Supporting Information

Design and Enantioselective Synthesis of 3-(α-Acrylic Acid) Benzoxaboroles to Combat Carbapenemase Antibiotic Resistance

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Supplementary Experiment (SE) Section

SE. 1 Chemistry

(1) General Experimental Methods

1,4-Dioxane was freshly distilled from CaH₂ under N₂. Unless otherwise specified, all reagents and solvents were from commercial sources and used as received. ¹H (400 MHz) and ¹³C (100 MHz) NMR spectra were recorded using a Bruker Avance 400 spectrometer in CDCl₃, CD₃OD or DMSO-d₆. Coupling constant (J) values are given in Hz. Multiplicities are designated by the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; br, broad; m, multiplet. Products were purified by flash column chromatography on silica gel from Qingdao Haiyang Chemical Co., Ltd. Optical rotations were measured using a Rudolph AUTOPOL I Automatic Polarimeter. HRMS were recorded using a Bruker microTOF spectrometer. HPLC analyses were performed with Daicel Chiralpak AD column (25 cm×4.6 mm×5 μm). Catalysts C1-C13 were synthesized according to the reported procedures¹-³ or obtained from commercial sources.

(2) General Experimental Procedure for the Synthesis of Substituted 2-Formylphenylboronic Acids 1a-1t⁴

![Diagram of synthesis process](image-url)
Syntheses of 7a-7t: To a round bottom flask (25 mL) were added bis(pinacolato)diboron (1.22 g, 4.8 mmol, 1.2 equiv.), substrate 6a-6t (4.0 mmol, 1.0 equiv.), PdCl₂(dppf) (88 mg, 0.12 mmol, 3 mol %) and KOAc (1.18 g, 12 mmol, 3.0 equiv.). The mixture was closed by a septum, then purged several times with argon gas; dried 1,4-dioxane (15 mL) was then added to the reaction mixture, which was stirred at 80 °C for 8 h. The crude reaction mixture was diluted with ethyl acetate, then extracted with saturated NaCl solution. The combined organic extracts were dried over Na₂SO₄, then concentrated in vacuo. The residue was purified by flash column chromatography using 40-60 petroleum ether and ethyl acetate as eluent to give 7a-7t in 60%-85% yield.

Syntheses of 1a-1t: To a solution of 7a-7t (4.0 mol, 1.0 equiv.) in THF:H₂O = 10:1 (32 mL) was added NaIO₄ (6.0 mmol, 1.5 equiv.). The mixture was stirred at room temperature for 20 minutes, until homogeneous; HCl (1.0 M in water, 10 mL) was then added and the mixture was stirred for 2 h. The resulting mixture was extracted with DCM (CH₂Cl₂) (3 × 50 mL), dried over anhydrous Na₂SO₄, then concentrated in vacuo. The residue was purified by flash column chromatography by using 40-60 petroleum ether and ethyl acetate as eluent to give 1a-1t in 41-68% yield. (1a, 1c, 1f, 1g, 1j, 1k were obtained from commercial sources).

(2-Formyl-4-methylphenyl) boronic acid (1b): 45% yield over two steps. ¹H NMR (400 MHz, Chloroform-d) δ 9.88 (s, 1H), 8.20 (d, J = 7.6 Hz, 1H), 7.72 (s, 1H), 7.53 – 7.47 (m, 3H), 2.49 (s, 3H).
(4-Ethoxy-2-formylphenyl) boronic acid (1d): 47% yield over two steps. $^1$H NMR (400 MHz, Chloroform-$d$) $\delta$ 9.86 (s, 1H), 8.22 (d, $J = 8.3$ Hz, 1H), 7.42 (d, $J = 2.7$ Hz, 1H), 7.17 (d, $J = 2.7$ Hz, 2H), 4.15 (q, $J = 7.0$ Hz, 2H), 1.48 (t, $J = 7.0$ Hz, 3H).

(2-Formyl-4-isopropoxyphenyl)boronic acid (1e): 38% yield over two steps. $^1$H NMR (400 MHz, Chloroform-$d$) $\delta$ 9.84 (s, 1H), 8.23 (d, $J = 8.3$ Hz, 1H), 7.41 (d, $J = 2.6$ Hz, 1H), 7.17 (dd, $J = 8.3$, 2.6 Hz, 1H), 4.75 – 4.66 (m, 1H), 1.40 (d, $J = 6.0$ Hz, 6H).

(2-Formyl-5-methylphenyl) boronic acid (1h): 56% yield over two steps. $^1$H NMR (400 MHz, Chloroform-$d$) $\delta$ 9.78 (s, 1H), 8.05 (s, 1H), 7.74 (d, $J = 7.7$ Hz, 1H), 7.51 – 7.42 (m, 2H), 2.42 (s, 3H).

(2-Formyl-5-methoxyphenyl) boronic acid (1i): 50% yield over two steps. $^1$H NMR (400 MHz, Chloroform-$d$) $\delta$ 9.61 (s, 1H), 7.96 (d, $J = 8.8$ Hz, 1H), 7.01 (dd, $J = 8.8$, 2.5 Hz, 1H), 6.75 (d, $J = 2.5$ Hz, 1H), 3.83 (s, 3H).

(2-Formyl-4,5-dimethoxyphenyl) boronic acid (1l): 45% yield over two steps $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 10.02 (s, 1H), 7.14 (s, 1H), 6.56 (s, 1H), 3.83 (s, 3H), 3.73 (s, 3H).
(2-Formyl-4-(p-tolyloxy) phenyl) boronic acid (1m): 35% yield over two steps. \(^1\)H NMR (400 MHz, Chloroform-\(d\)) \(\delta\) 9.73 (s, 1H), 8.16 (d, \(J = 8.3\) Hz, 1H), 7.40 (d, \(J = 2.5\) Hz, 1H), 7.22 (s, 1H), 7.20 – 7.16 (m, 1H), 7.16 (s, 1H), 7.14 – 7.13 (m, 1H), 6.92 (s, 1H), 2.31 (s, 3H).

(2-Formyl-4-(m-tolyloxy) phenyl) boronic acid (1n): 28% yield over two steps. \(^1\)H NMR (400 MHz, Chloroform-\(d\)) \(\delta\) 9.82 (s, 1H), 8.24 (d, \(J = 8.3\) Hz, 1H), 7.50 (d, \(J = 2.6\) Hz, 1H), 7.34 – 7.23 (m, 3H), 7.04 (d, \(J = 7.5\) Hz, 1H), 6.90 (s, 1H), 2.38 (s, 3H).

(2-Formyl-4-(4-(trifluoromethyl) phenoxy) phenyl) boronic acid (1o): 37% yield over two steps. \(^1\)H NMR (400 MHz, Chloroform-\(d\)) \(\delta\) 9.86 (s, 1H), 8.31 (d, \(J = 8.3\) Hz, 1H), 7.67 (d, \(J = 8.4\) Hz, 2H), 7.57 (d, \(J = 2.6\) Hz, 1H), 7.33 (dd, \(J = 8.3, 2.5\) Hz, 1H), 7.15 (d, \(J = 8.5\) Hz, 2H).

(4-(Benzyloxy)-2-formylphenyl) boronic acid (1p): 52% yield over two steps. \(^1\)H NMR (400 MHz, Chloroform-\(d\)) \(\delta\) 9.88 (s, 1H), 8.26 (d, \(J = 8.4\) Hz, 1H), 7.53 (d, \(J = 2.7\) Hz, 1H), 7.50 – 7.36 (m, 5H), 7.29 (d, \(J = 5.6\) Hz, 1H), 5.21 (s, 2H).
(2-Formyl-5-(4-methoxyphenoxy) phenyl) boronic acid (1q): 34% yield over two steps. $^1$H NMR (400 MHz, Chloroform-$d$) $\delta$ 9.77 (s, 1H), 7.85 (d, $J = 2.7$ Hz, 1H), 7.82 (d, $J = 8.5$ Hz, 1H), 7.08 (dd, $J = 8.5, 2.7$ Hz, 1H), 7.06 – 7.02 (m, 2H), 6.96 (d, $J = 2.3$ Hz, 1H), 6.94 (d, $J = 2.3$ Hz, 1H), 3.84 (s, 3H).

(2-Formyl-5-(3-nitrophenoxy) phenyl) boronic acid (1r): 27% yield over two steps. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 10.11 (s, 1H), 8.36 (s, 2H), 8.34 – 8.28 (m, 2H), 7.99 (d, $J = 8.3$ Hz, 1H), 7.27 (d, $J = 2.4$ Hz, 2H).

(5-(4-Chlorophenoxy)-2-formylphenyl) boronic acid (1s): 45% yield over two steps. $^1$H NMR (400 MHz, Chloroform-$d$) $\delta$ 9.81 (s, 1H), 7.89 – 7.81 (m, 2H), 7.41 – 7.38 (m, 2H), 7.15 (dd, $J = 8.4, 2.7$ Hz, 1H), 7.08 – 7.02 (m, 2H).

(5-(Benzyloxy)-2-formylphenyl) boronic acid (1t): 47% yield over two steps. $^1$H NMR (400 MHz, Chloroform-$d$) $\delta$ 9.68 (s, 1H), 7.86 (s, 1H), 7.77 (d, $J = 8.7$ Hz, 1H), 7.56 (s, 1H), 7.36 (dd, $J = 13.2, 7.6$ Hz, 2H), 7.33 – 7.25 (m, 1H), 7.11 (d, $J = 8.6$ Hz, 1H), 5.15 (s, 2H).

(3) Optimization of Reaction Conditions.
| Entry | Cat. | 1a: 2 | [M]: 1a | Additive (equiv.) | Tem. (°C) | Solvent | Time (h) | Yield (%) | Ee (%) |
|-------|------|-------|---------|------------------|-----------|---------|----------|-----------|--------|
| 1     | C1   | 1:3   | 0.1     | -                | rt        | THF     | 29       | 45        | 27     |
| 2     | C1   | 1:3   | 0.1     | 4Å MS (1.0)      | rt        | THF     | 43       | 13        | 6      |
| 3     | C1   | 1:3   | 0.1     | 2-Naphthol (1.0) | rt        | THF     | 36       | nr        | /      |
| 4     | C1   | 1:3   | 0.1     | Et3N (1.0)       | rt        | THF     | 10       | 84        | <5     |
| 5     | C1   | 1:3   | 0.1     | DIPEA (1.0)      | rt        | THF     | 24       | 77        | 21     |
| 6     | C1   | 1:3   | 0.1     | Na2CO3 (1.0)     | rt        | THF     | 44       | 20        | 25     |
| 7     | C1   | 1:3   | 0.1     | KF (1.0)         | rt        | THF     | 61       | 12        | 23     |
| 8     | C1   | 1:3   | 0.1     | Na3PO4 (1.0)     | rt        | THF     | 37       | 33        | 17     |
| 9     | C1   | 1:3   | 0.1     | NaHCO3 (1.0)     | rt        | THF     | 46       | 50        | 41     |
| 10    | C1   | 1:3   | 0.1     | Cs2CO3 (1.0)     | rt        | THF     | 22       | 43        | 13     |
| 11    | C1   | 1:3   | 0.1     | MgO (1.0)        | rt        | THF     | 19       | 88        | 19     |
| 12    | C1   | 1:3   | 0.1     | CaO (1.0)        | rt        | THF     | 19       | 57        | 45     |
| 13    | C1   | 1:3   | 0.1     | Al(OH)3 (1.0)    | rt        | THF     | 7        | 88        | 64     |
| 14    | C1   | 1:3   | 0.1     | Al2O3 (1.0)      | rt        | THF     | 17       | 82        | 70     |
| 15    | C1   | 1:3   | 0.1     | Al2O3 (1.0)      | 0         | THF     | 54       | 46        | 78     |
| 16    | C1   | 1:3   | 0.1     | Al2O3 (1.0)      | -10       | THF     | 72       | 38        | 76     |
| 17    | C1   | 1:3   | 0.1     | Al2O3 (1.0)      | -30       | THF     | 72       | nr        | /      |
| 18    | C2   | 1:3   | 0.1     | Al2O3 (1.0)      | rt        | THF     | 36       | 28        | 9      |
|   |   |   |   |   |   |
|---|---|---|---|---|---|
|   | **C3** | 1:3 | 0.1 | **Al₂O₃ (1.0)** | rt | **THF** | 48 | 49 | -37 |
| 20 | **C3** | 1:3 | 0.1 | **Na₂CO₃ (1.0)** | rt | **THF** | 68 | 68 | -8 |
| 21 | **C3** | 1:3 | 0.1 | **KF (1.0)** | rt | **THF** | 28 | 48 | -15 |
| 22 | **C3** | 1:3 | 0.1 | **Al(OH)₃ (1.0)** | rt | **THF** | 48 | 81 | -13 |
| 23 | **C4** | 1:3 | 0.1 | **Al₂O₃ (1.0)** | rt | **THF** | 50 | 70 | 48 |
| 24 | **C5** | 1:3 | 0.1 | **Al₂O₃ (1.0)** | rt | **THF** | 48 | 46 | 37 |
| 25 | **C6** | 1:3 | 0.1 | **Al₂O₃ (1.0)** | rt | **THF** | 28 | 83 | 74 |
| 26 | **C7** | 1:3 | 0.1 | **Al₂O₃ (1.0)** | rt | **THF** | 29 | 90 | -50 |
| 27 | **C8** | 1:3 | 0.1 | **Al₂O₃ (1.0)** | rt | **THF** | 41 | 87 | 24 |
| 28 | **C9** | 1:3 | 0.1 | **Al₂O₃ (1.0)** | rt | **THF** | 37 | 84 | 64 |
| 29 | **C10** | 1:3 | 0.1 | **Al₂O₃ (1.0)** | rt | **THF** | 90 | 64 | -40 |
| 30 | **C11** | 1:3 | 0.1 | **Al₂O₃ (1.0)** | rt | **THF** | 72 | nr | / |
| 31 | **C12** | 1:3 | 0.1 | **Al₂O₃ (1.0)** | rt | **THF** | 72 | <5 | nd |
| 32 | **C13** | 1:3 | 0.1 | **Al₂O₃ (1.0)** | rt | **THF** | 90 | <5 | nd |
| 33 | **C6** | 1:3 | 0.1 | **Al₂O₃ (2.0)** | rt | **THF** | 28 | 85 | 73 |
| 34 | **C6** | 1:3 | 0.1 | **Al₂O₃ (4.0)** | rt | **THF** | 28 | 87 | 76 |
| 35 | **C6** | 1:3 | 0.1 | **Al₂O₃ (6.0)** | rt | **THF** | 20 | 75 | 69 |
| 36 | **C6** | 1:3 | 0.1 | **Al₂O₃ (4.0)** | rt | **DCM** | 42 | 30 | 6 |
| 37 | **C6** | 1:3 | 0.1 | **Al₂O₃ (4.0)** | rt | **CH₃CN** | 42 | 30 | 26 |
| 38 | **C6** | 1:3 | 0.1 | **Al₂O₃ (4.0)** | rt | **DMF** | 120 | 68 | 65 |
| 39 | **C6** | 1:3 | 0.1 | **Al₂O₃ (4.0)** | rt | **Et₂O** | 120 | nr | / |
| 40 | **C6** | 1:3 | 0.1 | **Al₂O₃ (4.0)** | rt | **EA** | 47 | 25 | 55 |
| 41 | **C6** | 1:3 | 0.1 | **Al₂O₃ (4.0)** | rt | **Toluene** | 60 | 28 | 27 |
| 42 | **C6** | 1:3 | 0.1 | **Al₂O₃ (4.0)** | rt | **Dioxane** | 16 | 90 | 85 |
| 43 | **C6** | 1:3 | 0.1 | **Al₂O₃ (4.0)** | rt | **Dioxane** | 18 | 86 | 88 |
| 44 | **C6** | 1:3 | 0.1 | **Al₂O₃ (4.0)** | rt | **Dioxane** | 24 | 85 | 90 |
| 45 | **C6** | 1:3 | 0.1 | **Al₂O₃ (4.0)** | rt | **Dioxane** | 36 | 63 | 70 |
| 46 | **C7** | 1:3 | 0.1 | **Al₂O₃ (4.0)** | rt | **Dioxane** | 72 | 80 | -47 |
| 47 | **C7** | 1:3 | 0.1 | **Al₂O₃ (4.0)** | 0 | **Dioxane** | 96 | 90 | -60 |

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aStandard reaction conditions: 1a (0.1 mmol), 2 (0.3 or 0.5 mmol), catalyst (0.01 mmol), additive, solvent, rt.
bIsolated yields of 3a. ee was determined by chiral HPLC analysis. c5 mol% of C6 was used.

(4) General Procedure for the Catalytic Asymmetric MBH Cascade Reaction.
To a mixture of substituted 2-formylphenylboronic acids 1 (0.1 mmol), catalyst C6 (0.01 mmol), Al₂O₃ (0.4 mmol) in dioxane (4.0 mL) was added hexafluoroisopropyl acrylate 2 (HFIPA, 0.5 mmol, 53 μL) at room temperature. The reaction was stirred for the specified time until no remaining starting material 1 was observed by TLC. The reaction mixture was then filtered and concentrated in vacuo; the resulting residue was subsequently dissolved in MeOH (2.0 mL) and an NaOH solution (12 mg, 0.3 mmol dissolved in 0.5 mL water) was added dropwise. The reaction mixture was stirred at room temperature for 3 hours, then acidified with hydrochloric acid. The mixture was extracted with ethyl acetate; the combined extracts were was dried over sodium sulfate, filtered and evaporated under vacuum. The crude product was purified by chromatography to give 4.

(R)-2-(1-Hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-3-yl) acrylic acid (4a): white solid, 80% yield; mp = 89.8-91.9 °C. [α]_D²⁰: +94.50 (c = 0.20 in MeOH); 90% ee (96% ee after recrystallization from EA) determined by chiral HPLC (Chiralpak AD), n-hexane/i-PrOH/CH₃COOH = 980/19/1, 1.0 mL/ min, λ = 254 nm; t (minor) = 6.249 min, t (major) = 7.381 min; ¹H NMR (400 MHz, Methanol-d₄): δ = 7.64 (d, J = 7.4 Hz, 1H), 7.42 (t, J = 7.4 Hz, 1H), 7.38 (d, J = 7.4 Hz, 1H), 7.32 (t, J = 7.4 Hz, 1H), 6.25 (s, 1H), 6.05 (s, 1H), 5.77 (s, 1H); ¹³C NMR (100 MHz, Methanol-d₄): δ = 167.5, 155.6, 140.9, 130.7, 130.6, 129.9, 127.2, 124.4, 121.6, 79.7. ESI HR-MS: m/z = 203.9880, calcd. for [C₁₀H₈BO₄-H]⁻:203.0521, found:203.0522. (S)-4a: white solid, 88% yield; [α]_D²⁰: -63.50 (c = 0.20 in MeOH); 60% ee (99.5% ee after recrystallization from EA) determined by chiral HPLC (Chiralpak AD), n-hexane/i-PrOH/CH₃COOH = 980/19/1, 1.0 mL/ min, λ = 254 nm; t (minor) = 7.593 min, t (major) = 6.461 min
(R)-2-(1-Hydroxy-5-methyl-1,3-dihydrobenzo[c][1,2]oxaborol-3-yl) acrylic acid (4b): semi-solid, 80% yield; \([\alpha]_\text{D}^{20} = +66.03\) (c = 0.12 in MeOH); 89% ee, determined by chiral HPLC (Chiralpak AD), n-hexane/i-PrOH/CH₃COOH = 980/19/1, 1.0 mL/min, \(\lambda = 254\) nm; \(t\) (minor) = 6.122 min, \(t\) (major) = 7.447 min; \(^1\)H NMR (400 MHz, DMSO-\(d_6\)): \(\delta = 12.78\) (s, 1H), 9.23 (s, 1H), 7.60 (d, \(J = 7.4\) Hz, 1H), 7.23 – 7.09 (m, 2H), 6.12 (s, 1H), 5.90 (s, 1H), 5.71 (s, 1H), 2.33 (s, 3H); \(^{13}\)C NMR (100 MHz, DMSO-\(d_6\)): \(\delta = 167.4, 156.4, 141.7, 145.0, 130.9, 128.8, 125.1, 122.5, 78.8, 49.1, 22.0\); ESI HR-MS: \(m/z = 218.0150\), calcd. for [C\(_{11}\)H\(_{10}\)BO\(_4\)-H]: 217.0678, found: 217.0679.

(R)-2-(1-Hydroxy-5-methoxy-1,3-dihydrobenzo[c][1,2]oxaborol-3-yl) acrylic acid (4c): white solid, 85% yield; mp = 116.2-119.6 °C. \([\alpha]_\text{D}^{20} = +28.00\) (c = 0.10 in MeOH); 90% ee (99% ee after recrystallization from EA), determined by chiral HPLC (Chiralpak AD), n-hexane/i-PrOH/CH₃COOH = 980/19/1, 1.0 mL/min, \(\lambda = 254\) nm; \(t\) (minor) = 8.687 min, \(t\) (major) = 10.625 min; \(^1\)H NMR (400 MHz, Methanol-\(d_4\)): \(\delta = 7.45\) (d, \(J = 8.1\) Hz, 1H), 6.85 – 6.78 (m, 2H), 6.16 (s, 1H), 5.67 (s, 1H), 3.69 (s, 3H); \(^{13}\)C NMR (100 MHz, Methanol-\(d_4\)): \(\delta = 167.7, 162.6, 158.1, 141.1, 131.2, 124.2, 114.4, 106.4, 79.2, 54.3\); ESI HR-MS: \(m/z = 234.0140\), calcd. for [C\(_{11}\)H\(_{10}\)BO\(_5\)-H]: 233.0627, found: 233.0617. (S)-4c: white solid, 80% yield; \([\alpha]_\text{D}^{20} = -17.80\) (c = 0.20 in MeOH); 52% ee (96% ee after recrystallization from EA) determined by chiral HPLC (Chiralpak AD), n-hexane/i-PrOH/CH₃COOH = 980/19/1, 1.0 mL/min, \(\lambda = 254\) nm; \(t\) (minor) = 10.391 min, \(t\) (major) = 8.427 min.

(R)-2-(5-Ethoxy-1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-3-yl) acrylic acid (4d): semi-solid, 82% yield; \([\alpha]_\text{D}^{20} = +37.23\) (c = 0.13 in MeOH); 86% ee, determined by chiral HPLC (Chiralpak AD), n-hexane/i-PrOH/CH₃COOH = 980/19/1, 1.0 mL/min, \(\lambda = 254\) nm; \(t\) (minor) = 7.646 min, \(t\) (major) = 11.231 min; \(^1\)H NMR (400 MHz, Methanol-\(d_4\)): \(\delta = 7.54\) (d, \(J = 8.1\) Hz, 1H), 6.85 – 6.78 (m, 2H), 6.16 (s, 1H), 5.67 (s, 1H), 3.69 (s, 3H); \(^{13}\)C NMR (100 MHz, Methanol-\(d_4\)): \(\delta = 167.7, 162.6, 158.1, 141.1, 131.2, 124.2, 114.4, 106.4, 79.2, 54.3\); ESI HR-MS: \(m/z = 234.0140\), calcd. for [C\(_{11}\)H\(_{10}\)BO\(_5\)-H]: 233.0627, found: 233.0617.
6.97 – 6.80 (m, 2H), 6.25 (s, 1H), 5.99 (s, 1H), 5.77 (s, 1H), 4.02 (q, \( J = 7.0 \text{ Hz}, 2\text{H} \)), 1.37 (t, \( J = 7.0 \text{ Hz}, 3\text{H} \)); \(^{13}\text{C NMR (100 MHz, Methanol-}d_4\)): \( \delta = 167.7, 161.9, 158.1, 141.1, 131.2, 124.2, 121.2, 114.8, 107.0, 79.2, 63.2, 13.6 \); ESI HR-MS: \( m/z = 248.0410 \), calcd. for \([\text{C}_{12}\text{H}_{13}\text{BO}_5\text{-H}]^{-}\): 247.0783, found: 247.0780.

(R)-2-(1-Hydroxy-5-isopropoxy-1,3-dihydrobenzo[c][1,2]oxaborol-3-yl) acrylic acid (4e): semi-solid, 71% yield; \( [\alpha]_{D}^{20} \): +31.30 (c = 0.09 in MeOH); 82% ee, determined by chiral HPLC (Chiralpak AD), \( n\)-hexane/i-PrOH/CH\(_3\)COOH = 980/19/1, 1.0 mL/ min, \( \lambda = 254 \text{ nm} \); \( t \) (minor) = 6.481 min, \( t \) (major) = 9.261 min; \(^1\text{H NMR (400 MHz, Methanol-}d_4\)): \( \delta =7.54 \) (d, \( J = 8.1 \text{ Hz}, 1\text{H} \)), 6.91 (d, \( J = 2.2 \text{ Hz}, 1\text{H} \)), 6.87 (dd, \( J = 8.1, 2.2 \text{ Hz}, 1\text{H} \)), 6.25 (s, 1H), 5.99 (s, 1H), 5.77 (s, 1H), 1.30 (t, \( J = 6.0 \text{ Hz}, 9\text{H} \)); \(^{13}\text{C NMR (100 MHz, Methanol-}d_4\)): \( \delta =167.7, 160.8, 158.1, 141.1, 131.3, 124.0, 115.9, 108.2, 79.1, 69.6, 29.3, 20.9, 20.8 \); ESI HR-MS: \( m/z = 262.0680 \), calcd. for \([\text{C}_{13}\text{H}_{15}\text{BO}_5\text{-H}]^{-}\): 261.0959, found: 261.0962.

(R)-2-(5-Fluoro-1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-3-yl) acrylic acid (4f): white solid, 86% yield; mp = 91.9-93.4 °C. \( [\alpha]_{D}^{20} \): +50.01 (c= 0.09 in MeOH); 82% ee (90% ee after recrystallization from EA), determined by chiral HPLC (Chiralpak AD), \( n\)-hexane/i-PrOH/CH\(_3\)COOH = 980/19/1, 1.0 mL/ min, \( \lambda = 254 \text{ nm} \); \( t \) (minor) = 6.004 min, \( t \) (major) = 7.41 min; \(^1\text{H NMR (400 MHz, Methanol-}d_4\)): \( \delta =7.55 \) (dd, \( J = 8.1, 5.6 \text{ Hz}, 1\text{H} \)), 7.06 – 6.93 (m, 2H), 6.19 (s, 1H), 5.93 (s, 1H), 5.73 (s, 1H); \(^{13}\text{C NMR (100 MHz, Methanol-}d_4\)): \( \delta =167.3, 166.3, 163.8, 158.5, 158.4, 140.4, 132.0, 131.9, 124.7, 114.9, 114.7, 108.9, 108.7, 79.3, 79.3 \); ESI HR-MS: \( m/z = 221.9784 \), calcd. for \([\text{C}_{10}\text{H}_{7}\text{BFO}_4\text{-H}]^{-}\): 221.0427, found: 221.0434. (S)-4f: white solid, 79% yield; \( [\alpha]_{D}^{20} \): -28.65 (c = 0.20 in MeOH); 48% ee (90% ee after recrystallization from EA) determined by chiral HPLC (Chiralpak AD), \( n\)-hexane/i-PrOH/CH\(_3\)COOH = 980/19/1, 1.0 mL/ min, \( \lambda = 254 \text{ nm} \); \( t \) (minor) = 7.475 min, \( t \) (major) = 5.981 min.
**(R)-2-(5-Chloro-1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-3-yl) acrylic acid (4g):** semi-solid, 70% yield; \([\alpha]_D^{20}\): +45.00 (c = 0.07 in MeOH), 75% ee, determined by chiral HPLC (Chiralpak AD), n-hexane/ i-PrOH/CH$_3$COOH = 980/19/1, 1.0 mL/ min, \(\lambda = 254\) nm; \(t\) (minor) = 6.422 min, \(t\) (major) = 7.594 min; $^1$H NMR (400 MHz, Methanol-$d_4$): \(\delta = 7.50\) (d, \(J = 7.8\) Hz, 1H), 7.32 (d, \(J = 1.8\) Hz, 1H), 7.24 (dd, \(J = 7.8, 1.8\) Hz, 1H), 6.20 (s, 1H), 5.93 (s, 1H), 5.74 (s, 1H); $^{13}$C NMR (100 MHz, Methanol-$d_4$): \(\delta = 167.3, 157.5, 140.2, 136.9, 131.2, 127.6, 124.9, 122.0, 79.4\); ESI HR-MS: \(m/z = 238.4300\), calcd. for [C$_{10}$H$_7$BClO$_4$-H]: 237.0131, found: 237.0132.

**(R)-2-(1-Hydroxy-6-methyl-1,3-dihydrobenzo[c][1,2]oxaborol-3-yl) acrylic acid (4h):** semi-solid, 84% yield; \([\alpha]_D^{20}\): +19.24 (c = 0.11 in MeOH); 88% ee), determined by chiral HPLC (Chiralpak AD), n-hexane/ i-PrOH/CH$_3$COOH = 980/19/1, 1.0 mL/ min, \(\lambda = 254\) nm; \(t\) (minor) = 6.534 min, \(t\) (major) = 6.954 min; $^1$H NMR (400 MHz, DMSO-$d_6$): \(\delta = 12.81\) (s, 1H), 9.29 (s, 1H), 7.52 (s, 1H), 7.25 (q, \(J = 8.1\) Hz, 2H), 6.11 (s, 1H), 5.91 (s, 1H), 5.70 (s, 1H), 2.34 (s, 3H); $^{13}$C NMR (100 MHz, DMSO-$d_6$): \(\delta = 167.4, 153.2, 152.3, 141.8, 136.8, 132.2, 131.3, 124.8, 122.0, 78.8, 21.3\); ESI HR-MS: \(m/z = 218.0150\), calcd. for [C$_{11}$H$_{10}$BO$_4$-H]: 217.0678, found: 217.0669.

**(R)-2-(1-Hydroxy-6-methoxy-1,3-dihydrobenzo[c][1,2]oxaborol-3-yl) acrylic acid (4i):** semi-solid, 72% yield; \([\alpha]_D^{20}\): +35.45 (c = 0.11 in MeOH); 84% ee, determined by chiral HPLC (Chiralpak AD), n-hexane/ i-PrOH/CH$_3$COOH = 980/19/1, 1.0 mL/ min, \(\lambda = 254\) nm; \(t\) (minor) = 8.659 min, \(t\) (major) = 9.343 min; $^1$H NMR (400 MHz, DMSO-$d_6$): \(\delta = 12.82\) (s, 1H), 9.30 (s, 1H), 7.29 – 7.12 (m, 2H), 7.03 (dd, \(J = 8.4, 2.6\) Hz, 1H), 6.09 (s, 1H), 5.89 (s, 1H), 5.69 (s, 1H), 3.77 (s, 3H); $^{13}$C NMR (100 MHz, DMSO-$d_6$): \(\delta = 167.8, 159.6, 148.3, 142.2, 1
125.0, 123.6, 118.8, 114.6, 78.9, 56.0; ESI HR-MS: m/z = 234.0140, calcd. for \([C_{11}H_{10}BO_5-H]\): 233.0627, found: 233.0634.

(R)-2-(6-Fluoro-1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-3-yl) acrylic acid (4j): white solid, 91% yield; mp = 118.7-122.4 °C. \([\alpha]_D^{20}\): +68.54 (c = 0.15 in MeOH), 81% ee (96% ee after recrystallization from EA), determined by chiral HPLC (Chiralpak AD), n-hexane/i-PrOH/CH₃COOH = 980/19/1, 1.0 mL/ min, \(\lambda = 254\) nm; \(t_{\text{minor}} = 6.385\) min, \(t_{\text{major}} = 6.941\) min; \(^1H\) NMR (400 MHz, Methanol-d₄): \(\delta = 7.30\) (dd, \(J = 8.4, 4.5\) Hz, 1H), 7.18 (dd, \(J = 8.4, 2.5\) Hz, 1H), 7.06 (ddd, \(J = 9.3, 8.4, 2.5\) Hz, 1H), 6.17 (s, 1H), 5.93 (s, 1H), 5.71 (s, 1H); \(^{13}C\) NMR (100 MHz, Methanol-d₄): \(\delta = 167.7, 163.8, 162.2, 151.4, 141.0, 125.0, 123.91, 123.85, 118.3, 118.1, 115.7, 115.5, 79.9\); ESI HR-MS: m/z = 221.9784, calcd. for \([C_{10}H_{7}BO_5-H]\): 221.0427, found: 221.0421. (S)-4j: white solid, 65% yield; \([\alpha]_D^{20}\): -47.60 (c = 0.20 in MeOH); 57% ee (95% ee after recrystallization from EA) determined by chiral HPLC (Chiralpak AD), n-hexane/i-PrOH/CH₃COOH = 980/19/1, 1.0 mL/ min, \(\lambda = 254\) nm; \(t_{\text{minor}} = 7.053\) min, \(t_{\text{major}} = 6.373\) min.

(R)-2-(6-Chloro-1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-3-yl) acrylic acid (4k): semi-solid, 81% yield; \([\alpha]_D^{20}\): +51.11 (c = 0.09 in MeOH); 78% ee, determined by chiral HPLC (Chiralpak AD), n-hexane/i-PrOH/CH₃COOH = 980/19/1, 1.0 mL/ min, \(\lambda = 254\) nm; \(t_{\text{major}} = 4.750\) min, \(t_{\text{minor}} = 5.220\) min; \(^1H\) NMR (400 MHz, Methanol-d₄): \(\delta = 7.48\) (d, \(J = 2.0\) Hz, 1H), 7.38 – 7.24 (m, 2H), 6.19 (s, 1H), 5.93 (s, 1H), 5.73 (s, 1H); \(^{13}C\) NMR (100 MHz, Methanol-d₄): \(\delta = 167.2, 153.9, 140.3, 133.5, 130.6, 129.5, 129.4, 125.0, 123.3, 79.7\); ESI HR-MS: m/z = 238.4300, calcd. for \([C_{10}H_{7}BClO_4-H]\): 237.0131, found: 237.0138.

(R)-2-(1-Hydroxy-5,6-dimethoxy-1,3-dihydrobenzo[c][1,2]oxaborol-3-yl) acrylic acid (4l): semi-
solid, 84% yield; $\alpha_0^{20}$: +40.56 (c = 0.23 in MeOH); 82% ee, determined by chiral HPLC (Chiralpak AD), n-hexane/i-PrOH/CH$_3$COOH = 980/19/1, 1.0 mL/ min, $\lambda$ = 254 nm; $t$ (minor) = 12.348 min, $t$ (major) = 15.173 min; $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ = 12.79 (s, 1H), 9.10 (s, 1H), 7.21 (s, 1H), 6.90 (s, 1H), 6.11 (s, 1H), 5.85 (s, 1H), 5.68 (s, 1H), 3.77 (s, 3H), 3.74 (s, 3H); $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ = 167.9, 152.4, 149.8, 149.5, 142.2, 125.3, 122.2, 112.8, 105.7, 78.8, 56.2, 56.1; ESI HR-MS: $m/z$ = 264.0400, calcd. for [C$_{12}$H$_{12}$BO$_6$-H]: 263.0732, found: 263.0730.

(R)-2-(1-Hydroxy-5-(p-tolyloxy)-1,3-dihydrobenzo[c][1,2]oxaborol-3-yl) acrylic acid (4m):

semi-solid, 75% yield; $\alpha_0^{20}$: +20.24 (c = 0.25 in MeOH); 85% ee, determined by chiral HPLC (Chiralpak AD), n-hexane/i-PrOH/CH$_3$COOH = 980/19/1, 1.0 mL/ min, $\lambda$ = 254 nm; $t$ (minor) = 8.585 min, $t$ (major) = 12.019 min; $^1$H NMR (400 MHz, Methanol-$d_4$): $\delta$ = 7.59 (d, $J$ = 8.0 Hz, 1H), 7.17 (d, $J$ = 8.0 Hz, 2H), 6.96 – 6.86 (m, 4H), 6.24 (s, 1H), 5.98 (s, 1H), 5.77 (s, 1H), 2.32 (s, 3H); $^{13}$C NMR (100 MHz, Methanol-$d_4$): $\delta$ =167.5, 161.0, 158.1, 153.9, 140.8, 133.5, 131.5, 130.1, 124.3, 119.3, 117.3, 110.6, 79.2, 29.3, 19.4; ESI HR-MS: $m/z$ = 310.1120, calcd. for [C$_{17}$H$_{15}$BO$_5$-H]: 309.0940, found: 309.0936.

(R)-2-(1-Hydroxy-5-(m-tolyloxy)-1,3-dihydrobenzo[c][1,2]oxaborol-3-yl) acrylic acid (4n):

semi-solid, 80% yield; $\alpha_0^{20}$: +17.82 (c = 0.09 in MeOH); 97% ee, determined by chiral HPLC (Chiralpak AD), n-hexane/i-PrOH/CH$_3$COOH = 980/19/1, 1.0 mL/ min, $\lambda$ = 254 nm; $t$ (minor) = 7.672 min, $t$ (major) = 11.012 min; $^1$H NMR (400 MHz, Methanol-$d_4$): $\delta$ = 7.60 (d, $J$ = 8.0 Hz, 1H), 7.23 (t, $J$ = 7.8 Hz, 1H), 6.98 – 6.91 (m, 3H), 6.83 (t, $J$ = 2.4 Hz, 1H), 6.78 (dd, $J$ = 8.0, 2.4 Hz, 1H), 6.24 (s, 1H), 6.00 (s, 1H), 5.79 (s, 1H), 2.31 (s, 3H); $^{13}$C NMR (100 MHz, Methanol-$d_4$): $\delta$ =167.5, 160.6, 158.1, 156.4, 140.8, 140.0, 131.5, 129.3, 124.4, 124.2, 119.8, 117.7, 116.2, 111.1, 79.3, 20.0; ESI HR-MS: $m/z$ = 310.1120, calcd. for [C$_{17}$H$_{15}$BO$_5$-H]: 309.0940, found: 309.0937.
(R)-2-(1-Hydroxy-5-(4-(trifluoromethyl)phenoxy)-1,3-dihydrobenzo[c][1,2]oxaborol-3-yl) acrylic acid (4o): semi-solid, 72% yield; [α]D20 = +19.15 (c = 0.10 in MeOH); 78% ee, determined by chiral HPLC (Chiralpak AD), n-hexane/i-ProH/CH3COOH = 980/19/1, 1.0 mL/ min, λ = 254 nm; t (minor) = 7.822 min, t (major) = 11.579 min; 1H NMR (400 MHz, Methanol-d4): δ =7.71 – 7.65 (m, 2H), 7.64 (s, 1H), 7.13 (s, 1H), 7.12 – 7.07 (m, 2H), 7.04 (dd, J = 8.0, 2.1 Hz, 1H), 6.26 (s, 1H), 6.03 (s, 1H), 5.82 (s, 1H); 13C NMR (100 MHz, Methanol-d4): δ = 167.4, 160.1, 158.7, 158.3, 140.5, 131.9, 127.1, 127.01, 126.98, 126.94, 125.6, 125.2, 124.9, 124.52, 124.46, 122.9, 118.9, 118.3, 112.6, 79.4; ESI HR-MS: m/z = 364.0832, calcd. for [C17H12BF3O5-H]-: 363.0657, found: 363.0648.

(R)-2-(5-(Benzyloxy)-1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-3-yl) acrylic acid (4p): semi-solid, 81% yield; [α]D20 = +50.65 (c = 0.45 in MeOH); 87% ee, determined by chiral HPLC (Chiralpak AD), n-hexane/i-ProH/CH3COOH = 980/19/1, 1.0 mL/ min, λ = 254 nm; t (minor) = 11.906 min, t (major) = 17.899 min; 1H NMR (400 MHz, Methanol-d4): δ =7.55 (d, J = 8.2 Hz, 1H), 7.41 (d, J = 7.5 Hz, 2H), 7.35 (t, J = 7.4 Hz, 2H), 7.29 (t, J = 7.2 Hz, 1H), 7.02 (d, J = 2.2 Hz, 1H), 6.97 (dd, J = 8.2, 2.2 Hz, 1H), 6.24 (s, 1H), 5.99 (s, 1H), 5.74 (s, 1H), 5.07 (s, 2H); 13C NMR (100 MHz, Methanol-d4): δ =167.7, 161.6, 158.0, 141.0, 136.9, 131.2, 128.1, 127.6, 127.3, 124.3, 115.2, 107.5, 79.2, 69.6; ESI HR-MS: m/z = 310.1120, calcd. for [C17H15BO5-H]-: 309.0940, found: 309.0947.

(R)-2-(1-Hydroxy-6-(4-methoxyphenoxy)-1,3-dihydrobenzo[c][1,2]oxaborol-3-yl) acrylic acid (4q): white solid, 72% yield; mp = 97.2-101.1 °C. [α]D20 = +47.89 (c = 0.25 in MeOH); 88% ee (93% ee after recrystallization from EA), determined by chiral HPLC (Chiralpak AD), n-hexane/ i-ProH/ CH3COOH =
980/19/1, 1.0 mL/min, λ = 254 nm; t (minor) = 16.031 min, t (major) = 18.446 min; 

$^1$H NMR (400 MHz, Methanol-$d_4$): δ = 7.34 (d, $J = 8.4$ Hz, 1H), 7.09 (d, $J = 2.4$ Hz, 1H), 7.04 – 6.99 (m, 1H), 6.94 – 6.88 (m, 4H), 6.26 (s, 1H), 6.02 (s, 1H), 5.79 (s, 1H), 3.79 (s, 3H); $^{13}$C NMR (100 MHz, Methanol-$d_4$): δ = 167.4, 158.4, 156.1, 150.2, 150.0, 140.9, 142.4, 123.0, 120.7, 120.2, 117.5, 114.6, 79.4, 54.6, 23.8; ESI HR-MS: $m/z$ = 326.1110, calcd. for [C$_{17}$H$_{15}$BO$_6$-H]: 325.0889, found: 325.0896. 

(S)-4q: white solid, 79% yield; [α]$_D^{20}$: -28.80 (c = 0.20 in MeOH); 51% ee (90% ee after recrystallization from EA) determined by chiral HPLC (Chiralpak AD), n-hexane/i-PrOH/CH$_3$COOH = 980/19/1, 1.0 mL/min, λ = 254 nm; t (minor) = 15.670 min, t (major) = 13.418 min.

(R)-2-(1-Hydroxy-6-(4-nitrophenoxy)-1,3-dihydrobenzo[c][1,2]oxaborol-3-yl) acrylic acid (4r): semi-solid, 72% yield; [α]$_D^{20}$: +31.29 (c = 0.12 in MeOH); 86% ee, determined by chiral HPLC (Chiralpak AD), n-hexane/i-PrOH/CH$_3$COOH = 980/19/1, 1.0 mL/min, λ = 254 nm; t (minor) = 7.595 min, t (major) = 9.326 min; $^1$H NMR (400 MHz, Methanol-$d_4$): δ = 8.29 – 8.11 (m, 2H), 7.50 (d, $J = 8.3$ Hz, 1H), 7.34 (d, $J = 2.4$ Hz, 1H), 7.21 (dd, $J = 8.3$, 2.4 Hz, 1H), 7.12 – 6.96 (m, 2H), 6.30 (s, 1H), 6.08 (s, 1H), 5.86 (s, 1H); $^{13}$C NMR (100 MHz, Methanol-$d_4$): δ = 167.3, 163.5, 154.6, 152.4, 142.7, 140.5, 125.6, 124.8, 123.8, 123.4, 121.1, 116.9, 79.7, 53.4; ESI HR-MS: $m/z$ = 341.0820, calcd. for [C$_{16}$H$_{12}$BO$_6$-H]: 340.0634, found: 340.0634.

(R)-2-(6-(4-Chlorophenoxy)-1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-3-yl)acrylic acid (4s): semi-solid, 71% yield; [α]$_D^{20}$: +12.53 (c = 0.12 in MeOH); 84% ee, determined by chiral HPLC (Chiralpak AD), n-hexane/i-PrOH/CH$_3$COOH = 980/19/1, 1.0 mL/min, λ = 254 nm; t (minor) = 11.134 min, t (major) = 12.089 min; $^1$H NMR (400 MHz, Methanol-$d_4$): δ = 7.40 (d, $J = 8.4$ Hz, 1H), 7.36 – 7.28 (m, 2H), 7.19 (d, $J = 2.4$ Hz, 1H), 7.10 (dd, $J$ =

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(R)-2-(6-(Benzyloxy)-1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-3-yl) acrylic acid (4t): semi-solid, 83% yield; \([\alpha]_D^{20} = +29.05\) (c = 0.20 in MeOH); 80% ee, determined by chiral HPLC (Chiralpak AD), n-hexane/i-PrOH/CH₃COOH = 980/19/1, 1.0 mL/ min; \(t\) (major) = 16.429 min; \(^1\)H NMR (400 MHz, Methanol-\(d_4\)) \(\delta = 7.43\) (d, \(J = 7.1\) Hz, 2H), 7.39 – 7.33 (m, 2H), 7.32 – 7.26 (m, 2H), 7.20 (d, \(J = 2.5\) Hz, 1H), 7.07 (dd, \(J = 8.4, 2.5\) Hz, 1H), 6.18 (s, 1H), 6.00 (s, 1H), 5.75 (s, 1H), 5.08 (s, 2H); \(^{13}\)C NMR (100 MHz, Methanol-\(d_4\)) \(\delta = 167.6, 158.6, 148.1, 141.1, 137.3, 128.1, 127.9, 127.5, 127.2, 124.1, 122.8, 118.9, 114.2, 79.4, 69.8; ESI HR-MS: \(m/z = 310.1120\), calcd. for \([C_{17}H_{15}BO_3-H]\): 309.0940, found: 309.0934.

(6) The proposed mechanism for the enantioselective synthesis of (R)-enantiomers in the presence of catalyst C6

Based on the absolute stereochemistry of the products and a literature report,\(^5\) a mechanism for the reaction can be proposed as exemplified for catalyst C6. Following Michael addition of C6 to acrylate 2 to forms enolate intermediate I, aldol reaction with the boronic acid activated aldehyde 1a gives a mixture of two diastereomers IIA and IIB, stabilized by intramolecular hydrogen bonds between the oxy anion/boronic acid and N-H of C6. By contrast, the other two possible diastereomers IIC and IID cannot form such hydrogen bonding interactions. IIB may be less stable than IIA due to steric interactions between phenylboronic acid, the ester and quinuclidine moieties in the following E2 or E1cb elimination reactions, as apparent in Newman projection.
of IIb. Density functional theory (DFT) calculations revealed that transformation of IIA into cyclic boronate intermediate IIIA (predicted to be more stable than IIA) may be aided by hydrogen-bonding interactions between the boronate hydroxyl and N-H of C6 (see video in additional material); IIIA is transformed into (R)-4a by E2 or E1cb elimination then hydrolysis. In addition, (R)-3a’, which is generated after elimination of catalyst C6, can undergo intramolecular cyclization and hydrolysis to form (R)-4a. Note there was no evidence that (R)-3a’ reacts with 1a to form the potential dioxanone byproduct. The proposed mechanism is consistent both with the stereoselectivity and reaction substrate scope, in the latter case with respect to C-5 or C-6 substituents.
(5) Density Functional Theory (DFT) Calculations for Proposed Intermediates

To assist in the evaluation of the proposed mechanism (Scheme 2), we conducted DFT computations using the QChem program (v5.3). Using the 3-21G basis set and HF method, the four proposed key intermediates were optimized to lowest energy, and their single point energies calculated. Through the whole calculation process, implicit solvent was taken into consideration, which was implemented by the PCM solvent method with the solvent DIELECTRIC constant set as 2.2 (i.e., the dielectric constant of reaction solvent dioxane at 25°C). We selected the energy of the 13rd optimization step of II_A as a reference to compare the energies of final optimized intermediate structures as shown in following.

![Optimized structures of the proposed intermediates in the asymmetric MBH reaction](image)

Optimized structures of the proposed intermediates in the asymmetric MBH reaction (see Scheme 2 main text).
SE. 2 Biology

(1) Recombinant Protein Production and Purification

Recombinant KPC-2, AmpC, OXA-48, NDM-1, VIM-2, and Sfh-I proteins were produced in *Escherichia coli* and purified (to >90% by SDS-PAGE) using reported procedures.[6]

(2) Carbapenemase Inhibition Assays

All assays were performed as reported.[6] The concentrations of enzymes used were: KPC-2, 2.5 nM; AmpC, 0.8 nM; OXA-48, 20 nM; NDM-1, 0.2 nM; VIM-1, 0.2 nM; IMP-1, 0.8 nM; and VIM-2, 0.2 nM; and 10 µM or 5 µM FC-5[7] were employed for Sfh-I and other tested enzymes, respectively. The assay buffer supplemented with 0.01% (v/v) Triton X-100 was used for all the tested enzymes. In general, the enzyme was preincubated with compounds for 10 min at room temperature; reactions were initiated by adding FC-5 substrate; the fluorescence intensity at λ_{ex} of 380 nm and λ_{em} of 460 nm was measured. All IC_{50} values were fitted by using GraphPad Prism.

(3) Minimal Inhibitory Concentrations (MICs)

The clinically isolated strains were used for the antimicrobial susceptibility test, and the ATCC25922 strain was used for quality control. The standard broth micro-dilution method was used to determine MIC values according to the Clinical and Laboratory Standards Institute (CLSI) guideline (please find the details in our previous work[6a]). Meropenem was tested alone (from 128 µg/ml to 0.25 µg/ml in 2-fold dilution) and in combination with compounds (100 µM and 10 µM). The 96-well plates were incubated for 16-20 h at 37 °C and MIC values were mainly determined by visual reading.

(4) Crystallization and Data Collection

X-ray crystal structures of KPC-2:(S)-4a and OXA-48:(R)-4a complexes were obtained by co-crystallisation procedures. In brief, the mixtures of 10 mg/mL KPC-2 and 3.5 mM (S)-4a or 12 mg/mL OXA-48 and 3.5 mM (R)-4a were incubated for 60
min on ice. The crystallization drops contained 1:1 ratios of KPC-2:(S)-4\text{a} or OXA-
48:(R)-4\text{a} complex mixtures : reservoir solutions (Table S2). The crystals were
cryoprotected using a solution of ~30% (v/v) glycerol, and cooled in liquid nitrogen.
Data were collected and processed using HKL2000 at the Shanghai Synchrotron
Radiation Facility. Molecular replacement and refinement were carried out using
Phenix\textsuperscript{[8]} and Wincoot\textsuperscript{[9]}.
Copies of $^1$H and $^{13}$C NMR Spectra

$^1$H NMR Spectra of (R)-4a (400 MHz, CD$_3$OD)

$^{13}$C NMR Spectra of (R)-4a (100 MHz, CD$_3$OD)
$^1$H NMR Spectra of (R)-4b (400 MHz, DMSO-$d_6$)

$^{13}$C NMR Spectra of (R)-4b (100 MHz, DMSO-$d_6$)
$^1$H NMR Spectra of (R)-4c (400 MHz, CD$_3$OD)

$^{13}$C NMR Spectra of (R)-4c (100 MHz, CD$_3$OD)
$^1$H NMR Spectra of \((R)-4d\) (400 MHz, CD$_3$OD)

\(\text{H} - \text{NMR Spectra of (R)-4d (400 MHz, CD}_3\text{OD)}\)

$^{13}$C NMR Spectra of \((R)-4d\) (100 MHz, CD$_3$OD)

\(\text{C} - \text{NMR Spectra of (R)-4d (100 MHz, CD}_3\text{OD)}\)
$^1$H NMR Spectra of $(R)$-4e (400 MHz, CD$_3$OD)

$^{13}$C NMR Spectra of $(R)$-4e (100 MHz, CD$_3$OD)
$^1$H NMR Spectra of (R)-4f (400 MHz, CD$_3$OD)

$^{13}$C NMR Spectra of (R)-4f (100 MHz, CD$_3$OD)
$^1$H NMR Spectra of (R)-4g (400 MHz, CD$_3$OD)

\[
\begin{align*}
    7.51 & 1.13 \\
    7.48 & 1.14 \\
    7.42 & 1.32 \\
    7.28 & 1.32 \\
    7.24 & 1.32 \\
    7.23 & 1.32 \\
\end{align*}
\]

$^{13}$C NMR Spectra of (R)-4g (100 MHz, CD$_3$OD)

\[
\begin{align*}
    157.35 & 1 \\
    129.62 & 1 \\
    127.53 & 1 \\
    123.98 & 1 \\
    67.25 & 1 \\
\end{align*}
\]
$^1$H NMR Spectra of (R)-4h (400 MHz, DMSO-$d_6$)

$^{13}$C NMR Spectra of (R)-4h (100 MHz, DMSO-$d_6$)
$^1$H NMR Spectra of (R)-4i (400 MHz, DMSO-$d_6$)

[Image of 1H NMR spectrum for (R)-4i]

$^{13}$C NMR Spectra of (R)-4i (100 MHz, DMSO-$d_6$)

[Image of $^{13}$C NMR spectrum for (R)-4i]
$^1$H NMR Spectra of (R)-4j (400 MHz, CD$_3$OD)

$^{13}$C NMR Spectra of (R)-4j (100 MHz, CD$_3$OD)
$^1$H NMR Spectra of (R)-4k (400 MHz, CD$_3$OD)

$^{13}$C NMR Spectra of (R)-4k (100 MHz, CD$_3$OD)
$^1$H NMR Spectra of (R)-4I (400 MHz, DMSO-$d_6$)

$^{13}$C NMR Spectra of (R)-4I (100 MHz, DMSO-$d_6$)
$^1$H NMR Spectra of (R)-4m (400 MHz, CD$_3$OD)

$^{13}$C NMR Spectra of (R)-4m (100 MHz, CD$_3$OD)

$^1$H NMR Spectra of (R)-4n (400 MHz, CD$_3$OD)
$^{13}$C NMR Spectra of (R)-4n (100 MHz, CD$_3$OD)

$^1$H NMR Spectra of (R)-4n (400 MHz, CD$_3$OD)
$^{13}$C NMR Spectra of \((R)-4o\) (100 MHz, CD$_3$OD)

$^1$H NMR Spectra of \((R)-4p\) (400 MHz, CD$_3$OD)
$^{13}$C NMR Spectra of (R)-4p (100 MHz, CD$_3$OD)

$^1$H NMR Spectra of (R)-4q (400 MHz, CD$_3$OD)
\[
\begin{align*}
\text{13C NMR Spectra of (R)-4q (100 MHz, CD}_{3}\text{OD)}
\end{align*}
\]

\[
\begin{align*}
\text{1H NMR Spectra of (R)-4r (400 MHz, CD}_{3}\text{OD)}
\end{align*}
\]
$^{13}$C NMR Spectra of $(R)$-4r (100 MHz, CD$_3$OD)

$^1$H NMR Spectra of $(R)$-4s (400 MHz, CD$_3$OD)
$^{13}$C NMR Spectra of (R)-4s (100 MHz, CD$_3$OD)

$^1$H NMR Spectra of (R)-4t (400 MHz, CD$_3$OD)
$^{13}$C NMR Spectra of $(R)$-4t (100 MHz, CD$_3$OD)
Copies of HPLC Spectra

![HPLC Spectra Diagram](image)

| Ret Time [min] | Width [min] | Area     | Height | Area % |
|----------------|-------------|----------|--------|--------|
| 6.748          | 1.03        | 10177.34 | 1050.21| 49.96  |
| 7.802          | 0.96        | 10192.04 | 933.02 | 50.04  |
| Totals         |             | 20369.38 |        |        |

| Ret Time [min] | Width [min] | Area     | Height | Area % |
|----------------|-------------|----------|--------|--------|
| 6.249          | 0.12        | 6.78     | 0.82   | 5.00   |
| 7.381          | 0.16        | 128.78   | 12.53  | 95.00  |
| Totals         |             | 135.56   |        |        |
ee after recrystallization

Ret Time [min] | Width [min] | Area  | Height | Area %
---|---|---|---|---
6.897 | 0.14 | 614.85 | 70.79 | 1.93
7.956 | 1.33 | 31237.25 | 2373.52 | 98.07
Totals | | 31852.10 | |

\[(S)\text{-}4a\]
*ee after recrystallization*

| Ret Time [min] | Width [min] | Area    | Height   | Area % |
|----------------|-------------|---------|----------|--------|
| 6.484          | 0.14        | 11901.17| 1351.69  | 99.76  |
| 7.596          | 0.14        | 28.53   | 3.22     | 0.24   |
| **Totals**     |             | **11929.70** |          |        |
### (R)-4c

**Table 1:** Retention Time and Peak Characteristics

| Ret Time [min] | Width [min] | Area   | Height  | Area % |
|----------------|-------------|--------|---------|--------|
| 8.494          | 0.19        | 1562.94| 129.80  | 49.06  |
| 10.432         | 0.23        | 1622.51| 107.44  | 50.94  |
| **Totals**     |             | **3185.45** |         |        |

| Ret Time [min] | Width [min] | Area   | Height  | Area % |
|----------------|-------------|--------|---------|--------|
| 8.687          | 0.17        | 37.15  | 3.16    | 5.00   |
| 10.625         | 0.24        | 706.04 | 44.56   | 95.00  |
| **Totals**     |             | **749.19** |         |        |
ee after recrystallization

| Ret Time [min] | Width [min] | Area   | Height | Area % |
|----------------|-------------|--------|--------|--------|
| 9.276          | 0.20        | 42.28  | 3.29   | 1.05   |
| 11.416         | 0.28        | 3970.27| 218.23 | 98.95  |
| **Totals**     |             | 4012.55|        |        |

(S)-4c

| Ret Time [min] | Width [min] | Area   | Height | Area % |
|----------------|-------------|--------|--------|--------|
| 8.427          | 0.18        | 1515.55| 128.46 | 75.99  |
| 10.391         | 0.22        | 478.73 | 32.90  | 24.01  |
| **Totals**     |             | 1994.28|        |        |
ee after recrystallization

| Ret Time [min] | Width [min] | Area     | Height    | Area %   |
|----------------|-------------|----------|-----------|----------|
| 8.365          | 0.19        | 13706.72 | 1069.99   | 97.93    |
| 10.440         | 0.21        | 289.55   | 21.43     | 2.07     |
| Totals         |             | 13996.27 |           |          |


| Ret Time [min] | Width [min] | Area  | Height | Area % |
|----------------|-------------|-------|--------|--------|
| 7.939          | 0.18        | 546.71| 46.79  | 49.86  |
| 11.583         | 0.26        | 549.86| 32.53  | 50.14  |
| Totals         |             | 1096.57|        |        |

| Ret Time [min] | Width [min] | Area  | Height | Area % |
|----------------|-------------|-------|--------|--------|
| 7.646          | 0.16        | 28.78 | 2.44   | 6.93   |
| 11.231         | 0.26        | 386.35| 22.46  | 93.07  |
| Totals         |             | 415.13|        |        |
| Time  | Ret Time [min] | Width [min] | Area  | Height | Area % |
|-------|----------------|-------------|-------|--------|--------|
| 0     | 6.706          | 0.15        | 211.99| 20.84  | 50.15  |
| 10    | 9.612          | 0.22        | 210.71| 14.70  | 49.85  |
|       | Totals         |             | 422.70|        |        |

| Time  | Ret Time [min] | Width [min] | Area  | Height | Area % |
|-------|----------------|-------------|-------|--------|--------|
| 0     | 6.481          | 0.15        | 74.05 | 7.48   | 8.90   |
| 10    | 9.261          | 0.22        | 757.63| 53.09  | 91.10  |
|       | Totals         |             | 831.68|        |        |
\[
\text{(R)-4f}
\]

| Ret Time [min] | Width [min] | Area     | Height   | Area % |
|---------------|-------------|----------|----------|--------|
| 6.623         | 0.14        | 1922.77  | 205.11   | 50.30  |
| 7.995         | 0.17        | 1899.57  | 171.35   | 49.70  |
| **Totals**    | **-**       | **3822.35** | **-**    | **-**  |

| Ret Time [min] | Width [min] | Area     | Height   | Area % |
|---------------|-------------|----------|----------|--------|
| 6.004         | 0.10        | 269.72   | 42.28    | 8.35   |
| 7.410         | 0.69        | 2961.22  | 285.61   | 91.65  |
| **Totals**    | **-**       | **3230.94** | **-**    | **-**  |
ee after recrystallization

| Ret Time [min] | Width [min] | Area     | Height   | Area % |
|----------------|-------------|----------|----------|--------|
| 6.400          | 0.16        | 1298.60  | 127.23   | 5.04   |
| 7.968          | 0.20        | 24447.96 | 1882.83  | 94.96  |
| Totals         |             | 25746.56 |          |        |

(S)-4f

| Ret Time [min] | Width [min] | Area     | Height   | Area % |
|----------------|-------------|----------|----------|--------|
| 5.981          | 0.13        | 14281.17 | 1636.12  | 73.87  |
| 7.475          | 0.16        | 5050.51  | 493.90   | 26.13  |
| Totals         |             | 19331.68 |          |        |
ee after recrystallization

| Ret Time [min] | Width [min] | Area   | Height  | Area % |
|----------------|-------------|--------|---------|--------|
| 5.998          | 0.15        | 19521.87 | 2040.77 | 94.81  |
| 7.495          | 0.15        | 1068.83  | 112.68  | 5.19   |
| Totals         |             | 20590.70 |         |        |
| Ret Time [min] | Width [min] | Area     | Height   | Area % |
|----------------|-------------|----------|----------|--------|
| 6.422          | 0.14        | 16724.58 | 1852.31  | 50.56  |
| 7.594          | 0.16        | 16357.32 | 1615.85  | 49.44  |
| Totals         |             | 33081.90 |          |        |

| Ret Time [min] | Width [min] | Area     | Height   | Area % |
|----------------|-------------|----------|----------|--------|
| 6.234          | 0.13        | 15.48    | 1.71     | 12.42  |
| 7.366          | 0.16        | 109.20   | 10.53    | 87.58  |
| Totals         |             | 124.69   |          |        |
| Ret Time [min] | Width [min] | Area      | Height  | Area % |
|---------------|------------|-----------|---------|--------|
| 8.145         | 0.19       | 3926.31   | 324.16  | 48.76  |
| 8.712         | 0.20       | 4125.93   | 308.11  | 51.24  |
| Totals        |            | 8052.24   |         |        |

| Ret Time [min] | Width [min] | Area      | Height  | Area % |
|---------------|------------|-----------|---------|--------|
| 8.659         | 0.14       | 4.19      | 0.36    | 7.92   |
| 9.343         | 0.20       | 48.67     | 3.36    | 92.08  |
| Totals        |            | 52.86     |         |        |
### Table 1

| Ret Time [min] | Width [min] | Area   | Height | Area %  |
|----------------|-------------|--------|--------|---------|
| 6.840          | 0.15        | 27.11  | 2.75   | 49.16   |
| 7.399          | 0.16        | 28.04  | 2.72   | 50.84   |
| **Totals**     |             | **55.15** |        |         |

### Table 2

| Ret Time [min] | Width [min] | Area   | Height | Area %  |
|----------------|-------------|--------|--------|---------|
| 6.385          | 0.14        | 27.03  | 3.01   | 9.47    |
| 6.941          | 0.15        | 258.38 | 26.41  | 90.53   |
| **Totals**     |             | **285.41** |        |         |
ee after recrystallization

| Ret Time [min] | Width [min] | Area   | Height | Area % |
|----------------|-------------|--------|--------|--------|
| 6.489          | 0.13        | 11.74  | 1.34   | 1.94   |
| 7.094          | 0.15        | 594.49 | 60.10  | 98.06  |
| **Totals**     |             | **606.23** |        |        |

(S)-4j

| Ret Time [min] | Width [min] | Area   | Height | Area % |
|----------------|-------------|--------|--------|--------|
| 6.373          | 0.16        | 1344.18| 132.31 | 78.51  |
| 7.053          | 0.17        | 367.88 | 34.09  | 21.49  |
| **Totals**     |             | **1712.06** |        |        |
ee after recrystallization

| Ret Time [min] | Width [min] | Area  | Height | Area % |
|----------------|-------------|-------|--------|--------|
| 6.408          | 0.15        | 196.47| 20.76  | 97.42  |
| 7.037          | 0.13        | 5.20  | 0.52   | 2.58   |
| Totals         |             | 201.67|        |        |
| Ret Time [min] | Width [min] | Area     | Height   | Area % |
|---------------|------------|----------|----------|--------|
| 6.602         | 0.71       | 5017.34  | 527.26   | 49.43  |
| 7.250         | 1.00       | 5132.07  | 469.39   | 50.57  |
| **Totals**    |            | **10149.41** |          |        |

| Ret Time [min] | Width [min] | Area     | Height   | Area % |
|---------------|------------|----------|----------|--------|
| 4.750         | 0.65       | 5267.95  | 750.15   | 88.91  |
| 5.220         | 0.12       | 657.42   | 84.39    | 11.09  |
| **Totals**    |            | **5925.37** |          |        |
| Ret Time [min] | Width [min] | Area    | Height  | Area % |
|---------------|------------|---------|---------|--------|
| 12.071        | 1.31       | 6715.90 | 356.88  | 50.26  |
| 14.951        | 1.62       | 6645.44 | 270.79  | 49.74  |
| Totals        |            | 13361.33|         |        |

| Ret Time [min] | Width [min] | Area    | Height  | Area % |
|---------------|------------|---------|---------|--------|
| 12.348        | 0.31       | 141.51  | 6.66    | 9.22   |
| 15.173        | 0.38       | 1393.76 | 55.45   | 90.78  |
| Totals        |            | 1535.27 |         |        |
| Ret Time [min] | Width  [min] | Area   | Height  | Area %  |
|----------------|--------------|--------|---------|---------|
| 10.498         | 0.41         | 646.64 | 23.44   | 50.66   |
| 14.160         | 0.45         | 629.79 | 21.08   | 49.34   |
| Totals         |              | 1276.43|         |         |

| Ret Time [min] | Width  [min] | Area   | Height  | Area %  |
|----------------|--------------|--------|---------|---------|
| 8.585          | 0.19         | 293.61 | 23.98   | 7.42    |
| 12.019         | 1.91         | 3665.35 | 201.99 | 92.58   |
| Totals         |              | 3958.97|         |         |
| Ret Time [min] | Width [min] | Area   | Height | Area % |
|---------------|-------------|--------|--------|--------|
| 7.178         | 0.16        | 263.85 | 25.26  | 50.15  |
| 10.352        | 0.23        | 262.29 | 17.40  | 49.85  |
| Totals        |             | 526.13 |        |        |

| Ret Time [min] | Width [min] | Area   | Height | Area % |
|---------------|-------------|--------|--------|--------|
| 7.672         | 0.17        | 100.52 | 9.42   | 1.38   |
| 11.012        | 1.08        | 7205.84| 426.29 | 98.62  |
| Totals        |             | 7306.36|        |        |
| Ret Time [min] | Width [min] | Area   | Height | Area % |
|---------------|------------|--------|--------|--------|
| 12.515        | 0.29       | 178.68 | 8.70   | 50.78  |
| 18.974        | 0.35       | 173.18 | 6.02   | 49.22  |
| Totals        |            | 351.86 |        |        |

| Ret Time [min] | Width [min] | Area   | Height | Area % |
|---------------|------------|--------|--------|--------|
| 11.906        | 0.25       | 26.02  | 1.27   | 6.30   |
| 17.899        | 0.42       | 386.71 | 11.75  | 93.70  |
| Totals        |            | 412.72 |        |        |
(R)-4q

| Ret Time [min] | Width [min] | Area   | Height | Area % |
|----------------|-------------|--------|--------|--------|
| 16.314         | 0.49        | 1830.90| 53.00  | 49.87  |
| 18.815         | 0.40        | 1840.25| 69.19  | 50.13  |
| Totals         |             | 3671.15|        |        |

| Ret Time [min] | Width [min] | Area   | Height | Area % |
|----------------|-------------|--------|--------|--------|
| 16.031         | 0.30        | 75.35  | 2.96   | 6.17   |
| 18.446         | 0.42        | 1146.86| 41.67  | 93.83  |
| Totals         |             | 1222.22|        |        |
ee after recrystallization

| Ret Time [min] | Width [min] | Area   | Height | Area % |
|----------------|-------------|--------|--------|--------|
| 13.427         | 0.29        | 94.38  | 4.60   | 3.30   |
| 15.867         | 0.55        | 2768.36| 76.89  | 96.70  |
| **Totals**     |             | **2862.74** |        |        |

(S)-4q

| Ret Time [min] | Width [min] | Area   | Height | Area % |
|----------------|-------------|--------|--------|--------|
| 13.418         | 0.32        | 521.22 | 25.26  | 75.01  |
| 15.670         | 0.36        | 173.62 | 6.62   | 24.99  |
| **Totals**     |             | **694.84** |        |        |
ee after recrystallization

| Ret Time [min] | Width [min] | Area  | Height | Area % |
|----------------|-------------|-------|--------|--------|
| 16.588         | 0.41        | 954.22| 35.74  | 94.95  |
| 19.334         | 0.29        | 50.72 | 2.06   | 5.05   |
| Totals         |             | 1004.94|        |        |
| Ret Time [min] | Width [min] | Area   | Height | Area % |
|----------------|-------------|--------|--------|--------|
| 11.112         | 0.27        | 928.64 | 53.07  | 49.55  |
| 12.075         | 0.29        | 945.59 | 48.90  | 50.45  |
| **Totals**     |             | **1874.23** |        |        |

| Ret Time [min] | Width [min] | Area   | Height | Area % |
|----------------|-------------|--------|--------|--------|
| 11.134         | 0.21        | 92.33  | 5.75   | 7.78   |
| 12.089         | 1.49        | 1093.80| 57.62  | 92.22  |
| **Totals**     |             | **1186.13** |        |        |
| Ret Time [min] | Width [min] | Area  | Height | Area % |
|---------------|------------|-------|--------|--------|
| 12.194        | 0.29       | 71.96 | 3.79   | 50.51  |
| 14.925        | 0.36       | 70.51 | 2.97   | 49.49  |
| Totals        |            | 142.47|        |        |

| Ret Time [min] | Width [min] | Area  | Height | Area % |
|---------------|------------|-------|--------|--------|
| 12.649        | 0.45       | 58.10 | 1.54   | 10.03  |
| 16.429        | 0.15       | 521.02| 53.93  | 89.97  |
| Totals        |            | 579.12|        |        |
X-ray Crystallographic Data for 4a.

CDCC 2050141 contains supplementary crystallographic data for compound 4a.

| Table 1 Crystal data and structure refinement for cu_CFE_CXP_P2_1201_Om. |
|-------------------------------------------------|
| Identification code                      | cu_CFE_CXP_P2_1201_Om                       |
| Empirical formula                      | C_{10}H_{19}B_{10}O_{4}                      |
| Formula weight                        | 203.98                                        |
| Temperature/K                         | 295.0                                         |
| Crystal system                        | orthorhombic                                  |
| Space group                           | P2_12_1                                       |
| a/Å                                  | 8.1938(4)                                     |
| b/Å                                  | 8.3710(4)                                     |
| c/Å                                  | 28.4985(14)                                   |
| α/°                                  | 90                                             |
| β/°                                  | 90                                             |
| γ/°                                  | 90                                             |
| Volume/Å³                             | 1954.72(16)                                   |
| Z                                    | 8                                              |
| \(\rho_{calc}/\text{cm}^3\)          | 1.386                                          |
| \(\mu/\text{mm}^{-1}\)               | 0.885                                          |
| F(000)                               | 848.0                                          |
| Crystal size/mm³                     | 0.3 × 0.2 × 0.2                               |
| Radiation                            | CuKα (\(\lambda = 1.5418\))                  |
| 2Θ range for data collection/°      | 6.20 to 136.636                                |
| Index ranges                         | -9 ≤ h ≤ 9, -9 ≤ k ≤ 10, -33 ≤ l ≤ 34        |
| Reflections collected                | 19121                                          |
| Independent reflections              | 3566 [\(R_{int} = 0.0275, R_{sigma} = 0.0176\)] |
| Data/restraints/parameters           | 3566/0/275                                     |
| Goodness-of-fit on F²                | 1.063                                          |
| Final R indexes [I>2σ(I)]            | \(R_I = 0.0290, wR_2 = 0.0753\)               |
| Final R indexes [all data]           | \(R_I = 0.0313, wR_2 = 0.0770\)               |
| Largest diff. peak/hole / e Å⁻³      | 0.12/-0.14                                    |
| Flack parameter                      | 0.00(4)                                        |
Supplementary Figures

(R)-4a to class A KPC-2
IC$_{50}$ = 3.08 μM
pIC$_{50}$ = 5.51
s.e. pIC$_{50}$ = 0.05

(R)-4a to class C AmpC
IC$_{50}$ = 134.10 μM
pIC$_{50}$ = 3.87
s.e. pIC$_{50}$ = 0.41

(R)-4a to class D OXA-48
IC$_{50}$ = 15.84 μM
pIC$_{50}$ = 4.80
s.e. pIC$_{50}$ = 0.05

(R)-4a to class B1 NDM-1
IC$_{50}$ = 549.80 μM
pIC$_{50}$ = 3.269
s.e. pIC$_{50}$ = 0.665

(R)-4a to class B1 IMP-1
IC$_{50}$ = 380.4 μM
pIC$_{50}$ = 3.420
s.e. pIC$_{50}$ = 0.164

(R)-4a to class B1 VIM-1
IC$_{50}$ = 261.4 μM
pIC$_{50}$ = 3.583
s.e. pIC$_{50}$ = 0.154

(R)-4a to class B1 VIM-2
IC$_{50}$ = 225.40 μM
pIC$_{50}$ = 3.647
s.e. pIC$_{50}$ = 0.372
(R)-4e to class A KPC-2

\[ \text{IC}_{50} = 21.69 \mu M \]
\[ \text{pIC}_{50} = 4.654 \]
\[ \text{s.e. pIC}_{50} = 0.037 \]

(R)-4e to class C AmpC

\[ \text{IC}_{50} = 125.00 \mu M \]
\[ \text{pIC}_{50} = 3.903 \]
\[ \text{s.e. pIC}_{50} = 0.151 \]

(R)-4e to class D OXA-48

\[ \text{IC}_{50} = 30.82 \mu M \]
\[ \text{pIC}_{50} = 4.511 \]
\[ \text{s.e. pIC}_{50} = 0.070 \]

(R)-4e to class B1 NDM-1

\[ \text{IC}_{50} > 600 \mu M \]

(R)-4e to class B1 IMP-1

\[ \text{IC}_{50} > 300 \mu M \]
\[ \text{pIC}_{50} = \text{aa} \]
\[ \text{s.e. pIC}_{50} = \text{aa} \]

(R)-4e to class B1 VIM-1

\[ \text{IC}_{50} = 757.6 \mu M \]
\[ \text{pIC}_{50} = 3.121 \]
\[ \text{s.e. pIC}_{50} = 0.665 \]

(R)-4e to class B1 VIM-2

\[ \text{IC}_{50} = 189.8 \mu M \]
\[ \text{pIC}_{50} = 3.722 \]
\[ \text{s.e. pIC}_{50} = 0.138 \]
(R)-4f to class A KPC-2
IC$_{50}$ = 3.87 µM
pIC$_{50}$ = 5.413
s.e. pIC$_{50}$ = 0.065

(R)-4f to class C AmpC
IC$_{50}$ = 140.90 µM
pIC$_{50}$ = 3.851
s.e. pIC$_{50}$ = 0.058

(R)-4f to class D OXA-48
IC$_{50}$ = 10.13 µM
pIC$_{50}$ = 4.994
s.e. pIC$_{50}$ = 0.022

(R)-4f to class B1 NDM-1
IC$_{50}$ > 600 µM

(R)-4f to class B1 IMP-1
IC$_{50}$ = 300 µM
pIC$_{50}$ = aa
s.e. pIC$_{50}$ = aa

(R)-4f to class B1 VIM-1
IC$_{50}$ = 436.6 µM
pIC$_{50}$ = 3.36
s.e. pIC$_{50}$ = 0.412

(R)-4f to class B1 VIM-2
IC$_{50}$ = 82.60 µM
pIC$_{50}$ = 4.062
s.e. pIC$_{50}$ = 0.061
(S)-4j to class A KPC-2

ICS = 0.49 μM
pIC50 = 6.302
s.e. pIC50 = 0.067

(S)-4j to class C Ampc

ICS = 108.7 μM
pIC50 = 3.964
s.e. pIC50 = 0.056

(S)-4j to class D OXA-48

ICS = 12.03 μM
pIC50 = 4.920
s.e. pIC50 = 0.048

(S)-4j to class B1 NOM-1

ICS = 719.1 μM
pIC50 = 3.143
s.e. pIC50 = 0.497

(S)-4j to class B1 IMP-1

ICS = 170.6 μM
pIC50 = 3.768
s.e. pIC50 = 0.101

(S)-4j to class B1 VIM-1

ICS = 308.6 μM
pIC50 = 3.511
s.e. pIC50 = 0.053

(S)-4j to class B1 VIM-2

ICS = 105.7 μM
pIC50 = 3.976
s.e. pIC50 = 0.525
(R)-4m to class A KPC-2

IC_{50} = 3.59 \mu M
pIC\text{_{50}} = 5.447
s.e. pIC\text{_{50}} = 0.046

(R)-4m to class C AmpC

IC_{50} = 59.95 \mu M
pIC\text{_{50}} = 4.292
s.e. pIC\text{_{50}} = 0.050

(R)-4m to class D OXA-48

IC_{50} = 6.24 \mu M
pIC\text{_{50}} = 5.205
s.e. pIC\text{_{50}} = 0.025

(R)-4m to class B1 NDM-1

IC_{50} = 352.4 \mu M
pIC\text{_{50}} = 3.453
s.e. pIC\text{_{50}} = 0.363

(R)-4m to class B1 VIM-2

IC_{50} > 600 \mu M

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(R)-4o to class A KPC-2

IC_{50} = 3.76 \mu M  
\text{pIC}_{50} = 5.425  
s.e. \text{pIC}_{50} = 0.051

(R)-4o to class C AmpC

IC_{50} = 53.72 \mu M  
\text{pIC}_{50} = 4.270  
s.e. \text{pIC}_{50} = 0.046

(R)-4o to class D OXA-48

IC_{50} = 7.73 \mu M  
\text{pIC}_{50} = 5.112  
s.e. \text{pIC}_{50} = 0.022

(R)-4o to class B1 NDM-1

IC_{50} > 800 \mu M

(R)-4o to class B1 IMP-1

IC_{50} = 78.41 \mu M  
\text{pIC}_{50} = 4.11  
s.e. \text{pIC}_{50} = 0.085

(R)-4o to class B1 VIM-1

IC_{50} = 339.7 \mu M  
\text{pIC}_{50} = 3.469  
s.e. \text{pIC}_{50} = 0.251

(R)-4o to class B1 VIM-2

IC_{50} > 600 \mu M
(R)-4p to class A KPC-2

IC$_{50}$ = 1.17 µM
pIC$_{50}$ = 5.934
s.e. pIC$_{50}$ = 0.046

(R)-4p to class C AmpC

IC$_{50}$ = 40.13 µM
pIC$_{50}$ = 4.397
s.e. pIC$_{50}$ = 0.045

(R)-4p to class D OXA-48

IC$_{50}$ = 7.55 µM
pIC$_{50}$ = 5.122
s.e. pIC$_{50}$ = 0.026

(R)-4p to class B1 NDM-1

IC$_{50}$ > 300 µM
pIC$_{50}$ = aa
s.e. pIC$_{50}$ = aa

(R)-4p to class B1 IMP-1

IC$_{50}$ > 300 µM
pIC$_{50}$ = aa
s.e. pIC$_{50}$ = aa

(R)-4p to class B1 VIM-1

IC$_{50}$ = 3.71 µM
pIC$_{50}$ = 4.305
s.e. pIC$_{50}$ = 0.121

(R)-4p to class B1 VIM-2

IC$_{50}$ > 300 µM
pIC$_{50}$ = aa
s.e. pIC$_{50}$ = aa
Figure S1. IC_{50} curves of 4a-4t and avibactam with KPC-2, AmpC, OXA-48, NDM-1, IMP-1, VIM-1, and VIM-2. The concentrations of enzymes used were: KPC-2, 2.5 nM; AmpC, 0.8 nM; OXA-48, 20 nM; NDM-1, 0.2 nM; IMP-1, 0.8 nM; VIM-1, 0.2 nM; and VIM-2, 0.2 nM; and 5 μM FC-5 substrate were employed for these enzymes. The assay buffer was supplemented with 0.01% (v/v) Triton X-100 for all the tested enzymes.
Figure S2. The mode of (S)-4a binding to KPC-2 as defined by the electron density map. A view from a structure of the KPC-2:(S)-4a (PDB ID 7E9A) complex with the $mF_o - DF_c$ electron density (OMIT maps) around (S)-4a (blue mesh, contoured to 3σ) calculated from the final refined model shown.
Figure S3. The mode of (R)-4a binding to OXA-48 as defined by the electron density map. A view from a structure of OXA-48:(R)-4a (PDB ID 7DML) with the $mF_o-DF_c$ electron density (OMIT map) around (R)-4a and the catalytically relevant carbamylated Lys$_{73}$ (KCX$_{73}$) (blue mesh, contoured to 3σ) calculated from the final refined model shown.
Figure S4. Protein-ligand interactions between (S)-4a and KPC-2 as defined using the LigPlot+ program.\textsuperscript{[10]}
Figure S5. Protein-ligand interactions between (R)-4a and OXA-48 as defined using the LigPlot+ program.\textsuperscript{[9]}
Figure S6. Proposed binding modes of (S)-4q/(R)-4q with KPC-2 and OXA-48. (a) The C-6 4-methoxyphenoxyl group of (S)-4q may form an additional hydrogen bond with Asn$_{170}$ of KPC-2. (b) (S)-4q may occupy the hydrophobic subpocket surrounded by Ile$_{102}$, Trp$_{105}$, Val$_{120}$, and Leu$_{158}$ of OXA-48.
Figure S7. Comparison of KPC-2:((S)-4a/OXA-48:((R)-4a structures with those of KPC-2/OXA-48 reacted with β-lactam substrates. β-Lactam substrate reacted (designated by -P) complexes include with faropenem (PDB: 7A61, 5UJ4, and 6PSG), ampicillin (PDB: 6XD7), cefotaxime (PDB: 6Z23), imipenem (PDB: 6P97), ertapenem (PDB: 6P99), doripenem (PDB: 6P9C), cefotaxime (PDB: 6PQI), and cefoxitin (PDB: 6PT5). Note that (S)-4a and (R)-4a reaction / binding mimics that of β-lactams, particularly with respect to conserved anchoring features, in particular when comparing reaction of the electrophilic β-lactam carbonyl (observed in the acyl-enzyme complexes) and inhibitor boron, as well as in terms of the substrate/inhibitor carboxylate positions.
Figure S8. Comparison of KPC-2:((S)-4a/OXA-48:((R)-4a) structures with those of KPC-2/OXA-48 in complex with other boron-containing inhibitors. The latter comprise vaborbactam (PDB: 6TD0), taniboractam (PDB: 6TD1), QPX7728 (PDB: 6V1J and 6V1O), S02030 (PDB: 5EEC), and a phenyl boronic inhibitor (PDB: 5LL7); the comparisons reveal related binding modes, highlighting the importance of mimicking anchoring interactions involved in substate / intermediate binding.
Figure S9. Binding modes of the new C-3 substituted benzoaxaboroles mimics those of proposed intermediates in carbapenemase catalysis. (a) Carbapenem hydrolysis catalysed by serine and metallo β-lactamases. Comparisons of structures of KPC-2:(S)-4a (blue) with KPC-2:reacted imipenem (pink) (PDB: 6XJ8), and OXA-48:(R)-4a (green) with OXA-48:reacted meropenem (purple) (PDB: 6P98) imply that (S)-4a and (R)-4a have similar binding modes compared with those of (reacted) carbapenem (and other β-lactam, Fig. S7) antibiotics, particularly with respect to conserved ‘anchoring’ features, i.e. of the electrophilic β-lactam substrate carbonyl (observed as the acyl-enzyme)/inhibitor boron and the substrate/inhibitor carboxylate binding modes. (b) Superimposition of KPC-2:(S)-4a and OXA-48:(R)-4a structures reveals (S)-4a and (R)-4a have similar binding modes to both carbapenemases. (c) Comparison of structures of KPC-2:(S)-4a (blue) with KPC-2:reacted avibactam (yellow) (PDB: 4ZBE) reveals similar binding modes and evidence for flexibility of
Trp105 in substrate/inhibitor binding. (d) Designing new carbapenemase inhibitors by mimicking the conserved anchoring features, exemplified here for avibactam and benzoxaboroles (for other boron-containing inhibitors, see Fig. S8), is a viable strategy in drug discovery targeting carbapenemases.
Supplementary Tables

Table S1. The inhibitory activities (IC\textsubscript{50}, μM) of other synthesized benzoxaborole derivatives against representative serine- and metallo-carbapenemases.\textsuperscript{a}

| Cpd ID | Class A KPC-2 | Class C AmpC | Class D OXA-48 | Class B1 NDM-1 | Class B1 IMP-1 | Class B1 VIM-1 | Class B1 VIM-2 |
|--------|----------------|--------------|----------------|----------------|----------------|----------------|----------------|
| (R)-4b | 7.40           | 310.40       | 29.27          | >600           | >300           | 137.4          | 181.20        |
| (R)-4d | 1.88           | 110.30       | 2.57           | >600           | >300           | 271.3          | >600          |
| (R)-4e | 21.69          | 125.00       | 30.82          | >600           | >300           | 757.6          | 189.80        |
| (R)-4g | 3.18           | 113.10       | 9.92           | >600           | NT             | 345.1          | >600          |
| (R)-4h | 7.33           | 187.20       | 11.43          | >600           | 788            | >600           | 65.31         |
| (R)-4i | 1.68           | 146.40       | 24.91          | 430.5          | 421.4          | 118.8          | 127.70        |
| (R)-4k | 2.17           | 69.82        | 3.21           | >600           | 136.6          | 587.8          | 49.52         |
| (R)-4l | 5.73           | 152.90       | 27.91          | >600           | 120.1          | 763            | >600          |
| (R)-4m | 3.58           | 59.95        | 6.24           | 352.40         | NT             | NT             | >600          |
| (R)-4n | 2.11           | 27.38        | 4.10           | 109.90         | 17.39          | 425.3          | 233.70        |
| (R)-4o | 3.76           | 53.72        | 7.73           | >600           | 78.41          | 339.7          | >600          |
| (R)-4p | 1.17           | 40.13        | 7.55           | >300           | >300           | >300           | 3.71          |
| (R)-4r | 0.12           | 4.85         | 2.64           | 308.20         | >300           | >300           | 425.80        |
| (R)-4s | 0.27           | 9.03         | 0.85           | 146.50         | 123.6          | 300.9          | 133.50        |
| (R)-4t | 0.55           | 22.54        | 1.33           | 381.50         | 43.56          | 371.2          | 184.9         |

\textsuperscript{a} All of the tested compounds were obtained directly from the asymmetric MBH cascade reaction without further recrystallization.
Table S2. Co-crystallization Conditions for the OXA-48:(R)-4a and KPC-2:(S)-4a complexes.

| Structure   | Method         | Sample composition                                                                 | Crystallization condition                                                                 | Vapor diffusion condition                      |
|-------------|----------------|------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------|-----------------------------------------------|
| KPC-2:(S)-4a | Co-crystallization | KPC-2 in crystallization buffer + inhibitor (S)-4a (5 mM)                          | 32-35% PEG 8000, 0.1M lithium sulphate, 0.05M sodium acetate (pH 4.5)                     | Hanging drop, protein-to-well ratio, 1:1, 293K |
| OXA-48:(R)-4a | Co-crystallization | OXA-48 in crystallization buffer + inhibitor (R)-4a (3.5 mM)                       | 0.1 M HEPES pH7.5, 5% 1-butanol, 11~17% (v/v) polyethylene glycol 8000                   | Hanging drop, protein-to-well ratio, 1:1, 293K |
Table S3. Data Collection and Refinement Statistics for KPC-2:((S)-4a (PDB code 7E9A) and OXA-48:((R)-4a (PDB code 7DML) complex crystal structures.

| Structure                  | KPC-2:((S)-4a | OXA-48:((R)-4a |
|----------------------------|--------------|---------------|
| PDB ID                    | 7E9A         | 7DML          |
| **Processing**            |              |               |
| Radiation Source          | SSRF Beamline BL19U | SSRF Beamline BL17U |
| Space Group               | P 3 2 1      | P 1 2 1       |
| Unit Cell Dimensions: a, b, c (Å) | 165.42, 165.42, 94.86 | 58.45, 105.86, 94.12 |
| Unit Cell Dimensions: a, β, γ (˚) | 90.00, 90.00, 120.00 | 90.00, 107.81, 90.00 |
| *Mol/ASU                  | 4            | 4             |
| Resolution Range (outer shell) (Å) | 47.43-2.25 (2.29-2.25) | 19.81-1.94 (2.01-1.94) |
| Number of Unique Reflections | 70988       | 77650         |
| Completeness (outer shell) (%) | 95.5        | 88.04         |
| I/σ(I) (outer shell)      | 3.06         | 5.7           |
| Rmerge (outer shell)      | 1.701        | 0.258         |
| Wilson B Factor (Å²)      | 30.48        | 17.17         |
| **Refinement**            |              |               |
| Overall B Factor (Å²)     | 34.81        | 20.78         |
| Protein B Factor (Å²)     | 34.77        | 19.73         |
| Ligand B Factor (Å²) (occupancy) | 30.79 (1.0) | 25.72 (1.0) |
| Water B Factor (Å²)       | 34.25        | 28.98         |
| ¹RMSD from Ideal Bond Length (Å) | 0.012       | 0.014         |
| RMSD from Ideal Angles (˚) | 1.241        | 1.23          |
| Rwork (%)                 | 18.04        | 13.80         |
| Rfree (%)                 | 22.10        | 17.20         |

*Mol/ASU = molecules per asymmetric unit; ¹RMSD = root mean square deviation.
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