH2=CH-O).

13C NMR (101 MHz, CDCl3) δ 151.5, 136.2, 131.0, 129.2, 122.0, 87.8, 69.4.

IR 2359 (w), 2316 (w), 1325 (m), 1225 (m), 1091 (m), 993 (s), 895 (m), 847 (m), 684 (s).

1-Nitro-4-((vinyloxy)methyl)benzene (5i)

Following the procedure described above, compound 5i was synthesized starting from 1-(vinyloxy)butane (29) (17.0 mL, 131 mmol, 20.0 eq) and (4-nitrophenyl)methanol (1.00 g, 6.53 mmol, 1.00 eq) with palladium(II) trifluoroacetate (10.9 mg, 33.0 μmol, 0.500 mol%) and 4,7-diphenyl-1,10-phenanthroline (10.9 mg, 33.0 μmol, 0.500 mol%), and triethylamine (68.0 μL, 0.490 mmol, 0.075 eq). The crude product was purified by a short column chromatography using basic alumina and hexane as eluent to obtain 1-nitro-4-((vinyloxy)methyl)benzene (5i) as a colorless oil (973 mg, 5.43 mmol, 83% yield).

Rf 0.9 (9:1 Hexane/Et2O).

1H NMR (400 MHz, CDCl3) δ 8.23 (m, 2 H, Ar), 7.53 (m, 2 H, Ar), 6.57 (dd, 1 H, J = 14.3, 6.8 Hz, CH=C), 4.87 (s, 2 H, OCH2Ar), 4.30 (dd, 1 H, J = 14.3, 2.5 Hz, C=CH2), 4.16 (dd, 1 H, J = 6.8, 2.5 Hz, C=CH2).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 151.1, 147.5, 144.4, 127.6, 123.7, 88.2, 68.5. The $^1$H NMR data for 5i corresponded to the reported values.$^{18}$

**Synthesis of cyclopentylamines and tetrahydrofurylamines:**

\[ \text{Me} \quad \text{Me} \quad + \quad \text{CuCl}_2 \quad + \quad \text{AgX} \quad \xrightarrow{\text{DCM, 3A MS}} \quad \text{Me} \quad \text{Me} \quad \text{Cu} \]

**Synthesis of [Cu(BOX)](X)$_2$7**

Following a modified procedure,$^{19}$ an oven-dried Schlenk tube containing a magnetic stirrer was charged with CuCl$_2$ (1.1 mg, 8.0 $\mu$mol, 1.0 eq), silver salt (15 $\mu$mol, 1.9 eq) and previously activated 3 Å MS in an inert atmosphere (N$_2$). The flask was sealed with a septum, covered with aluminium foil and removed from the glovebox. Under argon atmosphere,$^{20}$ 0.40 mL of a solution of the corresponding BOX ligand (9.6 $\mu$mol, 1.2 eq) in dry dichloromethane were added via syringe. The mixture was stirred for 3 hours at room temperature and filtrated under Ar into a sealed oven-dried vial using a syringe filter (regenerated cellulose, 0.2 $\mu$m), to obtain a bright green solution that was used for the catalysis.$^{21}$

**General Procedure for the racemic [3+2] Annulation Reaction:**

A. Racemic cyclopentylamines or tetrahydrofurylamines were synthesized using 1 equivalent of cyclopropane with 2 equivalents of enol ether or aldehyde in presence of 20 mol% of scandium triflate in dry DCM at 0 °C. Conversion was followed by TLC and when full conversion was reached, the reaction mixture was filtered on a small silica plug. Purification by Preparative TLC afforded material that was submitted to HPLC.

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20 Argon from gas cylinder was used as using central nitrogen supply with Drierite filter gave blue complexes.
21 Blue complex gave lower er and poorly reproducible results.
B. Racemic cyclopentylamines were synthesized using 1 equivalent of cyclopropane with 2 equivalents of enol ether in presence of 20 mol% of tin tetrachloride in dry DCM at -40°C. Conversion was followed by TLC and when full conversion was reached, the reaction mixture was filtered on a small silica plug. Purification by Preparative TLC afforded material that was submitted to HPLC.

**General Procedure for the Screening of Conditions for the Catalytic Asymmetric [3+2] Annulation Reaction:**

The corresponding N-protected-aminocyclopropane\(^{22}\) (40.0 µmol, 1.00 eq) and freshly purified enol ether (50.0 µmol, 1.20 eq) were dissolved in 0.4 mL of dry dichloromethane. The solution was added into a sealed oven-dried vial containing a magnetic stirrer, pre-activated 3 Å MS and 0.4 mL of the solution of the desired complex (0.01 M, 4.00 µmol, 0.1 eq). Dry dichloromethane was used to complete a final volume of 1.0 mL. The mixture was stirred at rt until full conversion was obtained as verified by TLC. The reaction was quenched by addition of 0.3 mL of Et₂N and filtrated through a silica gel plug eluting with 5 mL of a mixture 1:1 Hexane/AcOEt to obtain a yellowish solution. The solvent was evaporated under reduced pressure and the crude analyzed by \(^1\)H NMR and chiral HPLC. The yields indicated in Scheme 2B was obtained using trimethoxybenzene as internal standard.

**Dimethyl-(2S,4S)-4-(1,3-dioxoisindolin-2-yl)-2-phenyl-2-((triisopropylsilyl)oxy) cyclopentane-1,1-dicarboxylate (6a)**

![Chemical structure of 6a]

Chiralcel IA Hexane/iPrOH 95:5, 0.5 mL/min, λ = 220 nm, tr1 = 19.8 min; tr2 = 21.2 min. The crude of the reaction using Isopropyl-BOX/Cu(SbF\(_6\))\(_2\) complex was analyzed: er = 76:24. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.87 (m, 2 H, Phth), 7.80-7.72 (m, 4 H, Phth + Ar), 7.34-7.25 (m, 3 H, Ar), 5.29 (m, 1 H, N-C-H), 3.86 (s, 3 H, OMe), 3.81 (t, 1 H, J = 12.2 Hz, CH\(_2\)), 3.47-3.39 (m, 1H, CH\(_2\)), 3.42 (s, 3H, OMe), 2.91 (dd, 1 H, J = 13.7, 8.7 Hz, CH\(_2\)), 2.46 (dd, 1 H, J = 12.4, 6.2 Hz, CH\(_2\)), 1.01-0.92 (m, 21 H, TIPS).

\(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 171.0, 168.7, 168.4, 141.8, 134.1, 132.0, 128.4, 128.0, 127.1, 123.2, 87.6, 70.1, 52.4, 52.1, 47.8, 41.7, 36.2, 18.2, 18.2, 13.7.\(^{23}\)

The characterization data for 6a corresponded to the reported values.\(^{24}\)

**Dimethyl-(2S,4S)-2-(benzyloxy)-4-(1,3-dioxoisindolin-2-yl)-2-phenylcyclopentane-1,1-dicarboxylate (30)**

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22 Dried by dissolving in benzene then removing the solvent under reduced pressure and drying in high vacuo.

23 The CH\(_3\) carbons of TIPS are splitting.

Chiralcel IA Hexane/iPrOH 95:5, 1 mL/min, λ = 254 nm, tr1 = 18.3 min; tr2 = 21.1 min. The crude of the reaction using tert-butyl-BOX/Cu(ClO₄)₂ complex was analyzed: er = 78:22. \( R_f \) 0.7 (5:5 Pentane/AcOEt).

M.p. 187.0 – 188.8 °C.

^1H NMR (400 MHz, CDCl₃) δ 7.85 (dd, J = 5.4, 3.0 Hz, 2 H, Phth), 7.73 (dd, J = 5.5, 3.0 Hz, 2 H, Phth), 7.66 – 7.58 (m, 2 H, Ar), 7.42 – 7.27 (m, 8 H, Ar), 5.06 (dddd, J = 11.6, 10.0, 7.5, 6.2 Hz, 1 H, N-C-H), 4.39 (d, J = 11.7 Hz, 1 H, CH₂ Benzyl), 4.08 (d, J = 11.7 Hz, 1 H, CH₂ benzyl), 3.82-3.73 (m, 1 H, CH₂), 3.76 (s, 3 H, OMe), 3.65 – 3.49 (m, 1 H, CH₂), 3.60 (s, 3 H, OMe ), 2.88 (dd, J = 14.0, 7.5 Hz, 1 H, CH₂), 2.57 (dd, J = 13.1, 6.3 Hz, 1 H, CH₂).

^13C NMR (101 MHz, CDCl₃) δ 170.3, 168.5, 168.3, 138.2, 136.5, 134.1, 131.9, 129.2, 128.3, 128.1, 127.3, 127.2, 126.5, 123.3, 89.8, 68.2, 63.5, 52.4, 52.2, 46.4, 36.1, 35.6.

IR 1737 (s), 1712 (s), 1645 (m), 1633 (m), 1595 (m), 1531 (m), 1435 (m), 1412 (m), 1360 (m), 1336 (s), 1263 (w), 1161 (m), 1127 (w), 1116 (w), 1115 (w), 1097 (m), 995 (m), 967 (m), 956 (m), 863 (m), 690 (m), 689 (m).

HRMS (ESI) calcd for C₃₀H₂₇NNaO₇⁺ [M+Na]⁺ 536.1680; found 536.1667.

Dimethyl-(2S,4S)-2-(benzyloxy)-4-(5-methoxy-1,3-dioxoisindolin-2-yl)-2-phenylcyclopentane-1,1-dicarboxylate (31)

Chiralcel IA Hexane/iPrOH 80:20, 1 mL/min, λ = 220 nm, tr1 = 15.4 min; tr2 = 56.1 min. The crude of the reaction using tert-butyl-BOX/Cu(ClO₄)₂ complex was analyzed: er = 74:26. \( R_f \) 0.8 (5:5 Pentane/AcOEt).

M.p. 128.3 – 130.7 °C.

^1H NMR (400 MHz, CDCl₃) δ 7.75 (d, J = 8.3 Hz, 1 H, Ar), 7.67 – 7.58 (m, 2 H, Ar), 7.41 – 7.27 (m, 9 H, Ar), 7.16 (dd, J = 8.3, 2.3 Hz, 1 H, Ar), 5.10 – 4.94 (m, 1 H, N-C-H), 4.38 (d, J = 11.7 Hz, 1H, CH₂ benzyl), 4.06 (d, J = 11.7 Hz, 1H, CH₂ benzyl), 3.93 (m, 3 H, OMe), 3.83-3.71 (m, 1 H, CH₂), 3.75 (s, 3 H, OMe), 3.59 (s, 3 H, OMe), 3.57 – 3.47 (m, 1 H, CH₂), 2.86 (dd, J = 14.0, 7.5 Hz, 1 H, CH₂), 2.55 (dd, J = 13.1, 6.3 Hz, 1 H, CH₂).

^13C NMR (101 MHz, CDCl₃) δ 170.3, 168.5, 168.1, 168.1, 164.8, 138.2, 136.6, 134.5, 129.2, 128.3, 128.1, 127.3, 127.1, 125.0, 125.0, 123.9, 119.8, 108.0, 89.7, 68.2, 63.4, 56.1, 52.3, 52.2, 46.4, 36.1, 35.6.

IR 1360 (m), 1336 (s), 1263 (w), 1161 (w), 1127 (w), 1116 (w), 1115 (w), 1065 (s), 995 (m), 967 (m), 956 (m), 863 (m), 690 (m), 689 (m).

HRMS (ESI) calcd for C₃₁H₂₉NNaO₇⁺ [M+Na]⁺ 566.1785; found 566.1788.

Dimethyl-(2S,4S)-2-(benzyloxy)-4-(5-nitro-1,3-dioxoisindolin-2-yl)-2-phenylcyclopentane-1,1-dicarboxylate (32)

S24
Chiralcel IA Hexane/iPrOH 85:15, 1 mL/min, λ = 220 nm, tr1 = 33.4 min; tr2 = 36.6 min. The crude of the reaction using tert-butyl-BOX/Cu(ClO₄)₂ complex was analyzed: er = 92:8. Rᵣ 0.8 (5:5 Pentane/AcOEt).

M.p. 95.5 – 98.3 °C.

¹H NMR (400 MHz, CDCl₃) δ 8.82 – 8.50 (m, 2 H, Ar), 8.05 (dd, J = 8.1, 0.7 Hz, 1 H, Ar), 7.80 – 7.57 (m, 2 H, Ar), 7.48 – 7.13 (m, 8 H, Ar), 5.06 (tdd, J = 7.7, 4.3, 2.2 Hz, 1 H, N-C-H), 4.36 (d, J = 11.8 Hz, 1 H, CH₂ benzyl), 4.10 (d, J = 11.7 Hz, 1 H, CH₂ benzyl), 3.84 – 3.67 (m, 1 H, CH₂), 3.76 (s, 3 H, OMe), 3.67 – 3.44 (m, 1 H, CH₂), 3.60 (s, 3 H, OMe), 2.86 (dd, J = 14.0, 7.4 Hz, 1 H, CH₂), 2.60 (dd, J = 13.1, 6.3 Hz, 1 H, CH₂).

¹³C NMR (101 MHz, CDCl₃) δ 170.2, 168.3, 166.1, 165.8, 151.8, 138.0, 136.3, 136.2, 133.3, 129.4, 129.1, 128.4, 128.3, 127.4, 127.3, 126.5, 124.5, 118.7, 89.8, 68.2, 63.6, 52.4, 52.3, 47.2, 36.0, 35.6.

IR 1393 (w), 1345 (s), 1201 (m), 1126 (w), 1115 (w), 1069 (m), 1043 (s), 972 (w), 868 (m), 691 (m).

HRMS (ESI) calcld for C₃₀H₂₆N₂NaO₉⁺ [M+Na]⁺ 581.1531; found 581.1540.

**General Procedure for the Catalytic Asymmetric [3+2] Annulation Reaction**

Dimethyl 2-(2,5-dioxopyrrolidin-1-yl)cyclopropane-1,1-dicarboxylate (4b) (51.0 mg, 0.200 mmol, 1.00 eq) and freshly purified enol ether or aldehyde (0.400 mmol, 2.00 eq) were dissolved in 2.0 mL of dry dichloromethane. The solution was added into a sealed oven-dried vial containing a magnetic stirrer, pre-activated 3 Å MS and 2.0 mL of the solution of the copper complex (0.01M, 0.020 mmol, 0.10 eq). Dry dichloromethane was used to complete a final volume of 5.0 mL. The mixture was stirred at rt until full conversion was observed by TLC. The reaction was quenched by addition of 0.5 mL of Et₃N and filtrated through a silica gel plug eluting with 10 mL of a mixture of 3:7 Hexane/AcOEt. The solvent was evaporated under reduced pressure and the crude analyzed by ¹H NMR. Purification by column chromatography using pentane/AcOEt (6:4 to 3:7) afforded the product as a mixture of diastereoisomers. In the case of the reaction with enol ether, it was possible to purify the major diastereomer by preparative TLC for characterization and HPLC analysis. For aldehydes, characterization was done directly on the obtained mixture of diastereoisomers.

**Racemization experiment of cyclopropane 4b**

Dimethyl 2-(2,5-dioxopyrrolidin-1-yl)cyclopropane-1,1-dicarboxylate (4b) (10 mg, 0.039 mmol, 1.00 eq) was dissolved in 0.5 mL of dry dichloromethane. The solution was added into a sealed oven-dried vial containing a magnetic stirrer, pre-activated 3 Å MS and 2.0 mL of the solution of the copper complex (0.0020 M, 0.0039 mmol, 0.10 eq). Two aliquots (1 mL each) were taken at 30 min and 3 h after the reaction was set up. The aliquots were filtered over a pad of alumina, eluting with AcOEt, and were submitted to chiral HPLC analysis.

er₃₀₀min = 50:50, Chiralcel IA Hexane/iPrOH 80:20, 1 mL/min, λ = 210 nm, tr1 = 23.9 min; tr2 = 26.8 min.
\( \text{er}_{94} = 50:50 \), Chiralcel IA Hexane/iPrOH 80:20, 1 mL/min, \( \lambda = 210 \) nm, tr1 = 23.7 min; tr2 = 26.4 min.

**Dimethyl-(2S,4S)-2-(benzyl)-4-(2,5-dioxopyrrolidin-1-yl)-2-phenylcyclopentane-1,1-dicarboxylate (6b)**

Following the general procedure, using 1-(benzyl)benzene (5b) (84.0 mg, 0.400 mmol, 2.00 eq), dimethyl 2-(benzyl)-4-(2,5-dioxopyrrolidin-1-yl)-2-phenylcyclopentane-1,1-dicarboxylate (6b) (90.3 mg, 0.194 mmol, 97 %) was obtained as a colorless solid.

**Crude analysis:** 
Dr = 7:1 between peaks at 5.01 (minor) and 4.67 (major).

\( \text{er}_{\text{major}} = 96:4 \), Chiralcel IA Hexane/iPrOH 80:20, 1 mL/min, \( \lambda = 210 \) nm, tr1 = 18.2 min; tr2 = 24.0 min.

\([\alpha]_D^{25.0} = 21.0 \) (c = 0.43, CHCl3).

\( \text{Rf} = 0.30 \) (5:5 Hexane/AcOEt).

\( \text{M.p.} 90.1 – 91.7 \, ^\circ\text{C}. \)

\(^1\text{H NMR}\) (400 MHz, CDCl3) \( \delta 7.57 – 7.41 \) (m, 2 H, Ar), 7.32 – 7.13 (m, 8 H, Ar), 5.01 – 4.67 (m, 1 H, N-C-H), 4.33 (d, \( J = 11.7 \) Hz, 1H, CH\(_2\) benzyl), 4.03 (d, \( J = 11.7 \) Hz, 1H, CH\(_2\) benzyl), 3.66 (s, 3 H, OMe), 3.56 (dd, \( J = 13.1, 11.6 \) Hz, 1 H, CH\(_2\)), 3.49 (s, 3 H, OMe), 3.37 (dd, \( J = 14.0, 10.3, 0.9 \) Hz, 1 H, CH\(_2\)), 2.71 (dd, \( J = 13.9, 7.2 \) Hz, 1 H, CH\(_2\)), 2.63 (s, 4 H, CH\(_2\) succinimide), 2.38 (dd, \( J = 13.0, 6.4 \) Hz, 1 H, CH\(_2\)).

\(^{13}\text{C NMR}\) (101 MHz, CDCl3) \( \delta 177.0, 170.1, 168.3, 138.0, 136.3, 129.1, 128.2, 128.0, 127.1, 127.0, 126.3, 89.6, 68.0, 63.2, 52.2, 52.1, 46.9, 34.9, 34.5, 28.0.

\( \text{IR} 2255 \) (w), 1738 (w), 1704 (m), 1382 (w), 1260 (w), 1178 (w), 906 (s).

\( \text{HRMS (ESI) calcd for C}_{26}\text{H}_{27}\text{NNaO}_{7}^{+} [\text{M+Na}]^{+} 488.1680; \text{found} 488.1687.\)

**Dimethyl-(2S,4S)-4-(2,5-dioxopyrrolidin-1-yl)-2-methoxy-2-(p-toly)cyclopentane-1,1-dicarboxylate (6c)**

Following the general procedure, using 1-(p-methoxyvinyl)-4-methylbenzene (5c) (59.3 mg, 0.400 mmol, 2.00 eq), dimethyl 4-(2,5-dioxopyrrolidin-1-yl)-2-methoxy-2-(p-toly)cyclopentane-1,1-dicarboxylate (6c) (77.0 mg, 0.191 mmol, 95 %) was obtained as a colorless solid.

**Crude analysis:** Dr = 20:1 between peaks at 5.17 (minor) and 4.84 (major).

\( \text{er}_{\text{major}} = 94.5:5.5 \), Chiralcel IA Hexane/iPrOH 80:20, 1 mL/min, \( \lambda = 220 \) nm, tr1 = 17.9 min; tr2 = 22.5 min.

\([\alpha]_D^{25.0} = 15.7 \) (c = 0.81, CHCl3).
RF 0.3 (3:7 Pentane/AcOEt).

M.p. 97.5 - 99.0 °C.

1H NMR (400 MHz, CDCl3) δ 7.36 (d, J = 8.3 Hz, 2 H, Ar), 7.13 (d, J = 8.1 Hz, 2 H, Ar), 4.83 (tt, J = 11.0, 6.6 Hz, 1 H, N-CH), 3.74 (s, 3 H, OMe), 3.58 (s, 3 H, OMe), 3.54 – 3.42 (m, 1 H, CH2), 3.36 (dd, J = 14.0, 10.7 Hz, 1 H, CH2), 2.97 (s, 3 H, Me), 2.80 – 2.60 (m, 1 H, CH2), 2.72 (s, 4 H, CH2 succinimide), 2.40 – 2.22 (m, 1 H, CH2), 2.36 (s, 3 H, Me).

13C NMR (101 MHz, CDCl3) δ 177.1, 170.2, 168.5, 137.6, 133.0, 129.3, 127.8, 89.5, 67.7, 52.2, 52.1, 49.5, 46.5, 34.9, 33.8, 28.0, 21.1.

IR 1740 (s), 1703 (s), 1436 (w), 1399 (w), 1382 (m), 1294 (w), 1276 (w), 1261 (w), 1178 (m).


**Dimethyl-(2S,4S)-4-(2,5-dioxopyrrolidin-1-yl)-2-phenyl-2-(2,2,2-trifluoroethoxy)cyclopentane-1,1-dicarboxylate (6d)**

Following the general procedure, using (1-(2,2,2-trifluoroethoxy)vinyl)benzene (5d) (81.0 mg, 0.400 mmol, 2.00 eq), dimethyl 4-(2,5-dioxopyrrolidin-1-yl)-2-phenyl-2-(2,2,2-trifluoroethoxy)cyclopentane-1,1-dicarboxylate (6d) (80.4 mg, 0.176 mmol, 88 %) was obtained as a colorless oil.

**Crude analysis: dr = 1.5:1 between peaks at 5.06 (minor) and 4.75 (major).**

**anti**

er = 95.5:4.5, Chiralcel IB Hexane/iPrOH 80:20, 1 mL/min, λ = 210 nm, tr1 = 14.6 min; tr2 = 17.4 min.

[a]D^25° -18.9 (c = 0.43, CHCl3).

RF 0.2 (4:6 Pentane/AcOEt).

1H NMR (400 MHz, CDCl3) δ 7.59 – 7.43 (m, 2 H, Ar), 7.43 – 7.28 (m, 3 H, Ar), 4.97 – 4.75 (m, 1 H, N-CH), 3.80 (s, 3 H, OMe), 3.60 (dd, J = 13.4, 11.6 Hz, 1 H, CH2), 3.56 – 3.44 (m, 1 H, CH2-CF3), 3.53 (s, 3 H, OMe), 3.43 – 3.30 (m, 2 H, CH2 + CH2-CF3), 2.84 – 2.75 (m, 1 H, CH2), 2.71 (s, 4 H, CH2 succinimide), 2.24 (dd, J = 13.3, 6.4 Hz, 1 H, CH2).

13C NMR (101 MHz, CDCl3) δ 177.0, 169.8, 167.7, 135.0, 129.0, 128.7, 127.6, 123.6 (q, J = 278 Hz), 90.4, 67.7, 60.50 (q, J = 35 Hz), 52.4, 52.3, 46.6, 34.8, 34.6, 28.0.

IR 1808 (m), 1771 (s), 1521 (w), 1520 (w), 1519 (w), 1515 (m), 1526 (s).

HRMS (ESI) calcd for C21H22F3iPrNaO7+ [M+Na]+ 480.1241; found 480.1243.

**syn**

er = 96.5:3.5, Chiralcel IA Hexane/iPrOH 90:10, 1 mL/min, λ = 220 nm, tr1 = 28.6 min; tr2 = 31.1 min.

[a]D^25° -2.3 (c = 0.39, CHCl3).

RF 0.3 (4:6 Pentane/AcOEt).

1H NMR (400 MHz, CDCl3) δ 7.64 – 7.52 (m, 2 H, Ar), 7.41 – 7.29 (m, 3 H, Ar), 5.20 – 5.06 (m, 1 H, N-CH), 4.06 (dq, J = 10.2, 8.4 Hz, 1 H, CH2-CF3), 3.75 (s, 3 H, OMe), 3.61 – 3.40

S27
(m, 1 H, CH$_2$ + CH$_2$-CF$_3$), 3.50 (s, 3 H, OMe), 3.01 (dd, J = 15.1, 11.0 Hz, 1 H, CH$_2$), 2.84 – 2.67 (m, 5 H, CH$_2$ succinimide+ CH$_2$), 2.34 (dd, J = 12.9, 7.4 Hz, 1 H, CH$_2$).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 177.1, 169.3, 167.6, 135.2, 129.1, 128.4, 127.6, 124.1 (q, J = 278 Hz), 90.7, 70.0, 60.4 (q, J = 35 Hz), 52.5, 52.1, 47.4, 36.5, 33.7, 28.0.

IR 1737 (m), 1705 (s), 1447 (m), 1383 (w), 1295 (m), 1279 (m), 1256 (w), 1170 (s).

HRMS (ESI) calcd for C$_{22}$H$_{22}$F$_3$NaO$_7^{+}$ [M+Na]$^+$ 480.1241; found 480.1237.

Dimethyl-(2S,4S)-2-benzyloxy)-4-(2,5-dioxopyrrolidin-1-yl)-2-(m-tolyl)cyclopentane-1,1-dicarboxylate (6e)

Following the general procedure, using 1-(1-(benzylxy)vinyl)-3-methylbenzene (5e) (90.0 mg, 0.400 mmol, 2.00 eq), dimethyl 2-(benzyloxy)-4-(2,5-dioxopyrrolidin-1-yl)-2-(m-tolyl)cyclopentane-1,1-dicarboxylate (6e) (96.0 mg, 0.199 mmol, 99%) was obtained as a colorless oil.

Crude analysis: dr >20:1.

er = 95:5, Chiralcel IA Hexane/iPrOH 80:20, 1 mL/min, $\lambda$ = 220 nm, tr1 = 16.2 min; tr2 = 22.1 min.

$[\alpha]_D$$^{25.0}$ -16.5 (c = 0.44, CHCl$_3$).

R$_f$ 0.25 (4:6 Pentane/AcOEt).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.37 – 7.29 (m, 4 H, Ar), 7.28 – 7.23 (m, 3 H, Ar), 7.20 (t, J = 7.7 Hz, 1 H, Ar), 7.11 (d, J = 7.5 Hz, 1 H, Ar), 4.97 – 4.81 (m, 1 H, N-CH), 4.31 (d, J = 11.7 Hz, 1 H, CH$_2$ benzyl), 4.03 (d, J = 11.7 Hz, 1 H, CH$_2$ benzyl), 3.73 (s, 3 H, OMe), 3.65 – 3.55 (m, 1 H, CH$_2$), 3.57 (s, 3 H, OMe), 3.44 (dd, J = 13.9, 10.4 Hz, 1 H, CH$_2$), 2.78 (dd, J = 13.9, 7.0 Hz, 1 H, CH$_2$), 2.70 (s, 4 H, CH$_2$ succinimide), 2.45 (dd, J = 13.0, 6.5 Hz, 1 H, CH$_2$), 2.34 (s, 3 H, Me).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 177.1, 170.2, 168.3, 138.2, 136.5, 136.3, 130.0, 128.8, 128.3, 127.1$^{25}$, 126.4, 126.2, 89.7, 68.1, 63.3, 52.2, 52.1, 46.9, 35.0, 34.6, 28.0, 21.7.

IR 2924 (w), 1739 (m), 1703 (s), 1435 (w), 1383 (m), 1295 (w), 1259 (w), 1181 (m), 738 (w).

HRMS (ESI) calcd for C$_{27}$H$_{29}$NaO$_{7}^{+}$ [M+Na]$^+$ 502.1836; found 502.1845.

$^{25}$ 2 carbon signal overlapping.

S28
**Dimethyl-(2R,4S)-2-(benzyloxy)-4-(2,5-dioxopyrrolidin-1-yl)-2-(thiophen-2-yl)cyclopentane-1,1-dicarboxylate (6f)**

Following the general procedure, using 2-((benzyloxy)methyl)benzene (5g) (53.7 mg, 0.400 mmol, 2.00 eq), dimethyl 2-(benzyloxy)-4-(2,5-dioxopyrrolidin-1-yl)-2-(thiophen-2-yl)cyclopentane-1,1-dicarboxylate (6g) (53.7 mg, 0.189 mmol, 94%) was obtained as a colorless oil.

**Crude analysis:** $d_r = 8:1$ between peaks at 5.11 (minor) and 4.86 (major).

$\text{er}_{\text{major}} = 94:6$, Chiralcel IA Hexane/iPrOH 80:20, 1 mL/min, $\lambda = 210$ nm, $t_{r1} = 27.0$ min; $t_{r2} = 40.2$ min.

$[\alpha]_{\text{D}}^{25.0} - 11.8$ (c = 0.44, CHCl$_3$).

$R_f$ 0.2 (4:6 Pentane/AcOEt).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.42 – 7.14 (m, 7 H, Ar), 6.97 (dd, $J = 5.1$, 3.6 Hz, 1 H, Thiophene), 4.86 (dddd, $J = 11.9$, 10.0, 7.9, 6.3 Hz, 1 H, N-CH), 4.33 (d, $J = 11.4$ Hz, 1H, CH$_2$ benzyl), 4.14 (d, $J = 11.4$ Hz, 1H, CH$_2$ benzyl), 3.79 (s, 3 H, OMe), 3.63 – 3.52 (m, 1 H, CH$_2$), 3.60 (s, 3 H, OMe), 3.38 (dd, $J = 13.9$, 10.1 Hz, 1 H, CH$_2$), 2.79 (dd, $J = 13.9$, 7.9 Hz, 1 H, CH$_2$), 2.70 (s, 4 H, CH$_2$ succinimide), 2.59 (dd, $J = 12.9$, 6.3 Hz, 1 H, CH$_2$).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 177.2, 170.2, 168.5, 141.4, 138.0, 128.9, 128.3, 127.4, 126.9, 126.6, 126.0, 87.7, 68.2, 63.9, 52.5, 52.4, 47.1, 36.8, 34.7, 28.2.

IR 1740 (s), 1704 (s), 1435 (w), 1384 (w), 1270 (w), 1175 (m).

HRMS (ESI) calcd for C$_{24}$H$_{25}$NNaO$_7$S$^+$ [M+Na]$^+$ 494.1244; found 494.1241.

**ROESY**

**Dimethyl-(2R,4S)-2-(benzyloxy)-4-(2,5-dioxopyrrolidin-1-yl)cyclopentane-1,1-dicarboxylate (6g)**

Following the general procedure, using ((vinylloxy)methyl)benzene (5g) (53.7 mg, 0.400 mmol, 2.00 eq), dimethyl 2-(benzyloxy)-4-(2,5-dioxopyrrolidin-1-yl)cyclopentane-1,1-
dicarboxylate (6g) (74.8 mg, 0.192 mmol, 96%) was obtained as a colorless solid. Recrystallized from isopropanol.

**Crude analysis: dr= 4:1 between peaks at 3.79 (major) and 3.75 (minor).**

\[\text{er}_{\text{major}} = 96.5:3.5, \text{Chiralcel IA Hexane/iPrOH 80:20, 1 mL/min, } \lambda = 210 \text{ nm, tr1 = 27.4 min; tr2 = 37.8 min.}\]

\[[\alpha]_{D}^{25.0} = -32.7 \text{ (c = 0.43, CHCl$_3$).}\]

**R$_f$ 0.3 (5:5 Pentane/AcOEt).**

**M.p. 106.8 – 109.5 °C.**

**$^1$H NMR** (400 MHz, CDCl$_3$) $\delta$ 7.36 – 7.24 (m, 5 H, Ar), 5.03 – 4.82 (m, 1 H, N-C-H), 4.75 (dd, $J$ = 4.7, 2.7 Hz, 1 H, O-C-H), 4.59 (d, $J$ = 11.9 Hz, 1H, CH$_2$ benzyl) 4.49 (d, $J$ = 11.9 Hz, 1H, CH$_2$ benzyl), 3.79 (s, 3 H, OMe), 3.68 (s, 3 H, OMe), 3.03 (dd, $J$ = 14.4, 10.6 Hz, 1 H, CH$_2$), 2.64 (s, 4 H, succinimide), 2.50 – 2.29 (m, 2 H, CH$_2$), 2.15 (dd, $J$ = 13.4, 8.3, 2.7 Hz, 1 H, CH$_2$).

**$^{13}$C NMR** (101 MHz, CDCl$_3$) $\delta$ 176.9, 171.0, 169.0, 138.0, 128.3, 127.6, 127.4, 83.0, 71.7, 65.1, 52.9, 52.7, 48.0, 34.0, 33.3, 28.0.

**IR** 1737 (m), 1702 (m), 1697 (w), 1397 (w), 1384 (w), 1283 (w), 1262 (w), 1175 (m), 1100 (w).

**HRMS (ESI)** calcd for C$_{20}$H$_{24}$NO$_7$ [M+H]$^+$ 390.1547; found 390.1554.

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**Procedure for the Catalytic Asymmetric [3+2] Annulation Reaction on 1 mmol scale:**

Dimethyl 2-(2,5-dioxopyrrolidin-1-yl)cyclopropane-1,1-dicarboxylate (4b) (255 mg, 1.00 mmol, 1.00 eq) and freshly purified enol ether 5g (268 mg, 2.00 mmol, 2.00 eq) were dissolved in 10.0 mL of dry dichloromethane. The solution was added into a sealed oven dried vial containing a magnetic stirrer, pre-activated 3 Å MS and 10.0 mL of the solution of the copper complex (0.01 M, 0.100 mmol, 0.10 eq). Dry dichloromethane was used to complete a final volume of 25.0 mL. The mixture was stirred at rt for 2 hours and full conversion was observed by TLC. The reaction was quenched by addition of 1 mL of Et$_3$N and filtrated through a silica gel plug eluting with 50 mL of a mixture of 3:7 Hexane/AcOEt. The solvent was evaporated under reduced pressure and the crude analyzed by $^1$H NMR. Purification by column chromatography using pentane/AcOEt (6:4 to 3:7) afforded dimethyl-2-(benzyloxy)-4-(2,5-dioxopyrrolidin-1-yl)cyclopentane-1,1-dicarboxylate (6g) (311 mg, 0.800 mmol, 80%) as a colorless solid.

**Crude analysis: dr= 4:1 between peaks at 3.03 (major) and 3.37 (minor).**

\[\text{er}_{\text{major}} = 95.5:4.5, \text{Chiralcel IA Hexane/iPrOH 80:20, 1 mL/min, } \lambda = 210 \text{ nm.}\]

**Dimethyl-(2R,4S)-2-((4-bromobenzyl)oxy)-4-(2,5-dioxopyrrolidin-1-yl)cyclopentane-1,1-dicarboxylate (6h)**

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$^{26}$ Structure is registered in CCDC under the number CCDC 988525
Following the general procedure, using 1-bromo-4-((vinylxy)methyl)benzene (5h) (85.0 mg, 0.400 mmol, 2.00 eq), dimethyl 2-((4-bromobenzyl)oxy)-4-(2,5-dioxopyrrolidin-1-yl)cyclopentane-1,1-dicarboxylate (6h) (68.2 mg, 0.146 mmol, 72.8 %) was obtained as a colorless oil.

Crude analysis: \( dr = 5:1 \) between peaks at 3.36 (minor) and 3.00 (major).

\( [\alpha]^\circ_{25.0} -28.9 \) (c = 0.46, CHCl₃).

\( R_f \) 0.20 (4:6 Hexane/AcOEt).

\( \text{H NMR} \) (400 MHz, CDCl₃) \( \delta \) 7.44 (d, \( J = 8.3 \) Hz, 2 H, Ar), 7.13 (d, \( J = 8.3 \) Hz, 2 H, Ar), 4.93 (dtd, \( J = 10.6, 8.7, 6.4 \) Hz, 1 H, O-C-H), 4.75 (dd, \( J = 4.9, 3.0 \) Hz, 1 H, O-C-H), 4.55 (d, \( J = 11.9 \) Hz, 1H, CH₂ benzyl), 4.44 (d, \( J = 12.1 \) Hz, 1H, CH₂ benzyl), 3.79 (s, 3 H, OMe), 3.68 (s, 3 H, OMe), 3.00 (dd, \( J = 14.4, 10.6 \) Hz, 1 H, CH₂), 2.65 (s, 4 H, CH₂ succinimide), 2.50 – 2.24 (m, 2 H, CH₂), 2.13 (ddd, \( J = 13.5, 8.4, 3.0 \) Hz, 1 H, CH₂).

\( \text{C NMR} \) (101 MHz, CDCl₃) \( \delta \) 176.8, 171.0, 169.0, 137.0, 131.4, 129.0, 121.4, 83.0, 71.0, 65.8, 52.9, 52.7, 47.8, 34.1, 33.4, 28.0.

IR 1739 (m), 1703 (s), 1397 (w), 1383 (w), 1283 (w), 1262 (w), 1261 (w), 1176 (w).

HRMS (ESI) calcd for \( C_{20}^{70}BrH_{23}NO_{7} \) [M+H]+ 468.0652; found 468.0661.

**ROESY**

**Dimethyl-(2R,4S)-4-(2,5-dioxopyrrolidin-1-yl)-2-((4-nitrobenzyl)oxy)cyclopentane-1,1-dicarboxylate (6i)**

Following the general procedure, using 1-nitro-4-((vinylxy)methyl)benzene (5i) (71.7 mg, 0.400 mmol, 2.00 eq), dimethyl 4-(2,5-dioxopyrrolidin-1-yl)-2-((4-}

\(^{27}\) Due to shoulder in the peaks, separation was not complete (cf HPLC spectra).
nitrobenzyl)oxy)cyclopentane-1,1-dicarboxylate (6i) (71.0 mg, 0.163 mmol, 82%) was obtained as a colorless solid.

**Crude analysis:** dr= 5:1 between peaks at 4.44 (minor) and 4.95 (major).

$\delta_{R}^{major}$ = 98:2, Chiralcel IF Hexane/iPrOH 70:30, 1 mL/min, $\lambda$ = 230 nm, tr1 = 49.9 min; tr2 = 67.0 min.

[α]$^{D}_{[\text{R}]}$ 25.0 -27.1 (c = 0.43, CHCl$_3$).

R$_f$ 0.39 (5:5 Hexane/AcOEt).

**M.p.** 67.9 – 70.5 °C.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.23 – 8.11 (m, 2 H, Ar), 7.46 – 7.39 (m, 2 H, Ar), 4.95 (ddt, $J$ = 10.5, 8.6, 6.5 Hz, 1 H, N-CH), 4.86 – 4.80 (m, 1 H, CHO), 4.72 (d, $J$ = 13.2 Hz, 1H, CH$_2$ benzyl), 4.62 (d, $J$ = 13.2 Hz, 1H, CH$_2$ benzyl), 3.80 (s, 3 H, Me), 3.70 (s, 3 H, Me), 3.00 (dd, $J$ = 14.4, 10.5 Hz, 1 H, CH$_2$), 2.66 (s, 4 H, CH$_2$ succinimide), 2.45 – 2.34 (m, 2 H, CH$_2$), 2.19 (ddd, $J$ = 13.6, 8.7, 3.6 Hz, 1 H, CH$_2$).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 176.8, 170.8, 168.9, 147.3, 145.5, 127.3, 123.5, 83.4, 70.5, 64.9, 52.9, 52.7, 47.6, 34.0, 33.5, 27.9.

IR 1737 (m), 1703 (s), 1637 (m), 1523 (s), 1436 (m), 1348 (s), 1275 (m), 1215 (s), 1203 (w), 1177 (s).

HRMS (ESI) calcld for C$_{20}$H$_{21}$N$_2$O$_2$Na$^+$ [M+Na]$^+$; found 457.1218; found 457.1232.

**Dimethyl-(2R,5R)-5-(2,5-dioxopyrrolidin-1-yl)-2-phenylidihydrofuran-3,3(2H)-dicarboxylate (9a)**

Following the general procedure, using benzaldehyde (8a) (42.4 mg, 0.400 mmol, 2.00 eq), dimethyl 5-(2,5-dioxopyrrolidin-1-yl)-2-phenylidihydrofuran-3,3(2H)-dicarboxylate (9a) (59.2 mg, 0. 164 mmol, 82%) was obtained as a colorless oil.

**Crude analysis:** dr = 13:1 between peaks at 5.35 (minor) and 5.78 (major).

$\delta_{R}^{major}$ = 92:8, Chiralcel IA Hexane/iPrOH 70:30, 1 mL/min, $\lambda$ = 210 nm, tr1 = 18.9 min; tr2 = 24.3 min.

$\delta_{R}^{minor}$ = 92:8, Chiralcel IA Hexane/iPrOH 70:30, 1 mL/min, $\lambda$ = 210 nm, tr1 = 11.1 min; tr2 = 13.0 min.

[α]$^{D}_{[\text{R}]}$ 50.9 (c = 0.49, CHCl$_3$).

R$_f$ 0.4 (4:6 Pentane/AcOEt).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.51 (d, $J$ = 7.5 Hz, 2 H, Ar), 7.35 – 7.23 (m, 3 H, Ar), 5.78 (m, 2 H, N-C-H + Ph-C-H), 4.24 – 4.05 (m, 1 H, CH$_2$), 3.83 (s, 3 H, OMe), 3.10 (d, $J$ = 1.7 Hz, 3 H, OMe), 2.75 (d, $J$ = 1.7 Hz, 4 H, CH$_2$ succinimide), 2.45 – 2.28 (m, 1 H, CH$_2$).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 176.2, 170.9, 167.8, 137.5, 128.5, 128.0, 127.6, 82.5, 79.6, 65.0, 53.4, 52.3, 33.1, 28.0.

IR 1737 (s), 1715 (s), 1436 (w), 1384 (w), 1275 (m), 1233 (w), 1169 (w).

HRMS (ESI) calcld for C$_{18}$H$_{20}$NO$_2$Na$^+$ [M+Na]$^+$; found 362.1234; found 362.1235.

**Dimethyl-(2R,5R)-5-(2,5-dioxopyrrolidin-1-yl)-2-(4-methoxyphenyl)dihydrofuran-3,3(2H)-dicarboxylate (9b)**

S32
Following the general procedure, using 4-methoxybenzaldehyde (8b) (54.5 mg, 0.400 mmol, 2.00 eq), dimethyl 5-(2,5-dioxopyrrolidin-1-yl)-2-(4-methoxyphenyl)dihydrofuran-3,3(2H)-dicarboxylate (9b) (54.1 mg, 0.138 mmol, 69%) was obtained as a colorless oil.

**Crude analysis: dr > 20:1.**

\( \text{er} = 96:4 \), Chiralcel IC Hexane/iPrOH 80:20, 1 mL/min, \( \lambda = 220 \text{ nm} \), tr1 = 34.9 min; tr2 = 38.5 min.

\([\alpha]_D^{25.9} +17.8 \) (c = 0.50, CHCl3).

\( R_f \) 0.30 (4:6 Pentane/AcOEt).

\( ^1H \) NMR (400 MHz, CDCl3) \( \delta \) 7.51 – 7.38 (m, 2 H, Ar), 6.94 – 6.70 (m, 2 H, Ar), 5.87 – 5.66 (m, 2 H, N-C-H + Ph-C-H), 4.14 (dd, \( J = 13.1 \), 11.0 Hz, 1 H, \( CH_2 \)), 3.83 (s, 3 H, OMe), 3.78 (s, 3 H, OMe), 3.17 (s, 3 H, OMe), 2.75 (s, 4 H, \( CH_2 \) succinimide), 2.35 (dd, \( J = 13.1 \), 5.1 Hz, 1 H, \( CH_2 \)).

\( ^13C \) NMR (101 MHz, CDCl3) \( \delta \) 176.2, 170.8, 167.7, 159.7, 129.7, 128.9, 113.3, 82.3, 79.5, 64.9, 55.2, 53.4, 52.4, 33.0, 28.0.

IR 1732 (s), 1708 (s), 1614 (w), 1516 (m), 1365 (m), 1274 (m), 1250 (s), 1174 (s).

HRMS (ESI) calcd for C_{10}H_{22}NO_5 \([M+H]^+\) 392.1340; found 392.1346.

**Dimethyl-(2R,5R)-5-(2,5-dioxopyrrolidin-1-yl)-2-(3-methoxyphenyl)dihydrofuran-3,3(2H)-dicarboxylate (9c)**

Following the general procedure, using 3-methoxybenzaldehyde (8c) (54.5 mg, 0.400 mmol, 2.00 eq), dimethyl 5-(2,5-dioxopyrrolidin-1-yl)-2-(3-methoxyphenyl)dihydrofuran-3,3(2H)-dicarboxylate (9c) (65.9 mg, 0.168 mmol, 84 %) was obtained as a colorless oil.

**Crude analysis: dr = 10:1 between peaks at 6.05 (minor) and 5.82 (major).**

\( \text{er} = 93:7 \), Chiralcel IA Hexane/iPrOH 70:30, 1 mL/min, \( \lambda = 210 \text{ nm} \), tr1 = 23.8 min; tr2 = 27.2 min.

\([\alpha]_D^{25.9} +57.8 \) (c = 0.47, CHCl3).

\( R_f \) 0.4 (4:6 Pentane/AcOEt).

\( ^1H \) NMR (400 MHz, CDCl3) \( \delta \) 7.24 – 7.15 (m, 2 H, Ar), 7.02 (d, \( J = 7.6 \text{ Hz} \), 1 H, Ar), 6.88 – 6.73 (m, 1 H, Ar), 5.87 – 5.68 (m, 2 H, N-C-H + Ph-C-H), 4.15 (dd, \( J = 13.2 \), 11.1 Hz, 1 H, \( CH_2 \)), 3.87 – 3.85 (m, 6 H, OMe + OMe), 3.16 (s, 3 H, OMe), 2.75 (s, 4 H, \( CH_2 \) succinimide), 2.36 (dd, \( J = 13.1 \), 5.0 Hz, 1 H, \( CH_2 \)).

\( ^13C \) NMR (101 MHz, CDCl3) \( \delta \) 176.2, 170.8, 167.7, 159.5, 139.2, 128.8, 120.1, 115.2, 112.1, 82.5, 79.6, 65.1, 55.4, 53.5, 52.4, 33.0, 28.0.

S33
IR 1736 (s), 1715 (s), 1382 (w), 1276 (m), 1233 (w), 1169 (m), 1048 (w).
HRMS (ESI) calcd for C_{10}H_{12}N_{3}O_{3}Na^+[M+Na]^+ 414.1159; found 414.1181.

**Dimethyl-(2R,5R)-2-(4-chlorophenyl)-5-(2,5-dioxopyrrolidin-1-yl)dihydrofuran-3,3(2H)-dicarboxylate (9d)**

Following the general procedure, using 4-chlorobenzaldehyde (8d) (56.2 mg, 0.400 mmol, 2.00 eq), dimethyl 2-(4-chlorophenyl)-5-(2,5-dioxopyrrolidin-1-yl)dihydrofuran-3,3(2H)-dicarboxylate (9d) (71.0 mg, 0.179 mmol, 90 %) was obtained as a colorless oil.

**Crude analysis:** \( dr = 14:1 \) between peaks at 6.36 (minor) and 5.80 (major).
\( er = 91:9 \).
Chiralcel IA Hexane/iPrOH 70:30, 1 mL/min, \( \lambda = 210 \) nm, tr1 = 19.5 min; tr2 = 47.2 min.
\( [\alpha]D \) 25.0 41.8 (c = 0.53, CHCl3).
\( R_f \) 0.3 (4:6 Pentane/AcOEt).

\( ^1H \) NMR (400 MHz, CDCl3) \( \delta \) 7.47 (d, \( J = 8.2 \) Hz, 2 H, Ar), 7.34 – 7.27 (m, 2 H, Ar), 5.84 – 5.70 (m, 2 H, N-C-H + Ph-C-H), 4.10 (dd, \( J = 13.2, 10.9 \) Hz, 1 H, CH2), 3.84 (d, \( J = 1.2 \) Hz, 3 H, OMe), 3.18 (d, \( J = 1.3 \) Hz, 3 H, OMe), 2.76 (s, 4 H, CH2 succinimide), 2.38 (dd, \( J = 13.2, 5.2 \) Hz, 1 H, CH2).

\( ^13C \) NMR (101 MHz, CDCl3) \( \delta \) 176.1, 170.7, 167.5, 136.1, 134.3, 129.0, 128.1, 128.1, 81.8, 79.6, 64.9, 53.5, 52.5, 33.0, 28.0.
IR 1737 (s), 1718 (s), 1659 (w), 1382 (w), 1278 (m), 1231 (m), 1212 (w), 1168 (m).
HRMS (ESI) calcd for C_{18}H_{19}N_{3}O_{7}Na^+[M+Na]^+ 396.0845; found 396.0844.

**Dimethyl-(2S,5R)-5-(2,5-dioxopyrrolidin-1-yl)-2-(thiophen-2-yl)dihydrofuran-3,3(2H)-dicarboxylate (9e)**

Following the general procedure, using thiophene-2-carbaldehyde (8e) (44.9 mg, 0.400 mmol, 2.00 eq), dimethyl 5-(2,5-dioxopyrrolidin-1-yl)-2-(thiophen-2-yl)dihydrofuran-3,3(2H)-dicarboxylate (9e) (71.6 mg, 0.195 mmol, 97 %) was obtained as a colorless oil.

**Crude analysis:** \( dr > 20:1 \).
\( er = 95:5 \).
Chiralcel IA Hexane/iPrOH 70:30, 1 mL/min, \( \lambda = 210 \) nm, tr1 = 24.4 min; tr2 = 31.9 min.
\( [\alpha]D \) 25.0 75.3 (c = 0.54, CHCl3).
\( R_f \) 0.4 (4:6 Pentane/AcOEt).
**Dimethyl-(2R,5R)-5-(2,5-dioxopyrrolidin-1-yl)-2-((E)-styryl)dihydrofuran-3,3(2H)-dicarboxylate (9f)**

Following the general procedure, using cinnamaldehyde (8f) (52.9 mg, 0.400 mmol, 2.00 eq), dimethyl 5-(2,5-dioxopyrrolidin-1-yl)-2-((E)-styryl)dihydrofuran-3,3(2H)-dicarboxylate (9f) (74.0 mg, 0.191 mmol, 96 %) was obtained as a colorless oil.

*Crude analysis:* $dr = 14:1$ between peaks at 5.58 (minor) and 5.83 (major).  
*$er = 94:6* Chiralcel IA Hexane/iPrOH 70:30, 1 mL/min, $\lambda = 210$ nm, $tr_1 = 30.2$ min; $tr_2 = 56.1$ min.  
*$[\alpha]D^{25.0} = 14.8$ ($c = 0.49$, CHCl$_3$).  
*$R_f$ 0.4 (4:6 Pentane/AcOEt).

**1H NMR** (400 MHz, CDCl$_3$) $\delta$ 7.43 – 7.36 (m, 2 H, Ar), 7.30 (dd, $J = 8.4$, 6.5 Hz, 2 H, Ar), 7.24 (m, 3 H, Ar), 6.76 – 6.51 (m, 2 H, CH olefin), 5.83 (dd, $J = 10.2$, 5.9 Hz, 1 H, N-C-H), 5.25 (dd, $J = 5.3$, 3.1 Hz, 1 H, O-C-H), 3.95 (dd, $J = 13.3$, 10.2 Hz, 1 H, CH$_2$), 3.85 (s, 3 H, OMe), 3.61 (s, 3 H, OMe), 2.72 (s, 4 H, CH$_2$ succinimide), 2.49 (dd, $J = 13.3$, 6.0 Hz, 1 H, CH$_2$).

**13C NMR** (101 MHz, CDCl$_3$) $\delta$ 176.3, 170.4, 167.4, 140.1, 127.0, 126.7, 125.9, 79.4, 78.4, 65.2, 53.6, 52.7, 32.2, 28.0.

**IR** 1739 (s), 1717 (s), 1435 (w), 1276 (m), 1231 (m), 1219 (w), 1169 (m).

**HRMS** (ESI) calcd for C$_{16}$H$_{18}$NO$_3$S$^+$ [M+H]$^+$ 368.0799; found 368.0819.

**Dimethyl-(2R,5R)-5-(2,5-dioxopyrrolidin-1-yl)-2-phenethylidihydrofuran-3,3(2H)-dicarboxylate (9g)**

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S35
Following the general procedure, using 3-phenylpropanal (8g) (53.7 mg, 0.400 mmol, 2.00 eq), dimethyl 5-(2,5-dioxopyrrolidin-1-yl)-2-phenethylidihydrofuran-3,3(2H)-dicarboxylate (9g) (65.9 mg, 0.169 mmol, 85%) was obtained as a colorless oil.

**Crude analysis:** $dr = 13:1$ between peaks at 6.15 (minor) and 5.79 (major).

$er = 91.5:8.5$, Chiralcel IA Hexane/iPrOH 70:30, 1 mL/min, $\lambda = 210$ nm, $tr_1 = 10.3$ min; $tr_2 = 18.5$ min.

$\left[ \alpha \right]_{D}^{25.0} 21.6 (c = 0.42, \text{CHCl}_3)$.

$R_f$ 0.4 (4:6 Pentane/AcOEt).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta 7.40 – 7.07$ (m, 5 H, Ar), 5.79 (dd, $J = 10.0, 6.1$ Hz, 1 H, N-C-H), 4.65 (dd, $J = 11.4, 2.7$ Hz, 1 H, O-C-H), 3.83 (s, 3 H, OMe), 3.79 – 3.73 (m, 1 H, $CH_2$ THF), 3.76 (s, 3 H, OMe), 2.85 (ddd, $J = 14.7, 10.5, 4.8$ Hz, 1 H, $CH_2$), 2.76 (s, 4 H, $CH_2$ succinimide), 2.57 (ddd, $J = 13.6, 10.1, 6.3$ Hz, 1 H, $CH_2$), 2.48 (dd, $J = 13.2, 6.1$ Hz, 1 H, $CH_2$ THF), 2.37 – 2.24 (m, 1 H, $CH_2$), 1.79 – 1.53 (m, 1 H, $CH_2$).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta 176.2, 170.3, 167.9, 141.8, 128.6, 128.3, 125.8, 80.8, 79.5, 63.6, 53.4, 53.0, 33.4, 32.3, 32.2, 28.0$.

IR 1736 (s), 1712 (s), 1436 (w), 1371 (w), 1274 (m), 1168 (m), 1041 (w).

HRMS (ESI) calcd for $C_{20}H_{23}NNaO_7^+$ [M+Na]$^+$ 412.1367; found 412.1349.

**Spectra**
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CDCl₃
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S45
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CDCl₃
100.1 MHz

S48
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HSQC

ROESY