SUPPORTING INFORMATION

Direct access to unnatural cyclobutane α-amino acids through visible light catalyzed [2+2]-cycloaddition

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1. General Information

1.1 General Methods

$^1$H and $^{13}$C and spectra were recorded in CDCl$_3$ (reference signals: $^1$H = 7.26 ppm, $^{13}$C = 77.16 ppm, CDCl$_3$), in DMSO-d$_6$ (reference signals: $^1$H = 2.50 ppm, $^{13}$C = 39.52 ppm, d$_6$-DMSO), in D$_2$O (reference signals: $^1$H = 4.79 ppm, D$_2$O) or in acetone-d$_6$ (reference signals: $^1$H = 2.05 ppm, $^{13}$C = 29.84, acetone-d$_6$) on a Bruker Avance II 300, Bruker Avance II 400 or Agilent DD2 600. Chemical shifts (δ) are given in ppm and spin-spin coupling constants (J) are given in Hz. Analytical thin layer chromatography was performed using silica gel 60 F254, KMnO$_4$, cerium ammonium molybdate (CAM) and vanillin served as staining agents. Column chromatography was performed on silica gel 60 (0.040-0.063 mm). Exact masses (HRMS) were recorded on a Bruker MicroTof ESI spectrometer or a Thermo Fisher Scientific Orbitrap LTQ XL spectrometer using electrospray ionization (ESI) techniques. FTIR measurements were carried out using a JASCO-FTIR-6800 with a JASCO Pro One single-reflection ATR accessory, the sample was applied neat. The optical rotations were measured on a Jasco P2000 polarimeter. Electrochemical measurements were performed on a Metrohm Autolab PGSTAT204 potentiostat. Fluorescence quenching experiments were performed on a Jasco FP-8500 spectrofluorometer. Dry solvents were purchased or dried according to standard laboratory procedures. $^2$MeCN was distilled over CaH$_2$. Unless otherwise noted, other solvents and commercially available reagents were used without any further purification.
1.2 Photoreactor Setup

**Batch reactor**
Reactions were performed in a custom-build photoreactor, manufactured by the precision engineering workshop of the organic chemistry institute of the WWU Münster (see pictures below). The 10 mL head space vials (ND20 from Carlo Erba, product nr.: 20091405) were irradiated from the bottom by a 3 W LED 410-420 nm (purchased from Avonec; product nr. 3W410420s) under defined temperature (20 °C) adjusted by a Huber Minichiller 280.

**Flow reactor**
Upscaling reactions were performed in a custom-built photoreactor, manufactured by the precision engineering workshop of the organic chemistry institute of the WWU Münster (see pictures below). The reaction mixture was irradiated from the side by 30 x 3 W LED 410-420 nm (purchased from Avonec; product nr. 3W410420s). The tubing for the reaction mixture (purchased from Bola; product nr. S1815-04) has an overall length of 12.7 m, with an inner diameter of 0.8 mm. The reaction mixture was moved by a Longer Pump BT-100-2J peristaltic pump.
2. Optimization

**Table S1: Screening of photocatalysts**

| Entry | Catalyst [mol%] | Yield [%]a | d.r. b |
|-------|-----------------|------------|--------|
| 1     | [Ir(dFCF3ppy)2(4,4'-dtbpy)]PF6 (1) | 73 | 8:1 |
| 2     | [Ir(dFCF3ppy)2(4,4'-dtbpy)]PF6 (2) | 82 | 8:1 |
| 3     | [Ir(dFCF3ppy)2(4,4'-dtbpy)]PF6 (4) | 83 | 8:1 |
| 4     | 4Cz-IPN (5) | 17 | 1.4:1 |
| 5     | 4Cz-IPN d (5) | 70 | 6.7:1 |
| 6     | [Ru(bpy)3]2(PF6)2 (5) | - | - |
| 7     | MesAcr-Me ClO4 (5) | - | - |
| 8     | Riboflavin (5) | - | - |
| 9     | Thioxanthon (10) | 54 | 3.2:1 |
| 10    | 2CzPN (5) | 46 | 8:1 |

a Isolated yields. b From Isolated Product. c Determined by 1H-NMR of the crude reaction. d 72 h reaction time

**Table S2: Screening of solvents, concentrations and styrene equivalents**

| Entry | solvent (M) | Styrene [equiv.] | Yield [%]a |
|-------|-------------|-----------------|------------|
| 1     | CH3CN (0.2) | 1.5 | 82 |
| 2     | DMF (0.2)   | 1.5 | 60 |
| 3     | CDCl3 (0.2) | 1.5 | 75 |
| 4     | DMSO (0.2)  | 1.5 | 73 |
| 5     | Acetone (0.2) | 1.5 | 56 |
| 6     | CH3CN (0.05) | 1.5 | 55 |
| 7     | CH3CN (0.1) | 1.5 | 68 |
| 8     | CH3CN (0.4) | 1.5 | 78 |
| 9     | CH3CN (0.2) | 1.1 | 73 |
| 10    | CH3CN (0.2) | 3.0 | 79 |

a Isolated yields.
Table S3: Control reactions

| Entry | divergence from std. conditions | Yield 3aa/3aa’ [%]* |
|-------|---------------------------------|---------------------|
| 1     | no light                        | -                   |
| 2     | no catalyst                     | -                   |
| 3     | under air                       | 70                  |
| 4     | no cat., UV light (350 nm)      | -                   |
| 5     | no styrene 2a                   | - b                 |
| 6     | no DhA 1a                       | - c                 |

* Determined by 1H-NMR using CH2Br2 as internal standard. b No conversion of the starting material was observed. c Formation of styrene cycloadducts.

3. Synthesis of Starting Materials

**Methyl 2-acetamidoacrylate (1a)**

A round bottom flask was charged with 2-acetaminoacrylic acid (269.0 mg, 2.8 mmol, 1.0 equiv.) and dissolved in dry DMF (10 mL). K2CO3 (790.0 mg, 5.7 mmol, 2.0 equiv.) and iodo-methane (1.62 g, 11.4 mmol, 4.0 equiv.) were added and the mixture was stirred for 18 h at r.t. Subsequently the solvent was removed under reduced pressure. The resulting residue was dissolved in CH2Cl2 and water. The aqueous phase was extracted with CH2Cl2 (3 x 10 mL). The combined organic layer was washed with sat. NaHCO3 (aq.), brine and dried over MgSO4. The solvent was then removed under reduced pressure and the resulting crude product was purified by flash column chromatography (20% to 50% EtOAc/pentane). The desired product was obtained as a white, crystalline solid (395.2 mg, 2.76 mmol, 97%). 1H NMR (400 MHz, CDCl3): δ 7.71 (s, 1H), 6.50 (s, 1H), 5.88 (d, J = 1.5 Hz, 1H), 3.85 (s, 3H), 2.13 (s, 3H). The analytical data were in accordance with the commercially available compound (CAS: 35356-70-8).

**Methyl 2-((tert-butoxycarbonyl)amino)acrylate (1b)**

D,L-Serine methyl ester hydrochloride (2.33 g, 15.0 mmol, 1.0 equiv.) was suspended in 40 mL CH2Cl2. Triethylamine (6.3 ml, 45.0 mmol, 3.0 equiv.) was added and the mixture was stirred for 20 min. Boc anhydride (3.6 g, 16.5 mmol, 1.1 equiv.) was added and stirred at room temperature overnight. Water (20 mL) was added and the mixture was extracted three times with CH2Cl2. The combined organic layer was washed with 1 M HCl, brine and dried over anhydrous MgSO4. After drying under vacuum, the product was obtained as colorless oil. The residue was re-dissolved in 60 mL CH2Cl2. At 0 °C, methyl sulfonyl chloride (1.51 mL, 19.5 mmol, 1.3 equiv.) was added and stirred at the same temperature for 10 min. Then, triethylamine (6.3 ml, 45.0 mmol, 3.0 equiv.) was added at 0 °C, stirred at the same temperature for an additional 30 min at room temperature for 16 h. The reaction was quenched with 15 mL water. The mixture was extracted three times with CH2Cl2, washed with NaHCO3 (sat.), brine, dried over MgSO4 and the solvent was removed under vacuum. The residue was purified by flash column chromatography (20% EtOAc/pentane), obtaining the product (2.51 g, 12.5 mmol, 83%) as a colorless oil. 1H NMR (300 MHz, CDCl3): δ 7.01 (s, 1H), 6.16 (s, 1H), 5.72 (d, J = 1.3 Hz, 1H), 3.83 (s, 3H), 1.48 (s, 9H). The analytical data were in accordance with the literature.3
**Methyl 2-[(bis(tert-butoxycarbonyl)amino)acrylate (1c)]**

Boc-D,L-serine methyl ester (0.62 g, 2 mmol, 1.0 equiv.) was dissolved in 4 mL CH$_3$CN. Boc-anhydride (1.05 g, 4.8 mmol, 2.4 equiv.), 4-dimethylaminopyridine (DMAP) (52 mg, 0.4 mmol, 0.2 equiv.) was added. The solution was stirred at room temperature for 8 h. Then, 1,8-diazabicyclo[5.4.0]undec-7-en (DBU) (29.9 µL, 0.2 mmol, 0.1 equiv.) was added and the mixture was stirred at room temperature for an additional 8 h. Afterwards, 10 mL EtOAc and 10 mL water was added and the phases were separated. The aqueous phase was extracted three times with 10 mL EtOAc. The combined organic phases were washed with 1 M HCl and brine, dried over anhydrous MgSO$_4$ and the solvent was removed under reduced pressure. The crude was purified by flash column chromatography (5% to 10% EtOAc/pentane), obtaining the product (0.53 g, 1.8 mmol, 90%) as a white, crystalline solid. $^1$H NMR (300 MHz, CDCl$_3$): δ 6.33 (s, 1H), 5.64 (s, 1H), 3.79 (s, 3H), 1.46 (s, 18H). The analytical data were in accordance with the literature.

**Methyl 2-(((9H-fluoren-9-yl)methoxy)carbonyl)amino)acrylate (1d)**

D,L-Serine methyl ester (1.1 g, 7.0 mmol, 1.0 equiv.) was dissolved in a solution of NaHCO$_3$ (2.94 g, 35.0 mmol, 5 equiv.) in 12 mL H$_2$O and 175 mL CH$_2$Cl$_2$. To this solution, Fmoc-Cl (1.90 g, 7.35 mmol, 1.05 equiv.) was added and the mixture was stirred at room temperature for 16 h. Water (10 mL) was added and the mixture was extracted three times with CH$_2$Cl$_2$. The combined organic layers were washed with 1 M HCl and brine and dried over MgSO$_4$. After drying under vacuum, the product was obtained as a pale yellow solid and was used without further purification. Under an argon atmosphere, Fmoc-Ser-OMe (2.4 g, 7.0 mmol, 1.0 equiv.) was dissolved in 50 mL dry CH$_2$Cl$_2$. At 0 °C, methyl sulfonfonyl chloride (0.65 mL, 8.4 mmol, 1.2 equiv.) was added and stirred at the same temperature for 10 min. Then, triethylamine (2.15 mL, 15.4 mmol, 2.2 equiv.) was added at 0 °C, stirred at the same temperature for additional 30 min and at room temperature for 16 h. Water (10 mL) was added and the mixture was extracted three times with CH$_2$Cl$_2$. The combined organic layers were washed with 1 M HCl, brine and dried over MgSO$_4$ and the solvent was removed under vacuum. The residue was purified by flash column chromatography (10% to 20% EtOAc/pentane), obtaining the product (375.7 mg, 1.16 mmol, 17 %) as a white, amorphous solid. $^1$H NMR (400 MHz, CDCl$_3$): δ 7.78 (d, J = 7.5 Hz, 2H), 7.65 – 7.56 (m, 2H), 7.42 (tt, J = 7.4, 0.9 Hz, 2H), 7.33 (td, J = 7.4, 1.2 Hz, 2H), 6.24 (s, 1H), 5.80 (d, J = 1.6 Hz, 1H), 4.46 (d, J = 7.0 Hz, 2H), 4.26 (t, J = 7.0 Hz, 1H), 3.86 (s, 3H). The analytical data were in accordance with the literature.

**Methyl 2-(((benzoyl)carbonyl)amino)acrylate (1e)**

D,L-Serine methyl ester hydrochloride (1.00 g, 6.4 mmol, 1.0 equiv.) was suspended in 20 mL CH$_2$Cl$_2$. Et$_3$N (2.7 ml, 19.3 mmol, 3.0 equiv.) was added and the mixture was stirred for 20 min. Cbz-Cl (1.14 mL, 7.7 mmol, 1.2 equiv.) was added and stirred at room temperature for 16 h. Water (20 mL) was added and the mixture was extracted three times with CH$_2$Cl$_2$. The combined organic layer was washed with 1 M HCl, brine and dried over anhydrous MgSO$_4$. After drying under vacuum, the product was obtained as colorless oil. The residue was re-dissolved in 10 mL anhydrous CH$_2$Cl$_2$. At 0 °C, methyl sulfonfonyl chloride (0.62 mL, 8.0 mmol, 1.25 equiv.) was added and
stirred at the same temperature for 10 min. Then, triethylamine (2.7 ml, 19.3 mmol, 3.0 equiv.) was added at 0 °C, stirred at the same temperature for an additional 30 min and at room temperature for 16 h. The reaction was quenched with 15 mL water. The mixture was extracted three times with CH₂Cl₂, washed with NaHCO₃ (sat.), brine, dried over MgSO₄ and the solvent was removed under vacuum. The residue was purified by flash column chromatography (5% to 10% EtOAc/pentane), obtaining the product (929.4 mg, 3.95 mmol, 61%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃): δ 7.40 – 7.33 (m, 1H), 7.24 (bs, 1H), 6.25 (s, 1H), 5.79 (d, J = 1.4 Hz, 1H), 5.17 (s, 1H), 3.83 (s, 3H). The analytical data were in accordance with the literature.⁶

**Methyl (Z)-2-acetimidobut-2-enoate (1f)**

L-Methyl-threoninate hydrochloride (1.7 g, 10.0 mmol, 1.0 equiv.) and Na₂CO₃ (3.18 g, 30.0 mmol, 3.0 equiv.) were dissolved in acetic anhydride (15 mL). The mixture was stirred and refluxed for 4 h. Excess acetic anhydride was removed under vacuum and the resulting residue was dissolved in water (25 mL). To this solution Na₂CO₃ was added until a pH of ~8-9 was reached. The aqueous solution was extracted four times with ethyl acetate, washed with water (25 mL), sat. NaHCO₃ (2 X 25 mL), brine and dried over MgSO₄. The solvent was removed under vacuum and the resulting slurry was dissolved in MeOH. To the resulting solution, NEt₃ was added and the mixture was stirred and refluxed overnight. MeOH was removed under vacuum and the crude was purified by flash column chromatography (50% to 75% EtOAc/pentane), obtaining the product (874.8 mg, 5.6 mmol, 56%) as a white, crystalline solid. ¹H NMR (400 MHz, CDCl₃): δ 6.81 (q, J = 7.2 Hz, 1H), 6.80 (bs, 1H), 3.76 (s, 3H), 2.12 (s, 3H), 1.77 (d, J = 7.2 Hz, 3H). The analytical data were in accordance with the literature.⁷

**Methyl (Z)-2-acetamido-3-phenylacrylate (1g)**

(Z)-2-Acetamido-3-phenylacrylic acid (1.44 g, 7.0 mmol, 1.0 equiv.) and K₂CO₃ (1.93 g, 14.0 mmol, 2.0 equiv.) were dissolved in anhydrous DMF (20 mL). Mel (3.97 g, 28.0 mmol, 4.0 equiv.) was added slowly and the resulting mixture was stirred at r.t. for 18 h. Water (30 mL) was added and the aqueous phase was extracted three times with DCM (20 mL). The combined organic phase was washed with NaHCO₃ (sat.), brine and dried over MgSO₄. The solvent was reduced under vacuum and the crude was purified by flash column chromatography (40% to 50% EtOAc/pentane), obtaining the product (614.3 mg, 2.8 mmol, 40%) as a white, crystalline solid. ¹H NMR (400 MHz, CDCl₃): δ 7.50 – 7.29 (m, 6H), 6.97 (s, 1H), 3.85 (s, 3H), 2.14 (s, 3H). The analytical data were in accordance with the literature.⁸

**Benzyl (2S,4R)-4-(((benzylthio)methyl)-2-(tert-butyl)-5-oxooxazolidine-3-carboxylate (6)**

(S)-Benzyl-L-cysteine (6.34 g, 30.0 mmol, 1.0 equiv.) was suspended in 100 mL anhydrous MeOH under argon, NaOH (1.20 g, 30.0 mmol, 1.0 equiv.) was added and the mixture stirred until it became translucent. Subsequently, 20 g activated 3 Å molecular sieves and pivaldehyde (2.58 g, 30.0 mmol, 1.0 equiv.) were added and stirred for 24 h at r.t. The mixture was then filtered over celite and washed with MeOH. The solvent was removed under reduced pressure and the residue was dried under high vacuum at 60 °C for 8 h to remove residual MeOH. The crude product was obtained as a white solid (8.03 g, ~96%) and used without further
purification. The crude was redissolved in 200 mL anhydrous DCM and cooled to -10 °C. Subsequently, benzyl chloroformate (6.91 g, 40.5 mmol, 1.5 equiv.) was added dropwise via syringe pump over the course of 1.5 h and stirred at -10 °C for 24 h. Then the mixture was allowed to warm to r.t. and was stirred for additional 24 h. Then, it was washed with 100 mL 1 M NaOH(aq) and the organic layer was dried over MgSO₄ and concentrated under reduced pressure. The resulting crude mixture was purified by multiple flash column chromatography (5% to 10% EtOAc/pentane) obtaining the product (1.91 g, 4.62 mmol, 16%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃): δ 7.37 (m, 5H), 7.32 – 7.19 (m, 5H), 5.53 (s, 1H), 5.19 (dd, J = 12.0, 19.5 Hz, 2H), 4.53 (dd, J = 7.9, 6.2 Hz, 1H), 3.77 (q, J = 13.5 Hz, 2H), 2.92 (dd, J = 13.9, 7.9 Hz, 1H), 2.78 (dd, J = 13.9, 6.2 Hz, 1H), 0.91 (s, 9H). The analytical data were in accordance with the literature.⁴

**Benzyl (2S,4R)-4-((benzylsulfonyl)methyl)-2-(tert-butyl)-5-oxooxazolidine-3-carboxylate (7)**

![Diagram of Benzyl (2S,4R)-4-((benzylsulfonyl)methyl)-2-(tert-butyl)-5-oxooxazolidine-3-carboxylate](image1)

(2S,4R)-4-((Benzy1thio)methyl)-2-(tert-butyl)-5-oxooxazolidine-3-carboxylate (1.91 g, 4.62 mmol, 1 equiv.) dissolved in 20 mL anhydrous DCM. mCPBA (2.0 g, 11.55 mmol, 2.5 equiv.) was added portion-wise over a period of 20 min. The resulting mixture was stirred for 17 h at r.t. Subsequently the mixture was washed with 1 M NaOH(aq) (3 x 10 mL). The combined organic phase was dried over MgSO₄ and the solvent was removed under reduced pressure. The crude was purified by flash column chromatography (10% to 20% EtOAc/pentane) obtaining the product (1.88 g, 4.23 mmol, 92%) as a white solid. ¹H NMR (400 MHz, CDCl₃): δ 7.44 – 7.31 (m, 10H), 5.62 (s, 1H), 5.30 – 5.19 (m, 2H), 5.08 (dd, J = 8.0, 4.1 Hz, 1H), 4.67 (d, J = 14.0 Hz, 1H), 4.42 (d, J = 14.0 Hz, 1H), 3.44 (dd, J = 15.3, 8.1 Hz, 1H), 3.15 (ddd, J = 15.3, 4.1, 1.5 Hz, 1H), 0.89 (s, 9H). The analytical data were in accordance with the literature.⁴

**Benzyl (S)-2-(tert-butyl)-4-methylene-5-oxooxazolidine-3-carboxylate (1h)**

![Diagram of Benzyl (S)-2-(tert-butyl)-4-methylene-5-oxooxazolidine-3-carboxylate](image2)

Benzyl (2S,4R)-4-((benzylsulfonyl)methyl)-2-(tert-butyl)-5-oxooxazolidine-3-carboxylate (1.88 g, 4.23 mmol, 1.0 equiv.) was dissolved in 10 mL anhydrous DCM and cooled to 0 °C. Subsequently DBU (707.8 mg, 4.65 mmol, 1.1 equiv.) was added dropwise over the course of 10 min. After completion of the reaction (monitored by TLC, ~45 min) the reaction was quenched at 0 °C by addition of sat. NH₄Cl(aq). The aqueous phase was extracted with DCM (3 x 10 mL). The combined organic phase was dried over MgSO₄ and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (5% to 10% EtOAc/pentane) obtaining the desired product (1.10 g, 3.81 mmol, 90%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃): δ 7.38 (s, 5H), 5.70 (d, J = 13.4 Hz, 2H), 5.68 (bs, 1H), 5.26 (d, J = 1.6 Hz, 2H), 0.93 (s, 9H). The analytical data were in accordance with the literature.⁴

**(1S,2S,5R)-2-isopropyl-5-methylcyclohexyl 2-acetamidoacrylate (1i)**

![Diagram of (1S,2S,5R)-2-isopropyl-5-methylcyclohexyl 2-acetamidoacrylate](image3)

2-Acetamidoacrylic acid (464.8 mg, 3.6 mmol, 1.2 equiv.), L-menthol (468.8 mg, 3.0 mmol, 1.0 equiv.) and PPh₃ (944.3 mg, 3.6 mmol, 1.2 equiv.) were dissolved in 15 mL anhydrous THF and the mixture was cooled to 0 °C. DIAD (731.6 mg, 3.6 mmol, 1.2 equiv.) was added dropwise and the mixture was allowed to warm to r.t. and was stirred for 24 h. The reaction was quenched by addition of water. The phases were
separated and the aqueous phase was extracted with DCM (3 x 20 mL). The combined organic phase was washed with brine and dried over MgSO₄. The solvent was removed under vacuum. The crude was purified by flash column chromatography (10% EtOAc/pentane) to afford the product (508.6 mg, 1.90 mmol, 63%) as a colorless oil. **¹H NMR** (400 MHz, CDCl₃): δ 7.78 (s, 1H), 6.56 (s, 1H), 5.85 (s, 1H), 5.32 (s, 1H), 2.13 (s, 3H), 2.01 – 1.93 (m, 1H), 1.84 – 1.75 (m, 2H), 1.61 (ddt, J = 12.7, 6.7, 3.4 Hz, 1H), 1.50 – 1.33 (m, 2H), 1.16 – 1.02 (m, 2H), 0.97 (td, J = 12.8, 3.3 Hz, 1H), 0.90 (d, J = 6.8 Hz, 3H), 0.86 (d, J = 6.6 Hz, 6H). **¹³C{¹H} NMR** (100 MHz, CDCl₃): δ 172.5, 169.2, 164.1, 158.6, 156.3, 133.9, 122.3, 111.9, 80.6, 62.1, 50.4, 48.3, 31.8, 29.8, 28.5, 24.9, 22.5. **HRMS** (ESI): m/z [M+Na⁺] calcd. for C₁₉H₂₉NO₄Na 394.1954; found 394.1948.

*Methyl (2-acetamidoacryloyl)-D-valinate (1j)*

![Structural formula](image)

2-Acetamidoacrylic acid (516.5 mg, 4.0 mmol, 1.0 equiv.) and H-D-Val-OMe-HCl (737.6 mg, 4.4 mmol, 1.1 equiv.) were suspended in anhydrous THF. N-methylmorpholin (1.42 g, 14.0 mmol, 3.5 equiv.) and isobutylchloroformate (600.9 mg, 4.4 mmol, 1.1 equiv.) were added and the mixture was stirred for 18 h at r.t.. The solvent was removed under vacuum. The residue was dissolved in water (40 mL) and EtOAc (40 mL). The phases were separated and the aqueous phase was extracted with EtOAc (3 x 25 mL). The combined organic phase was washed with 1 M HCl, sat. NaHCO₃(aq), brine and dried over MgSO₄. The solvent was removed under vacuum. The crude was purified by flash column chromatography (75% EtOAc/pentane) to afford the product (440.6 mg, 1.82 mmol, 45%) as a colorless oil. **¹H NMR** (400 MHz, CDCl₃): δ 8.00 (s, 1H), 6.61 (s, 1H), 6.51 (d, J = 1.9 Hz, 1H), 5.30 (s, 1H), 4.58 (ddd, J = 8.5, 4.9, 1.7 Hz, 1H), 3.77 (s, 3H), 2.22 (pd, J = 6.9, 5.0 Hz, 1H), 2.12 (s, 3H), 0.95 (dd, J = 7.9, 6.9 Hz, 6H). **¹³C{¹H} NMR** (100 MHz, CDCl₃): δ 172.2, 169.2, 164.1, 134.1, 101.7, 57.8, 52.5, 31.5, 24.8, 19.0, 18.0. **IR** (ATR, neat) ν 3330, 2966, 1741, 1655, 1513, 1270, 1210, 639, 505 cm⁻¹. **HRMS** (ESI): m/z [M+Na⁺] calcd. for C₁₉H₂₉NO₄Na 265.1164; found 265.1162.

*Methyl N²-(2-acetamidoacryloyl)-N⁶-(tert-butoxycarbonyl)-L-lysinate (1k)*

![Structural formula](image)

2-Acetamidoacrylic acid (516.5 mg, 4.0 mmol, 1.0 equiv.) was suspended in anhydrous THF. N-Methylmorpholin (1.42 g, 14.0 mmol, 3.5 equiv.) and isobutylchloroformate (655.6 mg, 4.8 mmol, 1.2 equiv.) were added and the mixture was stirred for 10 h at r.t.. H-L-Lys(Boc)-OMe-HCl (131.9 g, 4.4 mmol, 1.1 equiv.) was added and the mixture was stirred for 72 h at r.t.. The solvent was removed under vacuum. The residue was dissolved in water (40 mL) and EtOAc (40 mL). The phases were separated and the aqueous phase was extracted with EtOAc (3 x 25 mL). The combined organic phase was washed with 1 M HCl, sat. NaHCO₃(aq), brine and dried over MgSO₄. The solvent was removed under vacuum. The crude was purified by flash column chromatography (66% EtOAc/pentane) to afford the product (295.3 mg, 0.80 mmol, 20%) as a colorless oil. **¹H NMR** (400 MHz, CDCl₃): δ 8.01 (s, 1H), 6.84 (d, J = 7.5 Hz, 1H), 6.49 (d, J = 1.8 Hz, 1H), 5.37 (s, 1H), 4.66 – 4.50 (m, 2H), 3.76 (s, 3H), 3.10 (q, J = 6.6 Hz, 2H), 2.11 (s, 3H), 1.96 – 1.86 (m, 1H), 1.84 – 1.70 (m, 1H), 1.54 – 1.45 (m, 2H), 1.42 (s, 9H), 1.39 – 1.29 (m, 2H). **¹³C{¹H} NMR** (100 MHz, CDCl₃): δ 172.5, 169.2, 164.1, 156.3, 133.9, 122.3, 111.9, 80.6, 62.1, 50.4, 48.3, 31.8, 29.8, 28.5, 24.9, 22.5. **IR** (ATR, neat) ν 3328, 2933, 1685, 1503, 1365, 1250, 1169, 1039, 750, 584 cm⁻¹. **HRMS** (ESI): m/z [M+Na⁺] calcd. for C₁₅H₂₉N₃O₄Na 394.1954; found 394.1948.
**tert-Butyl 2-((tert-butoxycarbonyl)amino)acrylate (1l)**

Boc-L-serin tert-butyl ester (609.3 mg, 2.3 mmol, 1.0 equiv.) was dissolved in 9 mL anhydrous CH₂Cl₂. At 0 °C, methyl sulfonyl chloride (0.23 mL, 3.0 mmol, 1.25 equiv.) was added and stirred at the same temperature for 10 min. Then, triethylamine (0.98 mL, 7.0 mmol, 3.0 equiv.) was added at 0 °C, stirred at the same temperature for an additional 30 min and at room temperature for 16 h. The reaction was quenched with 5 mL water. The mixture was extracted three times with CH₂Cl₂, washed with NaHCO₃ (sat.), brine, dried over MgSO₄ and the solvent was removed under vacuum. The residue was purified by flash column chromatography (20% EtOAc/pentane), obtaining the product (157.9 mg, 0.65 mmol, 28%) as a colorless oil. **¹H NMR** (400 MHz, CDCl₃) δ 7.03 (s, 1H), 6.06 (s, 1H), 5.63 (d, J = 1.5 Hz, 1H), 1.51 (s, 9H), 1.48 (s, 9H). The analytical data were in accordance with the literature.

**tert-Butyl 2-(((9H-fluoren-9-yl)methoxy)carbonyl)amino)acrylate (1m)**

Fmoc-L-serin tert-butyl ester (500.0 mg, 1.3 mmol, 1.0 equiv.) was dissolved in 9 mL anhydrous CH₂Cl₂. At 0 °C, methyl sulfonyl chloride (0.12 mL, 1.6 mmol, 1.2 equiv.) was added and stirred at the same temperature for 10 min. Then, triethylamine (0.40 mL, 2.9 mmol, 2.2 equiv.) was added at 0 °C, stirred at the same temperature for an additional 30 min and at room temperature for 14 h. The reaction was quenched with 5 mL water. The mixture was extracted three times with CH₂Cl₂, washed with NaHCO₃ (sat.), brine, dried over MgSO₄ and the solvent was removed under vacuum. The residue was purified by flash column chromatography (4% EtOAc/pentane), obtaining the product (329.1 mg, 0.9 mmol, 69%) as a colorless oil. **¹H NMR** (400 MHz, CDCl₃) δ 7.78 (dt, J = 7.7, 0.9 Hz, 2H), 7.61 (dq, J = 7.4, 0.9 Hz, 2H), 7.44 - 7.39 (m, 2H), 7.33 (td, J = 7.5, 1.2 Hz, 2H), 7.30 - 7.28 (m, 1H), 6.16 (s, 1H), 5.71 (d, J = 1.5 Hz, 1H), 4.45 (d, J = 7.0 Hz, 2H), 4.25 (t, J = 7.0 Hz, 1H), 1.54 (s, 9H). The analytical data were in accordance with the literature.

### 4. Photocatalytic [2+2]-Cycloaddition

#### 4.1. General Procedure for the Photocatalytic [2+2]-Cycloaddition:

A headspace crimp vial was charged with Ir(dF(CF₃)ppy)₂(dtbbpy)PF₆ (4.5 mg, 4 µmol, 2 mol%), the dehydroamino acid 1 (0.2 mmol, 1.0 equiv.) and styrene derivative 2 (0.3 mmol, 1.5 equiv.) dissolved in 1 mL dry CH₃CN. The solution was degassed by bubbling argon for 1 min and the vial was sealed. The reaction mixture was irradiated through the vial’s plane bottom side using a 3 W blue LED (415 nm) for the appropriate time. The crude was purified by flash column chromatography.
4.2. Characterization of the Products

*Methyl 1-acetamido-2-(p-tolyl)cyclobutane-1-carboxylate (3aa/3aa’)*

Following the general procedure, methyl 2-acetamidoacrylate (1a) (28.6 mg, 0.2 mmol, 1.0 equiv.) and 4-methyl styrene (2a) (35.5 mg, 0.3 mmol, 1.5 equiv.) were reacted for 24 h. The crude product was purified by flash column chromatography (50% to 70% EtOAc/pentane) to obtain the desired product (combined yield, 43.5 mg, 166.5 μmol, 83%, 8:1 d.r.). **Major isomer (R*,R*)-3aa:** (28.4 mg, 147.0 μmol, 73%), white crystalline solid. **1H NMR** (500 MHz, CDCl₃) δ 7.21 – 7.18 (m, 2H), 7.11 – 7.07 (m, 2H), 5.43 (s, 1H), 3.94 (t, J = 9.2 Hz, 1H), 3.79 (s, 3H), 2.97 (dt, J = 12.1, 9.1 Hz, 1H), 2.44 – 2.39 (m, 1H), 2.36 (s, 3H), 2.29 – 2.15 (m, 2H), 1.82 (s, 3H). **13C{1H} NMR** (125 MHz, CDCl₃) δ 173.2, 170.3, 137.6, 133.4, 129.8, 127.9, 61.5, 52.7, 46.2, 27.2, 23.1, 21.2, 20.8. **IR** (ATR, neat) ν 3274, 2950, 1739, 1657, 1542, 1517, 1434, 1370, 1317, 1219, 1107, 1045, 815, 538 cm⁻¹. **Minor isomer (R*,S*)-3aa’:** (5.1 mg, 19.6 μmol, 10%), white crystalline solid.

**Methyl 1-((tert-butoxycarbonyl)amino)-2-(p-tolyl)cyclobutane-1-carboxylate (3ba/3ba’)**

Following the general procedure, methyl 2-((tert-butoxycarbonyl)amino)acrylate (1b) (40.2 mg, 0.2 mmol, 1.0 equiv.) and 4-methyl styrene (2a) (35.5 mg, 0.3 mmol, 1.5 equiv.) were reacted for 24 h. The crude product was purified by flash column chromatography (5% EtOAc/pentane) to obtain the desired product as a mixture of diastereoisomers with 8:1 d.r. (46.0 mg, 144.0 μmol, 72%). Only the Major isomer could be isolated as the pure substance. **Major isomer (R*,R*)-3ba:** (36.1 mg, 113.0 μmol, 57%), colorless oil. **1H NMR** (400 MHz, CDCl₃) δ 7.17 (d, J = 7.5 Hz, 2H), 7.07 (d, J = 7.8 Hz, 2H), 4.36 (s, 1H), 3.92 (s, 1H), 3.79 (s, 3H), 2.88 (dt, J = 11.9, 9.1 Hz, 1H), 2.46 (p, J = 9.9 Hz, 1H), 2.34 (s, 3H), 2.26 – 2.15 (m, 2H), 1.34 (s, 9H). **13C{1H} NMR** (125 MHz, CDCl₃) δ 173.9, 1552, 153.7, 133.6, 129.6, 128.1, 80.0, 61.9, 52.5, 46.1, 28.3, 27.3, 21.2, 20.8. **IR** (ATR, neat) ν 3420, 2976, 1704, 1470, 1365, 1225, 1162, 1103, 1060, 818, 775, 555 cm⁻¹. **HRMS (ESI):** m/z [M+Na]+ calcd. for C₁₃H₁₉NO₃ + Na: 284.1262; found 284.1257.

Sample preparation for crystal growth: 3aa was dissolved in DCM. The solvent was allowed to slowly evaporate under ambient conditions until single crystals formed.

**Methyl 1-(bis(tert-butoxycarbonyl)amino)-2-(p-tolyl)cyclobutane-1-carboxylate (3ca/3ca’)**

Following the general procedure, methyl 2-(bis(tert-butoxycarbonyl)amino)acrylate (1c) (60.3 mg, 0.2 mmol, 1.0 equiv.) and 4-methyl styrene (2a) (35.5 mg, 0.3 mmol, 1.5 equiv.) were reacted for 7 d. The crude product was purified by flash column chromatography (5% to 10% EtOAc/pentane) to obtain the desired product as a mixture of diastereoisomers with 4:1 d.r. (35.5 mg, 84.6 μmol, 42%) as a colorless oil. **Major isomer (R*,R*)-3ca:** **1H NMR** (500 MHz, CDCl₃) δ 7.23 – 7.20 (m, 2H), 7.08 (d, J = 7.9 Hz, 2H), 4.15 (dt, J = 9.0, 3.4 Hz, 1H), 3.80 (s, 3H), 2.99 – 2.90 (m, 1H), 2.65 (dt, J = 11.6, 9.9, 9.1 Hz, 1H), 2.51 (ddt, J = 13.1, 8.8, 3.3 Hz, 1H), 2.31 (s, 3H), 1.91 (ddt, J = 11.6, 10.6, 3.5 Hz, 1H), 1.32 (s, 18H).
Minor isomer (R*,S*)-3ca: 1H NMR (500 MHz, CDCl₃) δ 7.05 (d, J = 8.0 Hz, 2H), 3.45 (s, 3H), 2.29 (s, 3H), 1.49 (s, 18H). Note: Due to signal overlapping, only the representative signals of the minor isomer are assigned. Both isomers: 13C{1H} NMR (100 MHz, CDCl₃) δ 198.1, 174.4, 171.8, 152.5, 152.0, 146.5, 144.6, 140.8, 137.6, 136.6, 136.3, 136.1, 130.7, 130.0, 129.4, 129.0, 128.7, 128.5, 128.4, 128.3, 128.1, 127.3, 82.6, 82.3, 69.8, 65.8, 52.6, 51.9, 47.8, 46.6, 44.9, 36.5, 32.0, 31.9, 30.9, 29.8, 28.1, 28.0, 27.9, 27.8, 27.6, 24.3, 22.0, 21.8, 21.1, 21.1. IR (ATR, neat) v 3404, 2979, 1737, 1704, 1351, 1250, 1164, 1108, 1026, 549 cm⁻¹. HRMS (ESI): m/z [M+Na⁺] calcd. for C₂₃H₄₃NO₆ + Na: 442.2205; found 442.2199.

Methyl 1-(((9H-fluoren-9-ylmethoxy)carbonyl)amino)-2-(p-tolyl)cyclobutane-1-carboxylate (3da)

Following the general procedure, methyl 2-(((9H-fluoren-9-ylmethoxy)carbonyl)amino)acrylate (1d) (64.7 mg, 2.0 mmol, 1.0 equiv.) and 4-methyl styrene (2a) (35.5 mg, 0.3 mmol, 1.5 equiv.) were reacted for 24 h. The crude product was purified by flash column chromatography (5% to 10% EtOAc/pentane) to obtain the desired product (17.9 mg, 40.5 µmol, 20%) as a colourless oil. Note: Fast decomposition of the product after purification, the minor isomer could not be identified. Major isomer: 1H NMR (500 MHz, DMSO-d₆) δ 7.87 (dd, J = 2.6, 1.7 Hz, 1H), 7.85 (dd, J = 3.3, 1.2 Hz, 1H), 7.71 (s, 1H), 7.53 (d, J = 7.5 Hz, 1H), 7.40 (d, J = 7.2 Hz, 3H), 7.31 (td, J = 7.4, 1.2 Hz, 2H), 7.13 (d, J = 7.9 Hz, 2H), 6.93 (d, J = 7.7 Hz, 2H), 4.22 (t, J = 8.1 Hz, 1H), 4.11 (dd, J = 9.4, 5.0 Hz, 1H), 3.83 – 3.72 (m, 2H), 3.64 (s, 3H), 2.40 (q, J = 10.3 Hz, 1H), 2.29 – 2.23 (m, 1H), 2.23 – 2.15 (m, 2H), 1.98 (s, 3H). IR (ATR, neat) v 3364, 1652, 1090, 1024, 991, 824, 782 cm⁻¹. HRMS (ESI): m/z [M+Na⁺] calcd. for C₂₈H₂₇NO₄ + Na: 464.1837; found 464.1831.

Methyl 1-(((benzoxyl)carbonyl)amino)-2-(p-tolyl)cyclobutane-1-carboxylate (3ea/3ea’)

Following the general procedure, methyl 2-(((benzoxyl)carbonyl)amino)acrylate (1e) (47.1 mg, 2.0 mmol, 1.0 equiv.) and 4-methyl styrene (2a) (35.5 mg, 0.3 mmol, 1.5 equiv.) were reacted for 24 h. The crude product was purified by flash column chromatography (10% EtOAc/pentane) to obtain the desired product as a mixture of diastereoisomers with 6:1 d.r. (combined yield, 45.1 mg, 127.6 µmol, 64%). Only the major isomer could be isolated as the pure substance. Major isomer (R*,R*)-3ea: (32.9 mg, 93.1 µmol, 47%), as a colorless oil. Characterization as 3:1 mixture of rotamers: 1H NMR (400 MHz, CDCl₃) δ 7.38 – 7.25 (m, 5H), 7.15 (d, J = 7.8 Hz, 2H), 7.04 (d, J = 7.8 Hz, 2H), 5.02 (s, 2H), 4.78 and 4.62 (s, 1H), 3.95 (t, J = 9.2 Hz, 1H), 3.80 and 3.57 (s, 3H), 2.93 (dt, J = 12.5, 9.3 Hz, 1H), 2.55 – 2.42 (m, 1H), 2.33 (s, 3H), 2.30 – 2.16 (m, 2H). 13C{1H} NMR (100 MHz, CDCl₃) δ 137.6, 136.3, 129.8, 128.6, 128.4, 128.3, 128.0, 66.9, 62.0, 52.8, 46.3, 29.9, 27.2, 21.2, 20.8. IR (ATR, neat) v 3353, 2921, 1714, 1513, 1454, 1321, 1250, 1224, 1120, 1064, 822, 698, 549 cm⁻¹. HRMS (ESI): m/z [M+Na⁺] calcd. for C₂₁H₂₃NO₄ + Na: 376.1524; found 376.1514.

Methyl 1-acetamido-2-methyl-2-phenylcyclobutane-1-carboxylate (3ab/3ab’)

Following the general procedure, 2-acetamidooacrylate (1a) (28.6 mg, 0.2 mmol, 1.0 equiv.) and prop-1-en-2-ylbenzene (2b) (35.4 mg, 0.3 mmol, 1.5 equiv.) were reacted for 24 h. The crude product was purified by flash column chromatography (50% EtOAc/pentane) to obtain the desired product as a mixture of diastereoisomers with 3.8:1 d.r. (34.7 mg, 132.8 µmol, 66%). Only the major isomer could be isolated as the pure substance. Major isomer (R*,R*)-3ab: (20.1 mg, S12
77.1 µmol, 39%), pale yellow, amorphous solid. \(^{1}H\) NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.45 – 7.39 (m, 2H), 7.34 – 7.28 (m, 3H), 5.64 (s, 1H), 3.83 (s, 3H), 3.09 (ddd, \(J = 12.3, 10.3, 9.1\) Hz, 1H), 2.59 (q, \(J = 10.2\) Hz, 1H), 2.02 (ddd, \(J = 12.1, 9.3, 2.4\) Hz, 1H), 1.94 (ddd, \(J = 11.2, 9.1, 2.4\) Hz, 1H), 1.80 (s, 3H), 1.42 (s, 3H). \(^{13}C\)\(^{1}H\) NMR (125 MHz, CDCl\(_3\)) \(\delta\) 171.9, 170.1, 143.5, 129.2, 127.4, 126.5, 64.2, 52.4, 49.5, 28.0, 27.0, 25.0, 23.1. IR (ATR, neat) v 3417, 2919, 1736, 1456, 1376, 1272, 1234, 1205, 1111, 705, 529 cm\(^{-1}\). HRMS (ESI): m/z [M+Na]\(^{+}\) calcd. for C\(_{15}\)H\(_{19}\)NO\(_{3}\) + Na: 284.1262; found 284.1250.

Methyl 1-acetamido-3-methyl-2-phenylcyclobutane-1-carboxylate (3ac/3ac')

Following the general procedure, 2-acetamidoacrylate (1a) (28.6 mg, 0.2 mmol, 1.0 equiv.) and (E)-1-prop-1-en-ylbenzene (2c) (35.4 mg, 0.3 mmol, 1.5 equiv.) were reacted for 24 h. The crude product was purified by flash column chromatography (50% EtOAc/pentane) to obtain the desired product as a mixture of diastereoisomers with 14:1 d.r. (34.1 mg, 130.5 µmol, 65%). Only the major isomer could be isolated as the pure substance. **Major isomer (1R*,2R*,3R*)-3ac** (31.5 mg, 120.0 µmol, 60%) light brown, crystalline solid. \(^{1}H\) NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.40 (t, \(J = 7.4\) Hz, 2H), 7.33 (t, \(J = 7.3\) Hz, 1H), 7.19 (d, \(J = 7.1\) Hz, 2H), 5.42 (s, 1H), 3.79 (s, 3H), 3.49 (dd, \(J = 9.9\) Hz, 1H), 2.90 – 2.78 (m, 1H), 2.55 (dd, \(J = 12.0, 9.7\) Hz, 1H), 2.41 (dd, \(J = 11.9, 8.5\) Hz, 1H), 1.83 (s, 3H), 1.24 (d, \(J = 6.6\) Hz, 3H). \(^{13}C\)\(^{1}H\) NMR (100 MHz, CDCl\(_3\)) \(\delta\) 173.1, 170.5, 135.8, 129.2, 128.0, 128.0, 59.2, 54.1, 52.8, 34.6, 29.2, 23.3, 20.3. IR (ATR, neat) v 2921, 1737, 1657, 1456, 1376, 1316, 1227, 1127, 1038, 698, 650, 506 cm\(^{-1}\). HRMS (ESI): m/z [M+Na]\(^{+}\) calcd. for C\(_{15}\)H\(_{19}\)NO\(_{3}\) + Na: 284.1262; found 284.1253.

Sample preparation for crystal growth: 3ac was dissolved in DCM. The solvent was allowed to slowly evaporate under ambient conditions until single crystals formed.

Methyl 1-acetamido-2,3-diphenylcyclobutane-1-carboxylate (3ad/3ad')

Following the general procedure, 2-acetamidoacrylate (1a) (28.6 mg, 0.2 mmol, 1.0 equiv.) and (E)-1,2-diphenylethene (2d) (54.1 mg, 0.3 mmol, 1.5 equiv.) were reacted for 72 h. The crude product was purified by flash column chromatography (25% EtOAc/pentane) to obtain the desired product as a mixture of diastereoisomers with 20:1 d.r. (45.2 mg, 138.8 µmol, 70%) as a pale yellow oil.

Following the general procedure, 2-acetamidoacrylate (1a) (28.6 mg, 0.2 mmol, 1.0 equiv.) and (Z)-1,2-diphenylethene (2d') (54.1 mg, 0.3 mmol, 1.5 equiv.) were reacted for 72 h. The crude product was purified by flash column chromatography (25% EtOAc/pentane) to obtain the desired product as a mixture of diastereoisomers with 20:1 d.r. (39.5 mg, 122.1 µmol, 61%) as a pale yellow oil.

**Major isomer (1R*,2R*,3R*)-3ad**: \(^{1}H\) NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.44 – 7.39 (m, 2H), 7.37 – 7.33 (m, 1H), 7.33 – 7.30 (m, 4H), 7.28 (dq, \(J = 6.8, 1.1\) Hz, 2H), 7.25 – 7.20 (m, 1H), 5.55 (s, 1H), 4.08 (d, \(J = 10.4\) Hz, 1H), 4.00 (td, \(J = 10.1, 8.6\) Hz, 1H), 3.83 (s, 3H), 3.09 (dd, \(J = 12.0, 9.9\) Hz, 1H), 2.77 (dd, \(J = 12.0, 8.5\) Hz, 1H), 1.90 (s, 3H). **Minor isomer (1R*,2S*,3S*)-3ad**: \(^{1}H\) NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.61 (dd, \(J = 5.9, 2.0\) Hz, 1H), 7.53 – 7.48 (m, 3H), 6.76 (s, 1H), 5.65 (dd, \(J = 8.1, 2.4\) Hz, 1H), 4.59 (d, \(J = 10.2\) Hz, 1H), 3.45 (s, 3H), 2.10 (s, 3H). Note: Due to signal overlapping, only the representative signals of the minor isomer are assigned. **Both isomers**: \(^{13}C\)\(^{1}H\) NMR (100 MHz, CDCl\(_3\)) \(\delta\) 172.8, 170.8, 142.7, 135.3, 129.3, 128.6,
Following the general procedure, 2-acetamidoacrylate (1a) (28.6 mg, 0.2 mmol, 1.0 equiv.) and (E)-1-methoxy-4-(prop-1-en-1-yl) benzene (2e) (44.5 mg, 0.3 mmol, 1.5 equiv.) were reacted for 24 h. The crude product was purified by flash column chromatography (50% EtOAc/pentane) to obtain the desired product as a mixture of diastereoisomers with 17:1 d.r. (45.4 mg, 159.4 μmol, 80%). Only the major isomer could be isolated as the pure substance. Major isomer (1R*2R*,3R*): 3ae (43.6 mg, 149.7 μmol, 75%) pale yellow, crystalline solid. 1H NMR (400 MHz, CDCl3) δ 7.15 – 7.07 (m, 2H), 6.97 – 6.88 (m, 2H), 5.44 (s, 1H), 3.82 (s, 3H), 3.77 (s, 3H), 3.42 (d, J = 9.9 Hz, 1H), 2.84 – 2.71 (m, 1H), 2.52 (dd, J = 11.9, 9.8 Hz, 1H), 2.37 (dd, J = 11.9, 8.5 Hz, 1H), 1.84 (s, 3H), 1.21 (d, J = 6.6 Hz, 3H).

13C{1H} NMR (100 MHz, CDCl3) δ 173.2, 170.6, 159.3, 129.2, 127.5, 114.6, 59.2, 55.4, 53.6, 52.7, 34.4, 29.4, 23.2, 20.2. IR (ATR, neat) v 3296, 2953, 1736, 1651, 1572, 1473, 1376, 1293, 1176, 1033, 842, 527 cm^-1. HRMS (ESI): m/z [M+Na]^+ calcd. for C16H19NO3 + Na: 314.1368; found 314.1362.

Following the general procedure, 2-acetamidoacrylate (1a) (28.6 mg, 0.2 mmol, 1.0 equiv.) and 1,2-dihyronaphthalene (2f) (39.1 mg, 0.3 mmol, 1.5 equiv.) were reacted for 24 h. The crude product was purified by flash column chromatography (50% EtOAc/pentane) to obtain the desired product as a mixture of diastereoisomers with 2:9:1 d.r. (47.9 mg, 175.3 μmol, 88%). Major isomer (1S*2a*,3bR*): 3af (27.2 mg, 99.5 μmol, 50%), pale yellow crystalline solid. 1H NMR (400 MHz, CDCl3) δ 7.14 – 7.05 (m, 3H), 6.94 (d, J = 6.8 Hz, 1H), 6.67 (s, 1H), 3.64 (d, J = 9.1 Hz, 1H), 3.14 (s, 3H), 3.11 – 3.07 (m, 1H), 2.97 (dd, J = 15.9, 11.5, 4.6 Hz, 1H), 2.87 (dd, J = 13.1, 8.2 Hz, 1H), 2.66 (dt, J = 15.9, 4.2 Hz, 1H), 2.32 (dd, J = 12.8, 9.7, 2.2 Hz, 1H), 2.07 (s, 3H), 1.88 – 1.80 (m, 1H), 1.68 – 1.56 (m, 1H).

13C{1H} NMR (100 MHz, CDCl3) δ 170.8, 170.4, 139.0, 133.4, 129.4, 128.8, 126.8, 126.0, 63.7, 51.8, 46.5, 30.3, 27.1, 26.2, 24.3, 23.3. IR (ATR, neat) v 3293, 2924, 1738, 1648, 1540, 1453, 1372, 1290, 1214, 1116, 796, 749, 509 cm^-1. Minor isomer (1R*2a*,3bR*): 3af* (15.6 mg, 57.1 μmol, 29%), pale yellow crystalline solid. 1H NMR (400 MHz, CDCl3) δ 7.25 – 7.22 (m, 3H), 7.06 – 7.01 (m, 1H), 5.27 (s, 1H), 3.88 (d, J = 8.9 Hz, 1H), 3.82 (s, 3H), 3.17 – 3.05 (m, 1H), 2.97 (dq, J = 14.5, 7.9, 6.7 Hz, 1H), 2.83 (ddd, J = 15.3, 9.2, 5.7 Hz, 1H), 2.72 (dt, J = 16.1, 4.8 Hz, 1H), 1.94 (dd, J = 12.9, 6.9 Hz, 1H), 1.79 – 1.72 (m, 1H), 1.72 (s, 3H), 1.72 – 1.65 (m, 1H).

13C{1H} NMR (100 MHz, CDCl3) δ 174.0, 169.6, 139.7, 131.9, 130.2, 129.6, 127.5, 126.9, 59.4, 52.9, 43.5, 32.9, 27.6, 26.6, 25.2, 22.9. IR (ATR, neat) v 3273, 2925, 1739, 1658, 1542, 1432, 1373, 1303, 1216, 1120, 1047, 846, 745 cm^-1. HRMS (ESI): m/z [M+K]^+ calcd. for C16H19NO3 + K: 312.1002; found 312.0995, m/z [M+Na]^+ calcd. for C16H19NO3 + Na: 296.1263; found 296.1256.

Sample preparation for crystal growth: 3af/3af* respectively was dissolved in EtOAc. The solvent was allowed to slowly evaporate under ambient conditions until single crystals formed.
Methyl 1-acetamido-2-mesitylcyclobutane-1-carboxyate (3ag/3ag’)

Following the general procedure, 2-acetamidoacrylate (1a) (28.6 mg, 0.2 mmol, 1.0 equiv.) and 1,3,5-trimethyl-2-vinylbenzene (2g) (43.9 mg, 0.3 mmol, 1.5 equiv.) were reacted for 24 h. The crude product was purified by flash column chromatography (50% EtOAc/pentane) to obtain the desired product as a mixture of diastereoisomers with 1:1 d.r. (25.8 mg, 89.2 µmol, 45%). Only the major isomer could be isolated as the pure substance. Major isomer (R,R)-3ag: (12.2 mg, 42.2 µmol, 21%) white, crystalline solid. ^1H NMR (500 MHz, CDCl₃) δ 6.88 (s, 2H), 5.60 (s, 1H), 4.45 (t, J = 9.5 Hz, 1H), 3.74 (s, 3H), 3.09 (ddd, J = 12.7, 9.6, 7.6 Hz, 1H), 2.93 (dddd, J = 12.0, 10.3, 8.8, 7.5 Hz, 1H), 2.49 – 2.45 (m, 1H), 2.42 (q, J = 5.5 Hz, 1H), 2.41 – 2.34 (m, 6H), 2.26 (s, 3H), 1.88 (s, 3H). ^13C(^1H) NMR (125 MHz, CDCl₃) δ 173.9, 170.2, 138.7, 137.5, 131.3, 129.1, 61.8, 52.7, 43.2, 29.9, 28.1, 23.4, 22.0, 20.8. IR (ATR, neat) ν 3184, 2921, 1738, 1644, 1556, 1434, 1374, 1320, 1216, 1103, 1030, 849, 612, 543 cm⁻¹. HRMS (ESI): m/z [M-H] calcd. for C₁₇H₂₃NO₃ - H: 288.1605; found 288.1602.

Methyl 1-acetamido-2-phenylcyclobutane-1-carboxylate (3ah/3ah’)

Following the general procedure, 2-acetamidoacrylate (1a) (28.6 mg, 0.2 mmol, 1.0 equiv.) and styrene (2h) (31.3 mg, 0.3 mmol, 1.5 equiv.) were reacted for 24 h. The crude product was purified by flash column chromatography (50% EtOAc/pentane) to obtain the desired product as a mixture of diastereoisomers with 8:1 d.r. (39.6 mg, 160.1 µmol, 80%). Only the major isomer could be isolated as the pure substance. Major isomer (R,R)-3ah: 34.8 mg, 140.9 µmol, 70%), as a pale yellow oil. ^1H NMR (400 MHz, CDCl₃) δ 7.42 – 7.37 (m, 2H), 7.35 – 7.29 (m, 1H), 7.21 (dt, J = 8.2, 1.1 Hz, 2H), 5.44 (s, 1H), 4.00 (t, J = 9.1 Hz, 1H), 3.80 (s, 3H), 2.98 (dt, J = 12.1, 9.2 Hz, 1H), 2.44 (dq, J = 12.4, 10.6, 10.1 Hz, 1H), 2.32 – 2.17 (m, 2H), 1.82 (s, 3H). ^13C(^1H) NMR (100 MHz, CDCl₃) δ 173.2, 170.4, 136.7, 129.1, 128.1, 127.9, 61.6, 52.8, 46.4, 27.4, 23.2, 20.8. IR (ATR, neat) ν 3275, 2952, 1737, 1654, 1541, 1496, 1435, 1370, 1317, 1219, 1108, 1045, 699 cm⁻¹. HRMS (ESI): m/z [M+Na]+ calcd. for C₁₄H₁₂NO₃ + Na: 270.1106; found 270.1097.

Methyl 1-acetamido-2-(2-chlorophenyl)cyclobutane-1-carboxylate (3ai/3ai’)

Following the general procedure, 2-acetamidoacrylate (1a) (28.6 mg, 0.2 mmol, 1.0 equiv.) and 2-chloro-styrene (2i) (41.6 mg, 0.3 mmol, 1.5 equiv.) were reacted for 24 h. The crude product was purified by flash column chromatography (50% to 70% EtOAc/pentane) to obtain the desired product as a mixture of diastereoisomers with 8:1 d.r. (44.4 mg, 158.0 µmol, 79%), as a pale yellow oil. Major isomer (R,R)-3ai: ^1H NMR (400 MHz, CDCl₃) δ 7.46 – 7.33 (m, 3H), 7.30 – 7.24 (m, 1H), 5.29 (s, 1H), 4.46 (t, J = 9.5 Hz, 1H), 3.74 (s, 3H), 2.96 (dt, J = 12.1, 9.3 Hz, 1H), 2.60 (p, J = 10.0 Hz, 1H), 2.37 (ddd, J = 12.3, 9.5, 3.0 Hz, 1H), 2.18 (ddd, J = 11.5, 8.7, 3.0 Hz, 1H), 1.83 (s, 3H). Minor isomer (R,S)-3ai**: ^1H NMR (400 MHz, CDCl₃) δ 6.79 (s, 1H), 3.27 (s, 3H), 2.86 – 2.79 (m, 2H), 1.99 (s, 3H). Note: Due to signal overlapping, only the representative signals of the minor isomer are assigned. Both isomers: ^13C(^1H) NMR (100 MHz, CDCl₃) δ 172.7, 170.4, 135.3, 133.9, 130.3, 129.3, 129.2, 128.7, 128.5, 127.2, 126.8, 62.1, 52.7, 51.9, 44.2, 44.0, 30.2, 29.7, 28.2, 27.0, 23.4, 20.4, 18.9. IR (ATR, neat) ν 3285 2952, 1737, 1657, 1435, 1371, 1310, 1223, 1106, 1037, 846, 763, 526 cm⁻¹. HRMS (ESI): m/z [M-Na]^+ calcd. for C₁₄H₁₄ClNO₃ + Na: 304.0716; found 304.0710.
Methyl 1-acetamido-2-(3-chlorophenyl)cyclobutane-1-carboxylate (3aj/3aj*)

Following the general procedure, 2-acetamidoacrylate (1a) (28.6 mg, 0.2 mmol, 1.0 equiv.) and 3-chloro-styrene (2j) (41.6 mg, 0.3 mmol, 1.5 equiv.) were reacted for 24 h. The crude product was purified by flash column chromatography (50% to 70% EtOAc/pentane) to obtain the desired product as a mixture of diastereoisomers with 8:1 d.r. (39.8 mg, 141.3 μmol, 71%). Major isomer (R*R*)-3aj: (35.4 mg, 125.7 μmol, 63%), pale yellow oil. 1H NMR (400 MHz, CDCl3) δ 7.34 – 7.25 (m, 2H), 7.19 (td, j = 2.1, 0.7 Hz, 1H), 7.10 (ddt, j = 7.2, 1.8, 0.8 Hz, 1H), 5.54 (s, 1H), 4.01 (t, j = 8.9 Hz, 1H), 3.79 (s, 3H), 2.89 (dt, j = 12.1, 9.2 Hz, 1H), 2.39 (dq, j = 10.5, 9.0 Hz, 1H), 2.32 – 2.25 (m, 1H), 2.24 – 2.17 (m, 1H), 1.81 (s, 3H). 13C{1H} NMR (100 MHz, CDCl3) δ 172.9, 170.4, 139.2, 134.9, 130.2, 128.2, 127.9, 126.4, 61.6, 52.8, 45.8, 27.6, 23.0, 20.8. IR (ATR, neat) ν 3267, 2952, 1737, 1651, 1539, 1433, 1311, 1218, 1108, 1044, 787, 684, 592 cm⁻¹. Minor isomer (R*S*)-3aj: (4.4 mg, 15.6 μmol, 8%), pale yellow oil. 1H NMR (400 MHz, CDCl3) δ 7.21 – 7.17 (m, 2H), 7.10 (td, j = 1.8, 0.9 Hz, 1H), 6.98 (ddt, j = 6.8, 1.8, 0.8 Hz, 1H), 6.55 (s, 1H), 4.51 (t, j = 9.8 Hz, 1H), 3.42 (s, 3H), 2.90 (dt, j = 11.1, 9.6 Hz, 1H), 2.62 – 2.54 (m, 1H), 2.50 (dt, j = 10.9, 9.6 Hz, 1H), 2.32 – 2.26 (m, 1H), 2.07 (s, 3H). 13C{1H} NMR (100 MHz, CDCl3) δ 172.3, 170.2, 141.7, 134.3, 129.6, 127.1, 127.0, 125.0, 65.6, 52.3, 46.8, 27.4, 24.3, 19.3. IR (ATR, neat) ν 3284, 2853, 1732, 1649, 1535, 1434, 1315, 1219, 1121, 846, 791, 692, 558 cm⁻¹. HRMS (ESI): m/z [M-Na⁺] calcd. for C14H16ClNO3 + Na: 304.0716; found 304.0708.

Methyl 1-acetamido-2-(4-chlorophenyl)cyclobutane-1-carboxylate (3ak/3ak*)

Following the general procedure, 2-acetamidoacrylate (1a) (28.6 mg, 0.2 mmol, 1.0 equiv.) and 4-chloro-styrene (2k) (41.6 mg, 0.3 mmol, 1.5 equiv.) were reacted for 24 h. The crude product was purified by flash column chromatography (50% to 70% EtOAc/pentane) to obtain the desired product as a mixture of diastereoisomers with 8:1 d.r. (42.3 mg, 150.1 μmol, 75%). Major isomer (R*R*)-3ak: (37.0 mg, 131.3 μmol, 66%), pale yellow, amorphous solid. 1H NMR (400 MHz, CDCl3) δ 7.37 – 7.32 (m, 2H), 7.17 – 7.12 (m, 2H), 5.49 (s, 1H), 4.00 (t, j = 9.0 Hz, 1H), 3.78 (s, 3H), 2.89 (dt, j = 12.1, 8.9 Hz, 1H), 2.37 (dq, j = 11.0, 9.2 Hz, 1H), 2.31 – 2.24 (m, 1H), 2.23 – 2.15 (m, 1H), 1.80 (s, 3H). 13C{1H} NMR (100 MHz, CDCl3) δ 173.0, 170.3, 135.4, 133.6, 129.5, 129.1, 61.6, 52.8, 45.7, 27.5, 23.0, 20.9. IR (ATR, neat) ν 3290, 3066, 1738, 1655, 1546, 1494, 1315, 1223, 1108, 831, 512 cm⁻¹. Minor isomer (R*S*)-3ak: (5.3 mg, 18.8 μmol, 9%), pale yellow, crystalline solid. 1H NMR (400 MHz, CDCl3) δ 7.25 – 7.22 (m, 2H), 7.06 – 7.02 (m, 2H), 6.53 (s, 1H), 4.47 (t, j = 9.8 Hz, 1H), 3.40 (s, 3H), 2.88 (dt, j = 11.3, 9.8 Hz, 1H), 2.59 (ddt, j = 11.7, 9.2, 1.6 Hz, 1H), 2.48 (dq, j = 10.9, 9.6 Hz, 1H), 2.27 (ddt, j = 11.0, 9.7, 2.7 Hz, 1H), 2.06 (s, 3H). 13C{1H} NMR (100 MHz, CDCl3) δ 172.4, 170.2, 138.0, 132.7, 128.4, 128.2, 65.6, 52.3, 46.7, 27.4, 24.2, 19.4. IR (ATR, neat) ν 3284, 2952, 1736, 1650, 1539, 1493, 1435, 1372, 1317, 1219, 1120, 1092, 832, 532 cm⁻¹. HRMS (ESI): m/z [M-Na⁺] calcd. for C14H16ClNO3 + Na: 304.0716; found 304.0709.
Methyl 1-acetamido-2-(4-fluorophenyl)cyclobutane-1-carboxylate (3al/3al')

Following the general procedure, 2-acetamidoacrylate (1a) (28.6 mg, 0.2 mmol, 1.0 equiv.) and 4-fluoro-styrene (2l) (36.6 mg, 0.3 mmol, 1.5 equiv.) were reacted for 24 h. The crude product was purified by flash column chromatography (50% to 70% EtOAc/pentane) to obtain the desired product as a mixture of diastereoisomers with 8:1 d.r. (42.9 mg, 161.8 µmol, 81%). Only the major isomer could be isolated as the pure substance. **Major isomer (R,R)-3al:** (32.7 mg, 123.3 µmol, 62%), pale yellow, crystalline solid. **1H NMR** (400 MHz, CDCl₃) δ 7.23 – 7.13 (m, 2H), 7.11 – 7.03 (m, 2H), 5.45 (s, 1H), 3.99 (t, J = 9.0 Hz, 1H), 3.78 (s, 3H), 2.91 (dt, J = 12.1, 9.0 Hz, 1H), 2.44 – 2.32 (m, 1H), 2.31 – 2.24 (m, 1H), 2.23 – 2.16 (m, 1H), 1.80 (s, 3H). **13C{¹H} NMR** (100 MHz, CDCl₃) δ 173.1, 170.3, 162.3 (d, J = 246.8 Hz), 132.6 (d, J = 3.2 Hz), 130.0 (d, J = 8.1 Hz), 115.9 (d, J = 21.3 Hz), 61.6 (d, J = 1.1 Hz), 52.8, 45.6, 27.5, 23.0, 21.1. **19F{¹H} NMR** (377 MHz, CDCl₃) δ -114.45. **IR (ATR, neat)** ν 3274, 2952, 1737, 1652, 1510, 1435, 1371, 1314, 1220, 1160, 1106, 837, 539 cm⁻¹. **HRMS (ESI):** m/z [M-Na]^+ calcd. for C₁₄H₁₆FNO₃ + Na: 288.1011; found 288.1004.

Methyl 1-acetamido-2-(4-bromophenyl)cyclobutane-1-carboxylate (3am/3am')

Following the general procedure, 2-acetamidoacrylate (1a) (28.6 mg, 0.2 mmol, 1.0 equiv.) and 4-bromo-styrene (2m) (54.9 mg, 0.3 mmol, 1.5 equiv.) were reacted for 24 h. The crude product was purified by flash column chromatography (50% to 70% EtOAc/pentane) to obtain the desired product as a mixture of diastereoisomers with 5:3:1 d.r. (25.0 mg, 76.6 µmol, 39%). **Major isomer (R,R)-3am:** (20.0 mg, 61.3 µmol, 31%), pale yellow oil. **1H NMR** (400 MHz, CDCl₃) δ 7.53 – 7.48 (m, 2H), 7.12 – 7.06 (m, 2H), 5.43 (s, 1H), 3.98 (t, J = 9.0 Hz, 1H), 3.79 (s, 3H), 2.92 (dd, J = 12.0, 9.0 Hz, 1H), 2.38 (dq, J = 10.7, 9.2 Hz, 1H), 2.32 – 2.25 (m, 1H), 2.20 (ddd, J = 12.6, 9.4, 3.7 Hz, 1H), 1.82 (s, 3H). **13C{¹H} NMR** (100 MHz, CDCl₃) δ 173.0, 170.4, 135.9, 132.1, 129.9, 121.8, 61.6, 52.9, 45.8, 30.2, 29.8, 27.6, 23.1, 20.9. **IR (ATR, neat)** ν 3288, 2925, 1736, 1650, 1538, 1489, 1435, 1372, 1316, 1219, 1120, 1073, 1011, 829, 526 cm⁻¹. **HRMS (ESI):** m/z [M-Na]^+ calcd. for C₁₄H₁₆BrNO₃ + Na: 348.0211; found 348.0205.

**Methyl 1-acetamido-2-(4-nitrophenyl)cyclobutane-1-carboxylate (3an/3an')**

Following the general procedure, 2-acetamidoacrylate (1a) (28.6 mg, 0.2 mmol, 1.0 equiv.) and 1-nitro-4-vinylbenzene (2n) (44.7 mg, 0.3 mmol, 1.5 equiv.) were reacted for 24 h. The crude product was purified by flash column chromatography (50% EtOAc/pentane) to obtain the desired product as a mixture of diastereoisomers with 10:6:1 d.r. (35.1 mg, 120.1 µmol, 60%). Only the major isomer could be isolated as the pure substance. **Major isomer (R,R)-3an:** (29.2 mg, 100.1 µmol, 50%) brown, amorphous solid. **1H NMR** (600 MHz, CDCl₃) δ 8.26 – 8.16 (m, 2H), 7.48 – 7.35 (m, 2H), 5.59 (s, 1H), 4.26 (t, J = 8.8 Hz, 1H), 3.81 (s, 3H), 2.83 (dt, J = 12.3, 8.8 Hz, 1H), 2.46 (dq, J = 11.4, 9.0 Hz, 1H), 2.25 (m, 1H), 2.18 (s, 3H).
Following the general procedure, 2-acetamidoacrylate (1a) (28.6 mg, 0.2 mmol, 1.0 equiv.) and 1-(trifluoromethyl)-4-vinylbenzene (2o) (51.7 mg, 0.3 mmol, 1.5 equiv.) were reacted for 24 h. The crude product was purified by flash column chromatography (50% EtOAc/pentane) to obtain the desired product as a mixture of diastereoisomers with 8:1 d.r. (45.2 mg, 143.4 µmol, 72%). Only the major isomer could be isolated as the pure substance. **Major isomer (R,R)-3ao:** (36.5 mg, 115.8 µmol, 58%) pale yellow gum. **1H NMR** (400 MHz, CDCl₃) δ 7.63 (d, J = 8.2 Hz, 2H), 7.34 (d, J = 8.1 Hz, 2H), 5.51 (s, 1H), 4.12 (t, J = 8.9 Hz, 1H), 3.80 (s, 3H), 2.90 (dt, J = 12.1, 8.9 Hz, 1H), 2.50 – 2.38 (m, 1H), 2.37 – 2.28 (m, 1H), 2.24 (ddd, J = 12.9, 9.6, 3.8 Hz, 1H), 1.79 (s, 3H). **13C{1H} NMR** (100 MHz, CDCl₃) δ 172.9, 170.3, 141.3 (q, J = 1.2 Hz), 129.8 (q, J = 32.5 Hz), 128.5, 125.7 (q, J = 3.7 Hz), 124.15 (q, J = 27.0 Hz), 61.7, 52.9, 45.9, 27.8, 22.9, 20.8. **19F{1H} NMR** (377 MHz, CDCl₃) δ -62.56. **IR (ATR, neat)** ν 3265, 2954, 1738, 1651, 1545, 1324, 1162, 1117, 1068, 843, 597 cm⁻¹. **HRMS (ESI):** m/z [M+Na]+ calc'd. for C₁₅H₁₄NO₄ + Na: 315.0957; found 315.0951.

**Methyl 1-acetamido-2-(4-(methoxyphenyl)cyclobutane-1-carboxylate (3ap/3ap)**

Following the general procedure, 2-acetamidoacrylate (1a) (28.6 mg, 0.2 mmol, 1.0 equiv.) and 1-methoxy-4-vinylbenzene (2p) (40.3 mg, 0.3 mmol, 1.5 equiv.) were reacted for 24 h. The crude product was purified by flash column chromatography (50% EtOAc/pentane) to obtain the desired product as a mixture of diastereoisomers with 9:1:1 d.r. (46.5 mg, 167.7 µmol, 84%). Only the major isomer could be isolated as the pure substance. **Major isomer (R,R)-3ap:** (34.8 mg, 125.5 µmol, 63%) pale yellow, crystalline solid. **1H NMR** (400 MHz, CDCl₃) δ 7.15 – 7.10 (m, 2H), 6.95 – 6.90 (m, 2H), 5.42 (s, 1H), 3.92 (t, J = 9.2 Hz, 1H), 3.82 (s, 3H), 3.79 (s, 3H), 2.96 (dt, J = 11.9, 9.2 Hz, 1H), 2.46 – 2.34 (m, 1H), 2.29 – 2.14 (m, 2H), 1.83 (s, 3H). **13C{1H} NMR** (100 MHz, CDCl₃) δ 177.8, 170.4, 159.3, 129.3, 128.4, 114.5, 61.5, 55.4, 52.8, 45.9, 27.2, 23.2, 21.0. **IR (ATR, neat)** ν 3281, 2952, 1735, 1655, 1513, 1436, 1304, 1247, 1179, 1107, 1034, 833, 526 cm⁻¹. **HRMS (ESI):** m/z [M+Na]+ calc'd. for C₁₅H₁₄F₃NO₃ + Na: 338.0974; found: 338.0974.

**Methyl (S)-1-acetamido-2-(4-hydroxyphenyl)cyclobutane-1-carboxylate (3aq/3aq)**

Following the general procedure, 2-acetamidoacrylate (1a) (28.6 mg, 0.2 mmol, 1.0 equiv.) and 4-vinylphenol (2q) (36.1 mg, 0.3 mmol, 1.5 equiv.) were reacted for 24 h. The crude product was purified by flash column chromatography (50% EtOAc/pentane) to obtain the desired product as a mixture of diastereoisomers 4:7:1 d.r. (34.4 mg, 130.7 µmol, 65%) as a brown oil. **Major isomer (R,R)-3aq:** 1H NMR (400 MHz, CDCl₃) δ 7.09 – 7.04 (m, 2H), 6.87 – 6.82 (m, 2H), 5.99 (s, 1H), 5.49 (s, 1H), 3.93 (t, J = 9.2 Hz, 1H), 3.79 (s, 3H), 2.95 (dt, J = 12.0, 9.2 Hz, 1H), 2.42 – 2.36 (m, 1H), 2.29 – 2.22 (m, 1H), 2.20 – 2.15 (m, 1H), 1.85 (s, 3H). **Minor isomer (R,S)-3aq:** 1H NMR (400 MHz, CDCl₃) δ 7.01 – 6.93 (m, 2H), 6.79 (s, 1H), 6.75 – 6.67 (m, 2H), 4.10 – 4.04 (m, 1H), 3.38 (s, 3H), 2.80 – 2.71 (m, 1H), 2.56 – 2.44 (m, 2H), 2.04 (s, 3H). Note: Due to signal overlapping, only the representative signals of the minor isomer are assigned. **Both isomers:**

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Following the general procedure, 2-acetamidoacrylate (1a) (28.6 mg, 0.2 mmol, 1.0 equiv.) and tert-butyl (4-vinylphenyl) carbamate (2r) (65.8 mg, 0.3 mmol, 1.5 equiv.) were reacted for 24 h. The crude product was purified by flash column chromatography (50% EtOAc/pentane) to obtain the desired product as a mixture of diastereoisomers 2:1 d.r. (61.6 mg, 170.0, 85%). **Major isomer (R*,R*)-3ar:** (42.2 mg, 116.6 μmol, 58%), pale yellow, crystalline solid. **1H NMR** (400 MHz, CDCl$_3$) δ 7.34 (d, J = 8.2 Hz, 2H), 7.09 – 7.04 (m, 2H), 6.49 (s, 1H), 5.10 (d, J = 8.1 Hz, 1H), 4.73 (d, J = 9.4 Hz, 1H), 3.76 (s, 3H), 2.57 (ddd, J = 20.3, 13.0, 7.4 Hz, 1H), 2.20 (tdd, J = 13.3, 9.3, 6.4 Hz, 1H), 1.92 (dd, J = 13.3, 6.7 Hz, 1H), 1.87 (s, 3H), 1.83 (dd, J = 12.0, 6.7 Hz, 1H), 1.51 (s, 9H). **13C{1H} NMR** (100 MHz, CDCl$_3$) δ 172.8, 170.7, 152.9, 137.8, 137.3, 126.0, 119.1, 80.8, 62.2, 59.7, 52.4, 34.4, 28.4, 26.3, 22.5. **IR** (ATR, neat) ν 3342, 2958, 1736, 1654, 1515, 1259, 1107, 1029, 801, 526 cm$^{-1}$. **HRMS (ESI):** m/z [M+Na]$^+$ calcd. for C$_{14}$H$_{12}$N$_2$O$_5$ + Na: 286.1055; found 286.1048.

**Methyl acetamido-2-(4-((tert-butoxycarbonyl)amino)phenyl)cyclobutane-1-carboxylate (3ar/3as)**

Following the general procedure, 2-acetamidoacrylate (1a) (28.6 mg, 0.2 mmol, 1.0 equiv.) and tert-butyl (4-vinylphenyl) carbamate (2r) (65.8 mg, 0.3 mmol, 1.5 equiv.) were reacted for 24 h. The crude product was purified by flash column chromatography (50% EtOAc/pentane) to obtain the desired product as a mixture of diastereoisomers 2:1 d.r. (61.6 mg, 170.0, 85%). **Major isomer (R*,R*)-3ar:** (42.2 mg, 116.6 μmol, 58%), pale yellow, crystalline solid. **1H NMR** (400 MHz, CDCl$_3$) δ 7.58 – 7.51 (m, 2H), 7.36 (d, J = 8.3 Hz, 2H), 6.49 (s, 1H), 4.88 (dd, J = 7.6, 3.9 Hz, 1H), 4.54 (t, J = 7.3 Hz, 1H), 3.80 (s, 3H), 2.39 (qd, J = 8.3, 7.7, 4.1 Hz, 1H), 2.24 – 2.13 (m, 1H), 2.05 – 1.99 (m, 2H), 1.81 (s, 3H), 1.52 (s, 9H). **HRMS (ESI):** m/z [M+Na]$^+$ calcd. for C$_{19}$H$_{20}$N$_2$O$_5$ + Na: 385.1739; found 385.1733.

**Methyl 1-acetamido-2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)cyclobutane-1-carboxylate (3as/3as’)**

Following the general procedure, 2-acetamidoacrylate (1a) (28.6 mg, 0.2 mmol, 1.0 equiv.) and 4,4,5,5-tetramethyl-2-(4-vinylphenyl)-1,3,2-dioxaborolane (2s) (69.0 mg, 0.3 mmol, 1.5 equiv.) were reacted for 24 h. The crude product was purified by flash column chromatography (50% to 80% EtOAc/pentane) to obtain the desired product as a mixture of diastereoisomers with 8.2:1 d.r. (69.6 mg, 186.5 μmol, 93%). **Major isomer (R*,R*)-3as:** (62.7 mg, 160 μmol, 84%), pale yellow oil. **1H NMR** (400 MHz, CDCl$_3$) δ 7.81 (d, J = 8.1 Hz, 2H), 7.19 (d, J = 7.5 Hz, 2H), 5.43 (s, 1H), 4.00 (t, J = 9.1 Hz, 1H), 3.77 (s, 3H), 2.95 (dt, J = 12.1, 9.2 Hz, 1H), 2.44 (dq, J = 12.1, 10.4, 10.0 Hz, 1H), 2.31 – 2.15 (m, 2H), 1.79 (s, 3H), 1.34 (s, 12H). **13C{1H} NMR** (100 MHz, CDCl$_3$) δ 173.0, 170.4, 139.7, 135.4, 127.4, 84.0, 61.6, 52.7, 46.5, 27.4, 25.0, 24.9, 23.1, 20.6. **19B{1H} NMR** (128 MHz, CDCl$_3$) δ 31.31. **IR (ATR, neat) ν 3285, 2925, 1737, 1650, 1536, 1437, 1360, 1274, 1215, 1144, 1091, 1021, 962, 858, 7550, 658 cm$^{-1}$. **HRMS (ESI):** m/z [M+Na]$^+$ calcd. for C$_{20}$H$_{22}$BNO$_5$ + Na: 396.1956; found 396.1956.

S19
Methyl 1-acetamido-2-methyl-4-(p-toly)cyclobutane-1-carboxylate (3fa/3fa*)

Following the general procedure methyl (Z)-2-acetamidobut-2-enoate (1f) (31.4 mg, 0.2 mmol, 1.0 equiv.) and 4-methyl styrene (2a) (35.5 mg, 0.3 mmol, 1.5 equiv.) were reacted for 72 h. The crude product was purified by flash column chromatography (25% to 33% EtOAc/pentane) to obtain the desired product as a mixture of diastereoisomers with 4:1 d.r. (180. mg, 65.3 µmol, 33%). Only the major isomer could be isolated as the pure substance. Major isomer 3fa: (12.8 mg, 46.5 µmol, 23%), pale yellow oil. \(^1\)H NMR (400 MHz, CDCl₃) δ 7.20 (d, J = 7.8 Hz, 2H), 7.11 (d, J = 8.0 Hz, 2H), 5.30 (s, 1H), 3.78 (s, 3H), 3.71 (dd, J = 10.6, 8.4 Hz, 1H), 3.37 (ddq, J = 10.2, 8.2, 6.9 Hz, 1H), 2.36 (s, 3H), 2.35 – 2.28 (m, 1H), 1.90 (q, J = 10.9 Hz, 1H), 1.85 (s, 3H), 1.00 (d, J = 6.9 Hz, 3H). \(^{13}\)C\(^{1}\)H NMR (100 MHz, CDCl₃) δ 173.2, 170.8, 137.6, 133.1, 129.8, 128.2, 64.1, 52.6, 44.0, 32.9, 29.9, 28.3, 22.9, 21.3, 15.6, 14.3. IR (ATR, neat) v 3408, 2924, 1737, 1658, 1516, 1460, 1308, 1246, 1065, 816, 729 cm\(^{-1}\). HRMS (ESI): m/z [M+Na]\(^{+}\) calcd. for C₁₀H₁₃NO₃ + Na: 298.1419; found 298.1413.

Methyl 1-acetamido-2-phenyl-4-(p-toly)cyclobutane-1-carboxylate (3ga/3ga*)

Following the general procedure methyl methyl (Z)-2-acetamidomethyl-phenylacrylate (1g) (43.9 mg, 0.2 mmol, 1.0 equiv.) and 4-methyl styrene (2a) (35.5 mg, 0.3 mmol, 1.5 equiv.) were reacted for 72 h. The crude product was purified by flash column chromatography (25% to 33% EtOAc/pentane) to obtain the desired product as a mixture of diastereoisomers with 4:1 d.r. (5.6 mg, 15.4 µmol, 8%) as a pale yellow oil. Only the major isomer could be isolated as the pure substance. Major isomer 3ga: (3.4 mg, 10.0 µmol, 5%). \(^1\)H NMR (400 MHz, CDCl₃) δ 7.38 – 7.31 (m, 4H), 7.30 – 7.26 (m, 1H), 7.25 – 7.22 (m, 2H), 7.17 (d, J = 8.0 Hz, 2H), 5.28 (s, 1H), 4.29 (dd, J = 11.0, 8.3 Hz, 1H), 4.17 (dd, J = 10.9, 8.3 Hz, 1H), 3.83 (s, 3H), 2.72 (q, J = 11.0 Hz, 1H), 2.48 (dt, J = 11.1, 8.4 Hz, 1H), 2.35 (s, 3H), 1.49 (s, 3H). \(^{13}\)C\(^{1}\)H NMR (100 MHz, CDCl₃) δ 172.9, 169.2, 137.2, 133.8, 129.3, 128.7, 128.5, 128.4, 127.4, 65.9, 52.7, 42.7, 29.9, 25.3, 22.4, 21.3. IR (ATR, neat) v 3409, 3327, 2925, 1736, 1665, 1517, 1304, 1237, 1091, 1026, 817, 731, 699, 506 cm\(^{-1}\). HRMS (ESI): m/z [M+Na]\(^{+}\) calcd. for C₁₁H₁₄NO₃ + Na: 360.1575; found 360.1570.

Benzyl (6S)-(tert-butyl)-8-oxo-1-(p-toly)-7-oxa-5-azaspiro[3.4]octane-5-carboxylate (3ha/3ha*)

Following the general procedure, benzyl (S)-2-(tert-butyl)-4-methylene-5-oxooxazolidine-3-carboxylate (1h) (57.9 mg, 2.0 mmol, 1.0 equiv.) and 4-methyl styrene (2a) (35.5 mg, 0.3 mmol, 1.5 equiv.) were reacted for 24 h. The crude product was purified by flash column chromatography (5% EtOAc/pentane) to obtain the desired product as a mixture of diastereoisomers with 4:1 d.r. (65.8 mg, 161.5 µmol, 81%) as a colorless oil. Major isomer 3ha: \(^1\)H NMR (400 MHz, CDCl₃) δ 7.43 – 7.36 (m, 5H), 7.26 (d, J = 7.6 Hz 2H), 7.03 (d, J = 7.8 Hz, 2H), 5.58 (s, 1H), 5.26 (q, J = 11.9 Hz, 2H), 4.13 (t, J = 9.4 Hz, 1H), 2.99 – 2.88 (m, 1H), 2.69 – 2.58 (m, 2H), 2.31 (s, 3H), 2.28 – 2.25 (m, 1H), 0.51 (s, 9H). Minor isomer 3ha*: \(^1\)H NMR (400 MHz, CDCl₃) δ 7.33 (d, J = 8.0 Hz, 2H), 5.47 (s, 1H), 5.34 – 5.28 (m, 2H), 4.41 (t, J = 10.7 Hz, 1H), 2.29 (s, 3H), 1.55 (s, 3H), 0.60 (s, 9H). Note: *overlapping signals with the major isomer given as a multiplet. Due to signal overlapping, only the representative signals of the minor isomer are assigned. Both isomers: \(^{13}\)C\(^{1}\)H NMR (100 MHz, CDCl₃) δ 176.6, 173.4, 154.4, 137.3, 137.2, 135.2, 135.2, 130.1, 129.8, 129.0, 128.9, 128.9, 128.8, 128.7, 95.3, 94.4, 68.3, 68.0, 66.8, 49.9, 37.3, 30.4, 25.0, 24.8, 24.7, 21.2, 21.2. IR (ATR, neat) v 3390, 2950, 1656, 994, 823, 762, 619 cm\(^{-1}\). HRMS (ESI): m/z [M+Na]\(^{+}\) calcd. for C₂₅H₂₃NO₄ + Na: 430.1994; found 430.1985.

S20
(1'S,2'S,5'R)-2'-Isopropyl-5'-methylcyclohexyl (1-acetamido-2-(p-tolyl)cyclobutene)-1-carboxylate (3ia/3ia')

Following the general procedure (1'S,2'S,5'R)-2-isopropyl-5-methylcyclohexyl 2-acetamidoacrylate (1j) (53.3 mg, 0.2 mmol, 1.0 equiv.) and 4-methyl styrene (2a) (35.5 mg, 0.3 mmol, 1.5 equiv.) were reacted for 24 h. The crude product was purified by flash column chromatography (25% to 50% EtOAc/pentane) to obtain the desired product as a mixture of diastereoisomers with 2:1:1.1 d.r. and a 2:1 ratio of cis/trans arrangement of the NHAc/p-tol groups at the cyclobutane (62.2 mg, 161.3 µmol, 81%). **Characterization as a 1:1 mixture of major isomers (R*,R*)- & (S*,S*)-3ia:** (51.0 mg, 132.3 µmol, 66%), white amorphous solid. \(^1^H\) NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.18 (d, \(J = 7.5\) Hz, 2+2H), 7.11 – 7.06 (m, 2+2H), 5.37 (s, 1+1H), 5.31 (d, \(J = 3.0\) Hz, 1H), 5.26 (d, \(J = 3.0\) Hz, 1H), 3.96 – 3.88 (m, 1+1H), 3.00 – 2.89 (m, 1+1H), 2.48 – 2.38 (m, 1+1H), 2.36 (s, 3+3H), 2.29 – 2.19 (m, 2+2H), 2.04 (dt, \(J = 6.3, 3.1\) Hz, 1H), 2.01 (dt, \(J = 5.7, 2.9\) Hz, 1H), 1.81 (s, 3H), 1.80 (s, 3H), 1.78 – 1.70 (m, 2+2H), 1.66 – 1.53 (m, 1+1H), 1.51 – 1.35 (m, 1+1H), 1.33 – 1.19 (m, 1+1H), 1.12 – 1.03 (m, 1+1H), 0.97 – 0.90 (m, 1+1H), 0.95 – 0.83 (m, 9+9H). \(^13^C\)\(^{1}H\) NMR (100 MHz, CDCl\(_3\)) \(\delta\) 171.2, 172.1, 170.0, 170.0, 137.6, 137.5, 133.6, 133.6, 129.7, 129.7, 128.0, 128.0, 72.4, 72.1, 62.1, 62.0, 47.2, 47.0, 46.5, 46.4, 39.2, 39.0, 34.9, 34.9, 29.3, 29.2, 27.3, 27.2, 26.8, 25.6, 25.6, 23.2, 23.2, 22.4, 22.3, 21.3, 21.2, 21.0, 20.9, 20.9, 20.9. IR (ATR, neat) v 3299, 2948, 1724, 1658, 1515, 1367, 1242, 1104, 817, 526 cm\(^{-1}\). **Characterization as a 1:1 mixture of minor isomers (R*,S*)- & (S*,R*)-3ia':** (11.2 mg, 29.1 µmol, 15%), white amorphous solid. \(^1^H\) NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.05 – 7.00 (m, 2+2H), 6.98 – 6.90 (m, 2+2H), 6.82 (s, 1H), 5.26 (s, 1H), 5.15 – 5.07 (m, 1+1H), 4.80 (t, \(J = 9.7\) Hz, 1H), 4.59 (t, \(J = 9.4\) Hz, 1H), 3.21 – 3.09 (m, 1H), 3.02 – 2.91 (m, 1H), 2.52 – 2.30 (m, 3+3H), 2.29 – 2.26 (m, 3+3H), 2.07 (s, 3H), 2.05 (s, 3H), 1.73 -1.60 (m, 3+3H), 1.58-1.50 (m, 1+1H), 1.26 – 1.21 (m, 2+2H), 1.20 – 0.99 (m, 2+2H), 0.87 – 0.68 (m, 1+1H), 0.84 (d, \(J = 6.6\) Hz, 3H), 0.78 (d, \(J = 6.6\) Hz, 3H), 0.73 (d, \(J = 6.5\) Hz, 3H), 0.64 (d, \(J = 6.4\) Hz, 3H), 0.54 – 0.45 (m, 3+3H). \(^13^C\)\(^{1}H\) NMR (100 MHz, CDCl\(_3\)) \(\delta\) 172.8, 172.2, 170.0, 169.8, 169.8, 138.1, 137.4, 136.0, 135.7, 129.1, 128.9, 126.1, 125.5, 73.3, 72.7, 65.4, 64.9, 47.3, 47.1, 46.0, 45.2, 39.0, 38.5, 34.8, 34.5, 29.8, 29.1, 28.3, 27.8, 27.7, 26.6, 26.0, 25.6, 25.3, 24.6, 24.3, 22.3, 22.2, 21.2, 21.0, 20.9, 20.8, 20.3, 20.2. IR (ATR, neat) v 3284, 2948, 1722, 1649, 1212, 1454, 1369, 1196, 1119, 1023, 818, 543 cm\(^{-1}\). HRMS (ESI): m/z [M+Na]\(^+\) calcd. for C\(_{24}\)H\(_{36}\)NO\(_3\) + Na: 408.2514; found 408.2509.

Sample preparation for crystal growth: 3ia was dissolved in EtOH. The solvent was allowed to slowly evaporate under ambient conditions until single crystals formed.

**RP-HPLC analysis:** Daicel Chiralpack IA, MeCN:H\(_2\)O 60:40, F = 1, \(\lambda = 210\) nm.

**Mixture of minor isomers 3ia':**
Methyl (acetamido-2-{p-tolyl})cyclobutane-1-carbonyl)-D-valinate (3ja/3ja')

Following the general procedure methyl (2-acetamidoacryloyl)-D-valinate (1j) (48.5 mg, 0.2 mmol, 1.0 equiv.) and 4-methyl styrene (2a) (35.5 mg, 0.3 mmol, 1.5 equiv.) were reacted for 24 h. The crude product was purified by flash column chromatography (75% EtOAc/pentane) to obtain the desired product as a mixture of diastereoisomers with 1:1 d.r. (44.1 mg, 122.4 μmol, 61%) as a colorless oil. Characterization as a mixture of diastereoisomers: 

\[ \text{^1H NMR (500 MHz, DMSO-d_6)} \delta 7.51 (s, 1H), 7.45 (d, \text{ }J = 8.4 \text{ Hz}, 1H), 7.37 (d, \text{ }J = 8.3 \text{ Hz}, 1H), 7.16 (s, 4H), 7.13 (d^{**}, \text{ }J = 8.1 \text{ Hz}, 2H), 7.08 (d^{**}, \text{ }J = 8.5 \text{ Hz}, 2H), 6.85 (s^{**}, 1H), 4.23 - 4.17 (m, 1H), 4.20 - 4.14 (m, 1H), 4.08 (t, \text{ }J = 8.0 \text{ Hz}, 1H), 3.80 (t^{**}, \text{ }J = 8.7 \text{ Hz}, 1H), 3.67 (s, 3H), 3.63 (s, 3H), 2.61 (dt^{**}, \text{ }J = 11.4, 8.5 \text{ Hz}, 1H), 2.30 (s, 3H), 2.28 (s, 1H), 2.27 (s, 3H), 2.27 - 2.18 (m, 2H, 3H), 2.11 (ddd, \text{ }J = 16.2, 7.8, 2.8 \text{ Hz}, 3H), 2.05 - 1.99 (m, 3H), 1.66 (s, 3H), 1.54 (s, 3H), 0.83 (t, \text{ }J = 6.7 \text{ Hz}, 6H), 0.79 (t, \text{ }J = 7.0 \text{ Hz}, 6H). \]

Note: Due to peak overlapping only the representative signals of the individual compounds are assigned: *Isomer1, **Isomer2.

\[ \text{^13C NMR (125 MHz, DMSO-d_6)} \delta 172.9, 172.7, 172.2, 172.0, 169.7, 169.1, 136.4, 135.9, 135.3, 134.9, 128.8, 128.8, 128.7, 128.3, 62.6, 62.1, 57.6, 57.5, 51.7, 51.7, 45.4, 44.4, 29.9, 29.9, 29.9, 28.4, 26.4, 22.9, 22.4, 21.3, 20.8, 20.7, 20.7, 19.1, 19.1, 18.4, 18.2. \]

IR (ATR, neat): ν 3310, 2963, 1738, 1656, 1513, 1008, 658, 504 cm\(^{-1}\).

HRMS (ESI): m/z [M+Na]\(^+\) calcd. for C\(_{20}\)H\(_{20}\)N\(_2\)O\(_4\) + Na: 383,1947; found 383.1943, m/z [M+K]\(^+\) calcd. for C\(_{20}\)H\(_{20}\)N\(_2\)O\(_4\) + K: 399.1686; found 399.1682.

Methyl \(N^2\)-acetamido-2-{p-tolyl}cyclobutane-1-carbonyl)-\(N^6\)-(tert-butoxycarbonyl)-L-lysinate (3ka)

Following the general procedure, methyl \(N^2\)-(2-acetamidoacryloyl)-\(N^6\)-(tert-butoxycarbonyl)-L-lysinate (1k) (74.3 mg, 0.2 mmol, 1.0 equiv.) and 4-methyl styrene (2a) (35.5 mg, 0.3 mmol, 1.5 equiv.) were reacted for 24 h. The crude product was purified by flash column chromatography (75% to 100% EtOAc/pentane) to obtain the desired product as a mixture of diastereoisomers with 9:9:1 d.r. and a 9:1 ratio of cis/trans arrangement of the NHAc/p-Tol groups at the cyclobutane (45.9 mg, 93.7 μmol, 47%). Only the major cis-isomers could be isolated pure. Major isomers 3ka: (38.1 mg, 77.8 μmol, 39%) pale yellow, amorphous solid. Characterization as a 1:1 mixture of isomers: 

\[ \text{^1H NMR (400 MHz, CDCl_3)} \delta 7.44 (d, \text{ }J = 7.5 \text{ Hz}, 1H), 7.23 - 7.16 (m, 4+4H), 7.13 (d, \text{ }J = 8.1 \text{ Hz}, 1H), 5.42 (s, 1+1H), 4.98 (s, 1H), 4.86 (s, 1H), 4.59 (td, \text{ }J = 8.2, 4.8 \text{ Hz}, 1H), 4.48 (td, \text{ }J = 7.8, 5.0 \text{ Hz}, 1H), 4.27 (t, \text{ }J = 9.3 \text{ Hz}, 1H), 4.20 (t, \text{ }J = 8.8 \text{ Hz}, 1H), 3.73 (s, 3H), 3.72 (s, 3H), 3.16 - 2.97 (m, 2+2H), 2.77 - 2.63 (m, 1H), 2.57 (dt, \text{ }J = 12.1, 9.1 \text{ Hz}, 1H), 2.45 (ddd, \text{ }J = 12.0, 9.0, 3.0 \text{ Hz}, 1H), 2.39 - 2.30 (m, 3H), 2.36 (s, 3+3H), 2.15 (dddt, \text{ }J = 14.1, 8.5, 5.6, 3.2 \text{ Hz}, 1+1H), 1.87 (s, 3H), 1.85 (s, 3H), 1.83 - 1.78 (m, 2+1H), 1.71 - 1.60 (m, 1+1H), 1.51 - 1.44 (m, 2+2H), 1.44 - 1.37 (m, 9+9H), 1.36 - 1.26 (m, 2+2H). \]

\[ \text{^13C NMR (100 MHz, CDCl_3)} \delta 172.9, 172.8, 172.5, 172.1, 171.1, 156.2, 156.1, 137.6, 137.5, 133.5, 133.4, 129.9, 129.8, 128.4, 128.3, 79.1, 78.9, 63.1, 52.4, 52.4, 52.4, 44.4, 43.8, 40.1, 31.7, 29.8, 29.3, 29.1, 28.5, 28.5, 27.0, 26.7, 23.7, 23.6, 22.5, 22.3, 21.2, 20.1, 20.1. \]

IR (ATR, neat): ν 3397, 2947, 1739, 1669, 1516, 1025, 671, 504 cm\(^{-1}\).

HRMS (ESI): m/z [M+Na]\(^+\) calcd. for C\(_{29}\)H\(_{38}\)N\(_3\)O\(_6\) + Na: 512.2736; found 512.2731.
5. Deprotection reactions

tert-Butyl 1-((tert-butoxycarbonyl)amino)-2-(p-tolyl)cyclobutane-1-carboxylate (3la/3la’)

Following the general procedure, tert-butyl 2-((tert-butoxycarbonyl)amino)acrylate (1I) and 4-methyl styrene (2a) (35.5 mg, 0.3 mmol, 1.5 equiv.) were reacted for 24 h. The crude product was purified by flash column chromatography (5% to 10% EtOAc/pentane) to obtain the desired product as a mixture of diastereoisomers with 9:1 d.r. (54.4 mg, 150.0 µmol, 75%) as a colourless oil.

Major isomer (R*,R*)-3la: Characterization as 1:5:1 mixture of rotamers: 1H NMR (400 MHz, CDCl3) δ 7.17 (d, J = 7.6 Hz, 2H), 7.08 (d, J = 7.8 Hz, 2H), 4.50 and 4.32 (s, 1H), 3.86 (s, 1H), 2.85 (dt, J = 11.7, 9.2 Hz, 1H), 2.43 (dq, J = 11.1, 9.7 Hz, 1H), 2.34 (s, 3H), 2.20 – 2.10 (m, 2H), 1.50 (s, 9H), 1.37 (s, 9H). Minor isomer (R*,S*)-3la: 1H NMR (400 MHz, CDCl3) δ 7.01 (d, J = 8.3 Hz, 2H), 2.29 (s, 3H), 1.47 (s, 9H), 1.08 (s, 9H). Note: Due to signal overlapping, only the representative signals of the minor isomer are assigned.

Both isomers: 1H NMR (400 MHz, CDCl3) δ 172.5, 155.3, 137.0, 133.9, 129.5, 128.7, 128.1, 126.8, 81.0, 79.6, 64.6, 62.4, 46.0, 29.8, 28.5, 28.3, 28.1, 27.5, 26.8, 21.1, 21.1, 20.6. IR (ATR, neat) ν 3420, 2977, 1719, 1478, 1365, 1248, 1157, 1104, 819, 730 cm⁻¹. HRMS (ESI): m/z [M+Na⁺] calcd. for C21H31NO4 + Na: 384.2150; found 384.2145.

1-Carboxy-2-(p-tolyl)cyclobutan-1-aminium 2,2,2-trifluoroacetate (4/4’-TFA)

tert-Butyl 1-((tert-butoxycarbonyl)amino)-2-(p-tolyl)cyclobutane-1-carboxylate (3la/3la’) (54.4 mg, 150 µmol, 1.0 equiv; 9:1 d.r.) was dissolved in 5 mL of a 1:1 mixture of DCM and TFA. The reaction mixture was stirred for 4 at r.t.. The solvent was removed under reduced pressure to obtain the desired product as a mixture of diastereoisomers with 9:1 d.r. (41.3 mg, 129.4 µmol, 86%) as a colorless solid. Major isomer (R*R*)-4*TFA: 1H NMR (400 MHz, D2O) δ 7.23 (d, J = 7.9 Hz, 2H), 7.11 (d, J = 8.0 Hz, 2H), 4.25 (t, J = 9.4 Hz, 1H), 2.85 (dt, J = 13.0, 9.2 Hz, 1H), 2.64 (dq, J = 12.1, 9.7 Hz, 1H), 2.34 (dddt, J = 12.6, 9.1, 3.6 Hz, 1H), 2.28 (s, 3H), 2.16 (dddd, J = 13.1, 9.6, 3.6 Hz, 1H). Minor isomer (R*S*)-4*TFA: 1H NMR (400 MHz, D2O) δ 7.14 (d, J = 4.9 Hz, 2H), 4.05 (t, J = 9.4 Hz, 1H), 2.24 (s, 3H). Note: Due to signal overlapping, only the representative signals of the minor isomer are assigned.

Both isomers: 19F{1H} NMR (375 MHz, D2O) δ -75.59. 13C{1H} NMR (100 MHz, D2O) δ 172.5, 171.5, 162.6 (q, J = 35.8 Hz), 138.5, 137.9, 133.8, 131.5, 129.7, 129.1, 127.7, 127.1, 116.2 (q, J = 291.4 Hz), 63.1, 62.4, 47.2, 44.5, 29.5, 26.9, 26.0, 25.8, 20.1, 20.0, 18.9. IR (ATR, neat) ν 3418, 2952, 1703, 1515, 1365, 1163, 1086, 818, 506 cm⁻¹. HRMS (ESI): m/z [M+Na⁺] in MeOH: calcd. for C12H13NO2 + Na: 228.1000; found 228.0994.

(R*R*)-1-Carboxy-2-(p-tolyl)cyclobutan-1-aminium chloride (4-HCl)

Menthol derivative (R*,R*)-3ia (27.5 mg, 72.3 µmol, 1.0 equiv) was dissolved in 1 mL of a HCl (6 M) and the mixture was stirred 24 h at 120 °C. The crude mixture was filtered and the solvent was evaporated to obtain the desired product (12.6 mg, 52.1 µmol, 73%), as a white, crystalline solid. (R*R*)-4-HCl: 1H NMR (400 MHz, D2O) δ 7.34 – 7.30 (m, 2H), 7.25 – 7.20 (m, 2H), 4.39 (t, J = 9.4 Hz, 1H), 2.92 (dt, J = 13.0, 9.3 Hz, 1H), 2.73 (dq, J = 12.0, 9.6 Hz, 1H), 2.44 (dddt, J = 12.5, 9.1, 3.6 Hz, 1H), 2.36 (s, 3H), 2.23 (ddddd, J = 13.0, 9.5, 3.5, 0.9 Hz, 1H). 13C{1H} NMR (100 MHz, D2O) δ
Following the general procedure, tert-butyl 1-(((9-H-fluoren-9-yl)methoxy)carbonyl)amino)-2-(p-tolyl)cyclobutane-1-carboxylate (1m) (73.1 mg, 0.2 mmol, 1.0 equiv.) and 4-methyl styrene (2a) (35.5 mg, 0.3 mmol, 1.5 equiv.) were reacted for 24 h. The crude product was purified by flash column chromatography (5% to 10% EtOAc/pentane) to obtain the desired product as a mixture of diastereoisomers 7.5:1 d.r. (74.6 mg, 154.3 µmol, 77%) as a colourless oil. **Major isomer (R*,R*).**

Minor isomer (R*,S*):

**IR (ATR, neat) v 2882, 1737, 1575, 1493, 1402, 1161, 1124, 935, 819, 702, 660, 535 cm⁻¹.**

HRMS (ESI, 4 in MeOH): m/z [M+Na]{calcd.} for C_{16}H_{33}NO_{3} + Na: 228.1000; found 228.0995.

**tert-Butyl 1-(((9-H-fluoren-9-yl)methoxy)carbonyl)amino)-2-(p-tolyl)cyclobutane-1-carboxylate (3ma/3ma')**

Following the general procedure, tert-butyl 2-(((9-H-fluoren-9-yl)methoxy)carbonyl)amino)acrylate (1m) (73.1 mg, 0.2 mmol, 1.0 equiv.) and 4-methyl styrene (2a) (35.5 mg, 0.3 mmol, 1.5 equiv.) were reacted for 24 h. The crude product was purified by flash column chromatography (5% to 10% EtOAc/pentane) to obtain the desired product as a mixture of diastereoisomers 7.5:1 d.r. (74.6 mg, 154.3 µmol, 77%) as a colourless oil. **Major isomer (R*,R*).**

Minor isomer (R*,S*):

**1H NMR (500 MHz, acetone-d₆) δ 7.83 (ddt, J = 7.6, 2.4, 1.0 Hz, 2H), 7.52 (dd, J = 8.2 Hz, 2H), 7.39 (tdd, J = 7.5, 2.6, 1.1 Hz, 2H), 7.29 (q, J = 7.8 Hz, 2H), 7.20 (d, J = 7.7 Hz, 2H), 7.13 (d, J = 8.2 Hz, 2H), 5.77 (s, 1H), 4.30 – 4.22 (m, 1H), 4.13 – 4.07 (m, 1H), 4.05 (m, 2H), 2.66 (q, J = 9.6 Hz, 1H), 2.42 (dq, J = 10.9, 8.9 Hz, 1H), 2.34 – 2.24 (m, 2H), 2.21 (s, 3H), 1.48 (s, 9H).**

**Note:** Due to signal overlapping, only the representative signals of the minor isomer are assigned.

**Both isomers:**

**13C{1H} NMR (125 MHz, acetone-d₆) δ 172.5, 170.9, 155.7, 145.1, 144.7, 142.1, 142.0, 141.9, 137.3, 136.7, 135.6, 129.8, 129.2, 128.5, 128.5, 128.4, 128.2, 127.9, 127.8, 127.8, 127.8, 126.1, 125.9, 120.8, 120.7, 120.7, 81.0, 67.0, 66.7, 63.2, 47.9, 46.5, 28.3, 28.1, 27.7, 21.2, 21.0.**

**IR (ATR, neat) v 3412, 2976, 1726, 1490, 1248, 1163, 1106, 741 cm⁻¹.**

HRMS (ESI): m/z [M+Na]{calcd.} for C_{16}H_{33}NO_{3} + Na: 506.2307; found 506.2301.

**tert-Butyl 1-amino-2-(p-tolyl)cyclobutane-1-carboxylate (5)**

Following the general procedure, tert-butyl 1-(((9-H-fluoren-9-yl)methoxy)carbonyl)amino)-2-(p-tolyl)cyclobutane-1-carboxylate (3ma/3ma') (30.2 mg, 62.5 µmol, 1.0 equiv., 7.5:1 d.r.) was dissolved in 1 mL of a 3:1 mixture of DCM and piperidine. The mixture was stirred for 1 h at r.t. The solvent was removed and the crude product was purified by flash column chromatography (10% EtOAc/pentane) to obtain the desired product (9.1 mg, 38.8 µmol, 56%) as a colorless oil. Note: The expected minor diastereomer could not be obtained. **1H NMR (400 MHz, CDCl₃) δ 7.15 (d, J = 7.9 Hz, 2H), 7.08 (d, J = 8.0 Hz, 2H), 3.87 (t, J = 9.0 Hz, 1H), 2.61 (dt, J = 11.3, 8.9 Hz, 1H), 2.45 (dq, J = 11.0, 9.2 Hz, 1H), 2.33 (s, 3H), 2.18 (ddt, J = 11.0, 8.6, 3.4 Hz, 1H), 1.76 (dddd, J = 11.3, 9.1, 3.4, 0.8 Hz, 1H), 1.52 (s, 9H), 1.39 – 1.32 (m, 2H).**

**19F{1H} NMR (100 MHz, CDCl₃) δ 175.1, 136.3, 135.7, 129.1, 128.1, 81.0, 62.4, 47.0, 30.0, 28.2, 21.1, 20.3.**

**IR (ATR, neat) v 3382, 2977, 1719, 1514, 1367, 1245, 1162, 1090, 805, 509 cm⁻¹.**

HRMS (ESI): m/z [M+Na]{calcd.} for C_{16}H_{33}NO_{3} + Na: 284.1626; found 284.1621.
6. Scaling-up Reaction

**Batch reaction**

An oven-dried 50 ml round bottom flask was charged with 2-acetamidoacrylate (1a) (715.7 mg, 5.0 mmol, 1.0 equiv.) and [Ir(dFCFppy)₆(4,4'-dtbpy)]PF₆ (112.2 mg, 0.1 mmol, 2 mol%), and dissolved in dry CH₃CN (25 ml, 0.2 M). 4-Methyl-styrene (2a) (886.3 mg, 7.5 mmol, 1.5 equiv.) was added. A septum was applied. The mixture was degassed by bubbling argon for 10 min. The mixture was irradiated by three 3 W blue LEDs (410-420 nm) for 14 d (the reaction was monitored by TLC). The crude product was purified by flash column chromatography (50% EtOAc/pentane) to obtain the desired product as a mixture of diastereoisomers 3aa/3aa' with 8:1 d.r. (573.4 mg, 2.19 mmol, 44%).

**Flow reaction**

An oven-dried 50 ml round bottom flask was charged with 2-acetamidoacrylate (1a) (715.7 mg, 5.0 mmol, 1.0 equiv.) and [Ir(dFCFppy)₆(4,4'-dtbpy)]PF₆ (112.2 mg, 0.1 mmol, 2 mol%), and dissolved in dry CH₃CN (25 ml, 0.2 M). 4-Methyl-styrene (2a) (886.3 mg, 7.5 mmol, 1.5 equiv.) was added. A septum was applied. The mixture was degassed by bubbling argon for 5 min. The reaction was run continuously with a flow of approx. 6 ml/min for 52 h at 18 °C. The crude product was purified by flash column chromatography (50% EtOAc/pentane) to obtain the desired product as a mixture of diastereoisomers 3aa/3aa' with 8:1 d.r. (921.7 mg, 3.53 mmol, 71%).

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7. Cyclic Voltammetry

The cyclic voltammogram of methyl 2-acetamidoacrylate (1a) was taken on a Metrohm Autolab PGSTAT204 potentiostat using a platinum wire working electrode, a platinum mesh counter electrode and a silver reference electrode, which was referenced externally against the Fc/Fc+ couple. The pH was not adjusted and the voltammogram was taken at room temperature in a 0.1 M CH₃CN solution of tetrabutylammonium hexafluorophosphate containing 10 mM of the designated substrate. The scan rate was 50 mV/s. Ferrocene was added as internal standard. It is known that the Fc/Fc+ couple is 0.38 V more positive than the SCE. This value may be subtracted from the obtained difference to determine the potential against SCE.

![Cyclic Voltammogram](image)

8. Mechanistic Studies

**Stern-Volmer quenching**

Stern-Volmer experiments tracking the quenching of the phosphorescence of [Ir(dF(CF₃)ppy)₂(4,4'-dtbpy)]PF₆ were conducted on a Jasco FP-8500 spectrofluorometer. In a typical procedure, the sample was dissolved in a cuvette (1 cm) in 1 mL of a degassed stock solution of the photocatalyst in MeCN (concentration of [Ir] 0.1×10⁻⁶ M). Samples were irradiated at 415 nm and the emission was detected at 475 nm. The data are graphically represented by Microsoft Excel.

The Stern-Volmer quenching constant kₚ was calculated according to the Stern-Volmer equation:

\[
\frac{I_0}{I} = 1 + k_p \tau_0 [Q]
\]

where \(I_0\) is the luminescence without the quencher, \(I\) is the intensity with the quencher, \(\tau_0\) is the lifetime of the excited photocatalyst (2.3 µs for [Ir(dF(CF₃)ppy)₂(4,4'-dtbpy)]PF₆) and \([Q]\) is the concentration of the quencher.

![Stern-Volmer Equation](image)
Table S4: Quenching experiments with 4-methyl-styrene (2a)

| Entry | Quencher [mM] | Emission [415 nm] | I₀/I |
|-------|---------------|-------------------|------|
| 1     | 0             | 872               | 1.0  |
| 2     | 0.25          | 502               | 1.735|
| 3     | 0.5           | 352               | 2.474|
| 4     | 1.0           | 215               | 4.047|
| 5     | 2.5           | 101               | 8.631|
| 6     | 5.0           | 54                | 16.094|
| 7     | 10.0          | 28                | 31.292|

\[ y = 3.029x + 0.995 \]
\[ R^2 = 1 \]

\[ k_q = 1.32 \times 10^{-3} \text{ M}^{-1} \text{ s}^{-1} \]

Table S5: Quenching experiments with methyl 2-acetamidoacrylate (1a)

| Entry | Quencher [mM] | Emission [415 nm] | I₀/I |
|-------|---------------|-------------------|------|
| 1     | 0             | 1012              | 1    |
| 2     | 1.0           | 881               | 881  |
| 3     | 2.5           | 750               | 300  |
| 4     | 5.0           | 605               | 121  |
| 5     | 10.0          | 440               | 44   |

\[ y = 0.1292x + 1.0162 \]
\[ R^2 = 0.9995 \]

\[ k_q = 56.1 \times 10^{-6} \text{ M}^{-1} \text{ s}^{-1} \]
9. Crystallographic Information

**X-Ray diffraction:** Data sets for compounds 3aa, 3ac, 3af and 3ia are collected with a Bruker D8 Venture PHOTON III diffractometer. Programs used: data collection: APEX3 V2019.1-O \(^1\) (Bruker AXS Inc., 2019); cell refinement: SAINT V8.40A (Bruker AXS Inc., 2019); data reduction: SAINT V8.40A (Bruker AXS Inc., 2019); absorption correction, SADABS V2016/2 (Bruker AXS Inc., 2019); structure solution SHELXT-2015\(^2\) (Sheldrick, G. M. Acta Cryst., 2015, A71, 3-8); structure refinement SHELXL-2015\(^3\) (Sheldrick, G. M. Acta Cryst., 2015, C71 (1), 3-8). \(R\)-values are given for observed reflections, and \(wR^2\)-values are given for all reflections. Exceptions and special features: For compound 3aa the tolyl group and for compound 3af the ester (COOME) unit were found disordered over two positions in the asymmetric unit. Several restraints (SADI, SAME, ISOR and SIMU) were used in order to improve refinement stability.

**Crystal Structure Analysis of 3aa**. CCDC Nr.: 2174645 (gar10165). Ellipsoid contours are given at the 50% probability level. A colorless plate-like specimen of C\(_{15}\)H\(_{19}\)NO\(_3\), approximate dimensions 0.066 mm x 0.069 mm x 0.157 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured on a single crystal Bruker D8 Venture Photon III Diffractometer system equipped with a micro focus tube CuK\(_\alpha\) (CuK\(_\alpha\), \(\lambda = 1.54178\) Å) and a MX mirror monochromator. A total of 1629 frames were collected. The total exposure time was 19.53 hours. The frames were integrated with the Bruker SAINT software package using a wide-frame algorithm. The integration of the data using an orthorhombic unit cell yielded a total of 56200 reflections to a maximum \(\theta\) angle of 66.58° (0.84 Å resolution), of which 2540 were independent (average redundancy 22.126, completeness = 99.5%). The calculated minimum and maximum transmission coefficients (based on crystal size) are 0.9010 and 0.9570. The structure was solved and refined using the Bruker SHELXTL Software Package, using the space group \(Pbc\alpha\), with \(Z = 8\) for the formula unit, C\(_{15}\)H\(_{19}\)NO\(_3\). The final anisotropic full-matrix least-squares refinement on \(F^2\) with 244 variables converged at \(R_1 = 4.98\%\), for the observed data and \(wR_2 = 12.86\%\) for all data. The goodness-of-fit was 1.050. The largest peak in the final difference electron density synthesis was 0.354 e\(^{-}/\)Å\(^3\) and the largest hole was -0.185 e\(^{-}/\)Å\(^3\) with an RMS deviation of 0.041 e\(^{-}/\)Å\(^3\). On the basis of the final model, the calculated density was 1.201 g/cm\(^3\) and F(000), 1120 e\(^{-}\). The hydrogen at N1 atom was refined freely.

**Crystal Structure Analysis of 3ac**. CCDC Nr.: 2174646 (gar10199). Ellipsoid contours are given at the 50% probability level. A colorless plate-like specimen of C\(_{15}\)H\(_{19}\)NO\(_3\), approximate dimensions 0.042 mm x 0.114 mm x 0.148 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured on a single crystal Bruker D8 Venture Photon III Diffractometer system equipped with a micro focus tube CuK\(_\alpha\) (CuK\(_\alpha\), \(\lambda = 1.54178\) Å) and a MX mirror monochromator. A total of 1766 frames were collected. The total exposure time was 23.20 hours. The frames were integrated with the Bruker SAINT software package using a wide-frame algorithm. The integration of the data using a monoclinic unit cell yielded a total of 14459 reflections to a maximum \(\theta\) angle of 68.20° (0.83 Å resolution), of which 2498 were independent (average redundancy 5.788,
Crystal Structure Analysis of 3af. CCDC Nr.: 2174647 (gar10201). Ellipsoid contours are given at the 50% probability level.

A colorless plate-like specimen of C_{16}H_{19}NO_3, approximate dimensions 0.062 mm x 0.093 mm x 0.201 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured on a single crystal Bruker D8 Venture Photon III Diffractometer system equipped with a micro focus tube CuKα (CuKα, λ = 1.54178 Å) and a MX mirror monochromator. A total of 2018 frames were collected. The total exposure time was 24.90 hours. The frames were integrated with the Bruker SAINT software package using a wide-frame algorithm. The integration of the data using a triclinic unit cell yielded a total of 45129 reflections to a maximum θ angle of 68.42° (0.83 Å resolution), of which 5330 were independent (average redundancy 8.467, completeness = 99.6%, R_{int} = 9.68%, R_{sig} = 5.22%) and 3990 (74.86%) were greater than 2σ(F^2). The final cell constants of a = 9.5406(2) Å, b = 10.2760(3) Å, c = 15.1275(4) Å, α = 81.3170(10)°, β = 82.6220(10)°, γ = 89.4160(10)°, volume = 1453.89(7) Å³, are based upon the refinement of the XYZ-centroids of 9512 reflections above 20 σ(I) with 5.959° < 2Θ < 136.2°. Data were corrected for absorption effects using the Multi-Scan method (SADABS). The ratio of minimum to maximum apparent transmission was 0.875. The calculated minimum and maximum transmission coefficients (based on crystal size) are 0.8720 and 0.9580. The structure was solved and refined using the Bruker SHELXTL Software Package, using the space group P-1, with Z = 4 for the formula unit, C_{16}H_{19}NO_3. The final anisotropic full-matrix least-squares refinement on F^2 with 411 variables converged at R1 = 4.46%, for the observed data and wR2 = 11.19% for all data. The goodness-of-fit was 1.038. The largest peak in the final difference electron density synthesis was 0.377 e^-/Å³ and the largest hole was -0.280 e^-/Å³ with an RMS deviation of 0.045 e^-/Å³. On the basis of the final model, the calculated density was 1.249 g/cm³ and F(000), 584 e^-.

The hydrogen at N1 atom was refined freely.

Crystal Structure Analysis of 3af. CCDC Nr.: 2174648 (gar10206). Ellipsoid contours are given at the 50% probability level.

A colorless plate-like specimen of C_{16}H_{19}NO_3, approximate dimensions 0.043 mm x 0.069 mm x 0.159 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured on a single crystal Bruker D8 Venture Photon III Diffractometer system equipped with a micro focus tube CuKα (CuKα, λ = 1.54178 Å) and a MX mirror monochromator. A total of 1556 frames were collected. The total exposure time was 23.21 hours. The frames were integrated with the Bruker SAINT software package using a wide-frame algorithm. The

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integration of the data using a monoclinic unit cell yielded a total of 25952 reflections to a maximum θ angle of 66.61° (0.84 Å resolution), of which 2498 were independent (average redundancy 10.389, completeness = 99.7%, R_{int} = 8.84%, R_{sig} = 3.89%) and 2041 (81.71%) were greater than 2σ(F^2). The final cell constants of a = 16.7319(4) Å, b = 6.07230(10) Å, c = 14.4757(3) Å, β = 106.1120(10)^°, volume = 1412.98(5) Å^3, are based upon the refinement of the XYZ-centroids of 7541 reflections above 20 σ(I) with 15.22° < 2θ < 133.1°. Data were corrected for absorption effects using the Multi-Scan method (SADABS). The ratio of minimum to maximum apparent transmission was 0.900. The calculated minimum and maximum transmission coefficients (based on crystal size) are 0.8940 and 0.9700. The structure was solved and refined using the Bruker SHELXTL Software Package, using the space group P2_1/c, with Z = 4 for the formula unit, C_{18}H_{19}NO_3. The final anisotropic full-matrix least-squares refinement on F^2 with 187 variables converged at R1 = 3.69%, for the observed data and wR2 = 9.30% for all data. The goodness-of-fit was 1.032. The largest peak in the final difference electron density synthesis was 0.239 e^-Å^3 and the largest hole was -0.211 e^-Å^3 with an RMS deviation of 0.043 e^-Å^3. On the basis of the final model, the calculated density was 1.285 g/cm^3 and F(000), 584 e^-.

The hydrogen at N1 atom was refined freely.

**Crystal Structure Analysis of 3ia.** CCDC Nr.: 2192789 (gar10363). Ellipsoid contours are given at the 40% probability level. A colorless, needle-like specimen of C_{24}H_{13}NNO_3, approximate dimensions 0.031 mm x 0.039 mm x 0.092 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured on a single crystal diffractometer Bruker D8 Venture Photon III system equipped with a micro focus tube Cu ImS (CuKα, λ = 1.54178 Å) and a MX mirror monochromator. A total of 1468 frames were collected. The total exposure time was 23.34 hours. The frames were integrated with the Bruker SAINT software package using a wide-frame algorithm. The integration of the data using a monoclinic unit cell yielded a total of 37430 reflections to a maximum θ angle of 66.62° (0.84 Å resolution), of which 7130 were independent (average redundancy 5.250, completeness = 99.0%, R_{int} = 40.09%, R_{sig} = 26.48%) and 2558 (35.88%) were greater than 2σ(F^2). The final cell constants of a = 14.3131(13) Å, b = 5.7515(7) Å, c = 27.167(3) Å, β = 90.334(6)^°, volume = 2236.4(4) Å^3, are based upon the refinement of the XYZ-centroids of 558 reflections above 20 σ(I) with 6.963° < 2θ < 70.20°. Data were corrected for absorption effects using the Multi-Scan method (SADABS). The ratio of minimum to maximum apparent transmission was 0.793. The calculated minimum and maximum transmission coefficients (based on crystal size) are 0.9480 and 0.9820. The structure was solved and refined using the Bruker SHELXTL Software Package, using the space group P2_1, with Z = 4 for the formula unit, C_{24}H_{13}NNO_3. The final anisotropic full-matrix least-squares refinement on F^2 with 522 variables converged at R1 = 8.51%, for the observed data and wR2 = 22.51% for all data. The goodness-of-fit was 0.957. The largest peak in the final difference electron density synthesis was 0.303 e^-Å^3 and the largest hole was -0.279 e^-Å^3 with an RMS deviation of 0.084 e^-Å^3. On the basis of the final model, the calculated density was 1.145 g/cm^3 and F(000), 840 e^-.

The hydrogen at N1A and N1B atoms were refined freely, but with N-H distance restraints (DFIX).
10. References

(1) Fulmer, G. R.; Miller, A. J. M.; Sherden, N. H.; Gottlieb, H. E.; Nudelman, A.; Stoltz, B. M.; Bercaw, J. E.; Goldberg, K. I. NMR Chemical Shifts of Trace Impurities: Common Laboratory Solvents, Organics, and Gases in Deuterated Solvents Relevant to the Organometallic Chemist. *Organometallics* 2010, 29, 2176–2179.

(2) Armarégo, W.; Chai, C. *Purification of Laboratory Chemicals, 6th Edition*, Elsevier Science, 2009.

(3) Chalker, J. M.; Gunnoo, S. B.; Boutureira, O.; Gerstberger, S. C.; Fernández-González, M.; Bernardes, G. J. L.; Griffin, L.; Hailu, H.; Schofield, C. J.; Davis, B. G. Methods for converting cysteine to dehydroalanine on peptides and proteins. *Chem. Sci.* 2011, 2, 1666–1676.

(4) Aycock, R. A.; Vogt, D. B.; Jui, N. T. A practical and scalable system for heteroaryl amino acid synthesis. *Chem. Sci.* 2017, 8, 7998–8003.

(5) Koch, S.; Schollmeyer, D.; Löwe, H.; Kunz, H. C-Glycosyl amino acids through hydroboration-cross-coupling of exoglycals and their application in automated solid-phase synthesis. *Chem. Eur. J.* 2013, 19, 7020–7041.

(6) Degnan, A. P.; Chaturvedula, P. V.; Conway, C. M.; Cook, D. A.; Davis, C. D.; Denton, R.; Han, X.; Macci, R.; Mathias, N. R.; Moench, P. Discovery of (R)-4-(8-fluoro-2-oxo-1,2- dihydroquinazolin-3(4H)-yl)-N-(3-(7-methyl-1H-indazol-5-yl)-1-oxo-1-{4-(piperidin-1-yl)piperidin-1-yl)propan-2-yl)piperidine-1-carboxamide (BMS-694153): a potent antagonist of the human calcitonin gene-related peptide receptor for migraine with rapid and efficient intranasal exposure. *J. Med. Chem.* 2008, 51, 4858–4861.

(7) Chen, H.-X.; Kang, J.; Chang, R.; Zhang, Y.-L.; Duan, H.-Z.; Li, Y.-M.; Chen, Y.-X. Synthesis of α,α-Difluorinated Phosphonate pSer/pThr Mimetics via Rhodium-Catalyzed Asymmetric Hydrogenation of β-Difluorophosphonomethyl α-(Acylamino)acrylates. *Org. Lett.* 2018, 20, 3278–3281.

(8) Schlegel, M.; Schneider, C. Lewis Acid-Catalyzed Nucleophilic Addition of Indoles to in Situ-Generated 2-Aminoallyl Cations. *J. Org. Chem.* 2017, 82, 5986–5992.

(9) Allouche, E. M. D.; Charette, A. B. Non-stabilized diazoalkane synthesis via the oxidation of free hydrazones by iodosylbenzene and application in in situ MIRC cyclopropanation. *Chem. Sci.*, 2019, 10, 3802–3806.

(10) Lowry, M. S.; Goldsmith, J. I.; Slinker, J. D.; Rohl, R; Pascal, R. A., Jr.; Malliaras, G. G.; Bernhard, S. Single-Layer Electroluminescent Devices and Photoinduced Hydrogen Production from an Ionic Iridium(III) Complex. *Chem. Mater.* 2005, 17, 5712–5719.

(11) Bruker AXS (2019) APEX3 Version 2019.1-0, SAINT Version 8.40A and SADABS Bruker AXS area detector scaling and absorption correction Version 2016/2, Bruker AXS Inc., Madison, Wisconsin, USA.

(12) Sheldrick, G. M., SHELLT – Integrated space-group and crystal-structure determination, *Acta Cryst.* 2015, A71, 3-8.

(13) Sheldrick, G. M., Crystal structure refinement with SHELXL, *Acta Cryst.* 2015, C71, 3-8.
11. NMR Collection

*Methyl 2-acetamidoacrylate (1a)*

\[ \text{NMR spectrum (400 MHz, CDCl}_3\text{)} \]

*Methyl 2-((tert-butoxycarbonyl)amino)acrylate (1b)*

\[ \text{NMR spectrum (300 MHz, CDCl}_3\text{)} \]
Methyl 2-(bis(tert-butoxycarbonyl)amino)acrylate (1c)

\[
\begin{align*}
\text{Boc} & \quad \text{N} \\
\quad & \quad \text{O} \\
& \quad \text{Boc}
\end{align*}
\]

1H-NMR spectrum (300 MHz, CDCl₃)

Methyl 2-(((9H-fluoren-9-yl)methoxy)carbonyl)amino)acrylate (1d)

\[
\begin{align*}
\text{Fmoc} & \quad \text{N} \\
\quad & \quad \text{O} \\
\end{align*}
\]

1H-NMR spectrum (400 MHz, CDCl₃)

S33
Methyl 2-(((benzyloxy)carbonyl)amino)acrylate (1e)

Methyl (Z)-2-acetamidobut-2-enoate (1f)

$^{1}$H-NMR spectrum (400 MHz, CDCl$_3$)
Methyl (Z)-2-acetamido-3-phenylacrylate (1g)

\[
\text{\[\text{Diagram}\]
}\]

1H-NMR spectrum (400 MHz, CDCl₃)

Benzyl (S)-2-(tert-butyl)-4-methylene-5-oxooxazolidine-3-carboxylate (1h)

\[
\text{\[\text{Diagram}\]
}\]

1H-NMR spectrum (400 MHz, CDCl₃)
(1S,2S,5R)-2-Isopropyl-5-methylcyclohexyl 2-acetamidoacrylate (1I)

1H-NMR spectrum (400 MHz, CDCl₃)

13C(1H)-NMR spectrum (100 MHz, CDCl₃)
Methyl (2-acetamidoacryloyl)-D-valinate (1j)

$\text{Ac} - \text{H} - \text{N} - \text{CH} - \text{C} - \text{O} - \text{H}$

$^1H$-NMR spectrum (400 MHz, CDCl$_3$)

$^{13}C{\{H\}}$-NMR spectrum (100 MHz, CDCl$_3$)

S37
Methyl N²-(2-acetamidoacryloyl)-N⁶-(tert-butoxycarbonyl)-L-lysinate (1k)

H-NMR spectrum (400 MHz, CDCl₃)

C{H}-NMR spectrum (100 MHz, CDCl₃)

S38
tert-Butyl 2-{(tert-butoxycarbonyl)amino}acrylate (1l)

$\text{Boc} \overset{\text{N}}{\text{H}} \overset{\text{O}}{\text{C}}$

$^1$H-NMR spectrum (400 MHz, CDCl$_3$)

tert-Butyl 2-(((9H-fluoren-9-yl)methoxy)carbonyl)amino)acrylate (1m)

$\text{Fmoc} \overset{\text{N}}{\text{H}} \overset{\text{O}}{\text{C}}$

$^1$H-NMR spectrum (400 MHz, CDCl$_3$)
Methyl (1R*,2R*)-1-acetamido-2-(p-tolyl)cyclobutane-1-carboxylate (3aa) (major isomer)
Methyl (1R*,2S*)-1-acetamido-2-(p-tolyl)cyclobutane-1-carboxylate (3aa') (minor isomer)

$\text{H-NMR spectrum (500 MHz, CDCl}_3\text{)}$

$\text{C\{H\}-NMR spectrum (125 MHz, CDCl}_3\text{)}$
Methyl (1R*,2R*)-1-((tert-butoxycarbonyl)amino)-2-(p-tolyl)cyclobutane-1-carboxylate (3ba) (major isomer)
Methyl \((1R^*, 2R^*)\)-1-(bis(tert-butoxycarbonyl)amino)-2-(p-tolyl)cyclobutane-1-carboxylate (3ca) (major isomer, mixture of diastereoisomers)

\[
{\text{MeO}_2C} \quad \text{Boc}_2\text{N} \quad \text{(p-tolyl)} \quad \text{C}_2\text{H}_4\text{N} \quad \text{MeCN}
\]

\(^1\text{H}-\text{NMR spectrum (500 MHz, CDCl}_3\text{)}

\[^{13}\text{C}({\text{H}})\text{-NMR spectrum (100 MHz, CDCl}_3\text{)}\]
Methyl 1-(((9H-fluoren-9-yl)methoxy)carbonyl)amino)-2-(p-tolyl)cyclobutane-1-carboxylate (3da) (major isomer)

\[ \text{MeO}_2\text{C-}\text{FmocHN} \]

\( ^1\text{H}-\text{NMR spectrum (500 MHz, CDCl}_3 \)
Methyl (1R*,2R*)-1-(((benzyloxy)carbonyl)amino)-2-(p-tolyl)cyclobutane-1-carboxylate (3ea) (major isomer, mixture of rotamers, 3:1)

$\text{MeO}_2\text{C}$

$\text{CbzHN}$

$\text{C}_8\text{H}_5$

$^1\text{H}-\text{NMR spectrum (400 MHz, CDCl}_3)$

$\text{MeO}_2\text{C}$

$\text{CbzHN}$

$\text{C}_8\text{H}_5$

$^{13}\text{C}(^1\text{H})-\text{NMR spectrum (100 MHz, CDCl}_3)$

S45
Methyl (1R*,2R*)-1-acetamido-2-methyl-2-phenylcyclobutane-1-carboxylate (3ab) (major isomer)
Methyl (1R\textsuperscript{*},2R\textsuperscript{*},3R\textsuperscript{*})-1-acetamido-3-methyl-2-phenylcyclobutane-1-carboxylate (3ac) (major isomer)
Methyl (1R*,2R*,3R*)-1-acetamido-2,3-diphenylcyclobutane-1-carboxylate (3ad) (major isomer)

$\text{MeO}_2\text{C} - \text{AcHN}$

$\text{H-NMR spectrum (400 MHz, CDCl}_3$)

$\text{C}^{13}(\text{H})$-NMR spectrum (100 MHz, CDCl$_3$)
Methyl (1\text{R$,2R$,3R$}$)-1-acetamido-2-(4-methoxyphenyl)-3-methylcyclobutane-1-carboxylate (3ae) (major isomer)

\[ \text{MeO}_2\text{C} \quad \text{AcHN} \quad \text{(4-MeO-Ph)} \quad \text{MeO}_2\text{C} \quad \text{AcHN} \]

\text{H-NMR spectrum (400 MHz, CDCl$_3$)}

\text{C$^{13}$-NMR spectrum (100 MHz, CDCl$_3$)}
Methyl (1S*,2aS*,8bR*)-1-acetamido-1,2,2a,3,4,8b-hexahydrocyclobuta[a]napthalene-1-carboxylate (3af) (major isomer)
Methyl (1R*,2aS*,8bR*)-1-acetamido-1,2,2a,3,4,8b-hexahydrocyclobuta[a]naphthalene-1-carboxylate (3af) (minor isomer)
Methyl (1R*,2R*)-1-acetamido-2-mesitylcyclobutane-1-carboxylate (3ag) (major isomer)

$\text{H-NMR spectrum (500 MHz, CDCl}_3\}$

$\text{C-}{\text{H}}\text{-NMR spectrum (125 MHz, CDCl}_3\}$
Methyl (1R*,2R*)-1-acetamido-2-phenylcyclobutane-1-carboxylate (3ah) (major isomer)
Methyl (1R*,2R*)-1-acetamido-2-(2-chlorophenyl)cyclobutane-1-carboxylate (3ai) (major isomer)

$\text{MeO}_2\text{C}$

**$^1$H-NMR spectrum (400 MHz, CDCl$_3$)**

$\text{AcHN}$

$\text{Cl}$

$\text{MeO}_2\text{C}$

$\text{AcHN}$

$\text{Cl}$

**$^{13}$C($^1$H)-NMR spectrum (100 MHz, CDCl$_3$)**
Methyl (1R*,2R*)-1-acetamido-2-(3-chlorophenyl)cyclobutane-1-carboxylate (3af) (major isomer)
Methyl (1'R,2'S)-1-acetamido-2-(3-chlorophenyl)cyclobutane-1-carboxylate (3af') (minor isomer)

$^{1}$H-NMR spectrum (400 MHz, CDCl$_3$)

$^{13}$C($^1$H)-NMR spectrum (100 MHz, CDCl$_3$)

S56
Methyl (1R*,2R*)-1-acetamido-2-(4-chlorophenyl)cyclobutane-1-carboxylate (3ak) (major isomer)
Methyl (1R*,2S*)-1-acetamido-2-(4-chlorophenyl)cyclobutane-1-carboxylate (3ak') (minor isomer)
Methyl (1R*,2R*)-1-acetamido-2-(4-fluorophenyl)cyclobutane-1-carboxylate (3al) (major isomer)
Methyl (1R*,2R*)-1-acetamido-2-(4-bromophenyl)cyclobutane-1-carboxylate (3am) (major isomer)

$\text{MeO}_2\text{C}$
$\text{AcHN}$
$\text{Br}$

$\text{H-NMR}$ spectrum (400 MHz, CDCl$_3$)

$\text{C{H}-NMR}$ spectrum (100 MHz, CDCl$_3$)

S60
Methyl (1R*,2S*)-1-acetamido-2-(4-bromophenyl)cyclobutane-1-carboxylate (3q') (minor isomer)

$\text{MeO}_2\text{C} \quad \text{AcHN}$

![H-NMR spectrum](image)

$\text{MeO}_2\text{C} \quad \text{AcHN}$

![C{H}-NMR spectrum](image)
Methyl (1R*,2R*)-1-acetamido-2-(4-nitrophenyl)cyclobutane-1-carboxylate (3an) (major isomer)

1H-NMR spectrum (600 MHz, CDCl₃)

13C{¹H}-NMR spectrum (150 MHz, CDCl₃)
Methyl (1R*,2R*)-1-acetamido-2-(4-(trifluoromethyl)phenyl)cyclobutane-1-carboxylate (3ao) (major isomer)

$\text{MeO}_2\text{C}$

$\text{CF}_3$

$\text{AchN}$

$\text{H}_NMR$ spectrum (400 MHz, CDCl$_3$)

$\text{C}^{13}NMR$ spectrum (100 MHz, CDCl$_3$), $\text{F}^{19}NMR$ spectrum (377 MHz, CDCl$_3$)

$\text{S63}$
Methyl (1R*,2R*)-1-acetamido-2-(4-methoxyphenyl)cyclobutane-1-carboxylate (3ap) (major isomer)

$\mathrm{H-NMR}$ spectrum (400 MHz, CDCl$_3$)

$\mathrm{C}^{13}$($\mathrm{H}$)-NMR spectrum (100 MHz, CDCl$_3$)
Methyl (1R*,2R*)-1-acetamido-2-(4-hydroxyphenyl)cyclobutane-1-carboxylate (3aq) (major isomer)
Methyl (1R*,2R*)-1-acetamido-2-{4-((tert-butoxycarbonyl)amino)phenyl)cyclobutane-1-carboxylate (3ar) (major isomer)
Methyl (1R*,2S*)-1-acetamido-2-(4-(tert-butoxycarbonylamino)phenyl)cyclobutane-1-carboxylate (3ar*) (minor isomer)
Methyl (1R*,2R*)-1-acetamido-2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)cyclobutane-1-carboxylate (3as) (major isomer)

\[
\text{MeO}_2\text{C} \quad \begin{array}{c}
\text{AcHN} \\
\text{BPin}
\end{array}
\]

\[
^1\text{H-NMR} \text{ spectrum (400 MHz, CDCl}_3\text{)}
\]

\[
^13\text{C}[^1\text{H}]\text{-NMR} \text{ spectrum (100 MHz, CDCl}_3\text{), } ^1\text{B-NMR} \text{ spectrum (128 MHz, CDCl}_3\text{)}
\]

S68
Methyl \((1R^*,2S^*)\)-1-acetamido-2-\((4,4,5,5\text{-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl}cyclobutane-1-carboxylate \((3\text{as}'\)) (minor isomer)

\[
\text{MeO}_2\text{C} \quad \text{AcHN} \quad \text{BPIn}
\]

\[
\text{\textbf{1H-NMR spectrum (400 MHz, CDCl}_3)}
\]

\[
\text{MeO}_2\text{C} \quad \text{AcHN} \quad \text{BPIn}
\]

\[
\text{\textbf{13C(\text{H})-NMR spectrum (100 MHz, CDCl}_3), 1B-NMR spectrum (128 MHz, CDCl}_3)}
\]

S69
Methyl 1-acetamido-2-methyl-4-(p-tolyl)cyclobutane-1-carboxylate (3fa) (major isomer)
Methyl 1-acetamido-2-phenyl-4-(p-tolyl)cyclobutane-1-carboxylate (3ga) (major isomer)
(6S)-6-(tert-Butyl)-1-(p-tolyl)-7-oxa-5-azaspiro[3.4]octan-8-one (3ha) (major isomer)(mixture of diastereoisomers)
(1'S,2'S,5'R)-2'-Isopropyl-5'-methylcyclohexyl ((1R*,2R*)-1-acetamido-2-(p-tolyl)cyclobutene)-1-carboxylate (3iα) (mixture of cis-CBAA major isomers, 1:1)

$^{1} \text{H}-\text{NMR}$ spectrum (400 MHz, CDCl$_3$)

$^{13}$C($^{1}$H)-NMR spectrum (100 MHz, CDCl$_3$)
(1'S,2'S,5'R)-2'-Isopropyl-5'-methylcyclohexyl ((1'R*,2'S*)-1-acetamido-2-(p-tolyl)cyclobutane)-1-carboxylate (3ia') (mixture of trans-CBAA minor isomers, 1:1)
Methyl (1-acetamido-2-(p-tolyl)cyclobutane-1-carbonyl)-D-valinate (3ja) (mixture of diastereoisomers, 1:1 d.r.)

$^1$H-NMR spectrum (400 MHz, DMSO-d$_6$)

$^{13}$C($^1$H)-NMR spectrum (100 MHz, DMSO-d$_6$)
Cosy 2-D spectrum (500 MHz, DMSO-d$_6$)
Methyl $N_2$-($1R^*,2R^*$)-1-acetamido-2-(p-tolyl)cyclobutane-1-carbonyl-$N_6$-(tert-butoxycarbonyl)-L-lysinate (3ka) (mixture of cis-CBAA major isomers, 1:1)

$^1$H-NMR spectrum (400 MHz, CDCl$_3$)

$^{13}$C($^1$H)-NMR spectrum (100 MHz, CDCl$_3$)
tert-Butyl (1R*,2R*)-1-((tert-butoxycarbonyl)amino)-2-(p-tolyl)cyclobutane-1-carboxylate (3la) (major isomer, mixture of rotamers, 1.5:1)

$^1$H-NMR spectrum (400 MHz, CDCl$_3$)

$^{13}$C$^1$H-NMR spectrum (100 MHz, CDCl$_3$)
**tert-Butyl (1R*,2R*) 1-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-2-(p-tolyl)cyclobutane-1-carboxylate (3ma)**

**^1^H-NMR spectrum (500 MHz, acetone-d₆)**

**^1^C(^1^H)-NMR spectrum (125 MHz, acetone-d₆)**
(1R*,2R*)-1-Carboxy-2-(p-tolyl)cyclobutan-1-aminium 2,2,2-trifluoroacetate (4-TFA) (mixture of diastereoisomers, 9:1)
(1R*,2R*)-1-Carboxy-2-(p-tolyl)cyclobutan-1-aminium chloride (4•HCl)
tert-Butyl (1R*,2R*)-1-amino-2-(p-toly1)cyclobutane-1-carboxylate (5)